Universitat Autònoma de Barcelona

Evidencias en Dermatología: Ensayos clínicos, revisiones sistemáticas y guías de práctica clínica

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TESIS DOCTORAL

TÍTULO:

Evidencias en Dermatología: Ensayos clínicos, revisiones sistemáticas y guías de práctica clínica

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Barcelona, Mayo 2016

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"Evidence-based dermatology is no longer a dirty word in dermatology. Nowadays, all dermatologists are practicing evidence-based dermatology to some degree. Rather than just mutter the word "evidence" every now and again at meetings, the real challenge is to improve the skills of integrating the best external evidence to clinical care of individual patients."

Hywel Williams

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PRESENTACIÓN

En la práctica dermatológica actual o futura es necesario incorporar no sólo la experiencia propia, sino el conocimiento derivado de una investigación clínica válida, confiable y reproducible, basada en la mayor evidencia científica disponible. Es así como cada diseño de investigación, dependiendo del tipo que sea, aporta en sí mismo mayor o menor conocimiento. Esta tesis pretende mostrar evidencias en el campo de la Dermatología partiendo de lo meramente descriptivo hasta lo analítico.

En los apartados siguientes se presenta el contexto del aporte de cada diseño de investigación como base para obtener evidencias científicas en Dermatología, con el planteamiento de la respectiva pregunta de investigación resuelta a partir de cada uno de estos diseños.

Topical tacrolimus for atopic dermatitis
Efficacy and Safety of 308-nm Monochromatic Excimer Lamp Versus Other Phototherapy Devices for Vitiligo: A Systematic Review with Meta-Analysis

RESUMEN

RESUMEN

ANTECEDENTES:

La enorme variabilidad que existe en Dermatología respecto al manejo de algunas enfermedades crónicas de la piel es una clara demostración de la incertidumbre que existe para seleccionar la mejor terapia. Es así como la Dermatología Basada en la Evidencia (DBE) representa la mejor manera de integrar y articular la investigación clínica con la práctica clínica dermatológica. Entre las enfermedades dermatológicas que más afectan a la imagen y la calidad de vida de cada uno se incluyen las relacionadas con zonas visibles de la piel (la cara) como el acné vulgar y el fotodaño, y aquellas que pueden afectar a prácticamente toda la superficie cutánea y que, además, van acompañadas de síntomas como el prurito o el ardor, como es el caso de la psoriasis.

Para el tratamiento del daño actínico, existe limitada evidencia científica a favor del uso preferencial de alguna de las terapias. Por otra parte, las formas moderadas a severas de la psoriasis pediátrica suelen ser más difíciles de manejar, debido a las limitaciones en la aprobación de terapias sistémicas en niños y a la incertidumbre reinante acerca del uso de la terapia biológica. Teniendo en cuenta que los dos diseños epidemiológicos que permitirían determinar, por una parte, el efecto real de la TFD en el fotodaño y, por otra, la eficacia y seguridad de los anti TNF en la psoriasis pediátrica corresponderían a un ensayo clínico controlado con asignación aleatoria (ECA) y a una revisión sistemática (RS), respectivamente, es relevante plantear y desarrollar estudios de este tipo en estos temas específicamente.

Con respecto a la terapia del acné vulgar (AV), su selección está determinada por la edad y las preferencias del paciente, así como por su severidad. Existen algunas terapias para cuyo uso en el AV hay evidencia científica a favor (ej.: la isotretinoina por vía oral). No obstante, la mayoría de tratamientos de acné han sido incluidos en guías de práctica clínica alrededor del mundo, sin que se haya realizado una evaluación crítica de las mismas hasta la fecha.

OBJETIVOS DE ESTE TRABAJO DE TESIS:

Objetivo n. º 1: Identificar y describir de manera exhaustiva y rigurosa los ensayos clínicos controlados con asignación aleatoria (ECAs) que hayan sido publicados en revistas de Dermatología en español.

Objetivo n. º 2: Evaluar la calidad metodológica de los ensayos clínicos controlados con asignación aleatoria (ECA) que hayan sido publicados en revistas de Dermatología en español.

Objetivo n. º 3: Determinar la eficacia clínica del MAL + dos horas de luz solar en comparación con placebo + dos horas de luz solar en adultos con daño actínico facial.

Objetivo n. º 4: Evaluar la eficacia y seguridad de los agentes anti-TNF en el tratamiento de la psoriasis pediátrica.

Objetivo n. º 5: Evaluar la calidad de las guías de práctica clínica publicadas sobre el tratamiento del acné vulgar.

METODOLOGÍA:

Este trabajo de tesis se ha desarrollado en la modalidad de compendio de publicaciones. En el primer trabajo se realizó una revisión de la literatura que consideró los elementos clave de una revisión sistemática —la búsqueda exhaustiva de los ECA publicados—, mientras que en el segundo se realizó una revisión crítica de los ensayos clínicos encontrados. En el tercer trabajo se diseñó y ejecutó un experimento clínico controlado, de fase II con asignación aleatoria, de tipo explicativo y con evaluación del efecto en diseño doble ciego. En el cuarto trabajo se efectuó una revisión sistemática Cochrane. Por último, en el quinto se llevó a cabo una revisión crítica de las GPC disponibles acerca de la terapia del acné.

RESULTADOS

Trabajos 1 y 2: De las 28 revistas que reunieron los criterios de elegibilidad, se incluyeron finalmente 21. Se identificaron un total de 144 ECAs desde el año 1969. Además, se

identificaron 70 ECAs desde el año 1997 (implementación del CONSORT) hasta el 2012. El 73 % (51 ECAs) de estos fueron publicados en 16 revistas latinoamericanas, y el 27 % (19 ECAs) en cinco revistas españolas. La mayoría de los estudios se clasificaron en su conjunto como de "alto riesgo de sesgo" porque no se reportó en ellos la información necesaria para evaluar la calidad y el rigor metodológico del estudio. Un total de 15 estudios reportaron sus fuentes de financiación, y solo los autores de cinco estudios describieron los conflictos de interés. De todas las revistas evaluadas, únicamente *Actas Dermo-Sifilográficas* se adhiere a la normativa CONSORT en sus instrucciones para autores desde el año 2008.

Trabajo 3: Entre los 84 pacientes seleccionados, 19 no cumplieron con los criterios de elegibilidad y 5 se negaron a participar; por lo tanto, 60 pacientes fueron asignados al azar a alguno de los dos grupos. Todos los pacientes se expusieron al sol durante 120 minutos. El promedio de iluminancia en cada sesión fue de 82.478, 70.419 y 72.528 lux (sesiones 1, 2 y 3, respectivamente). El promedio de irradiancia solar (Watts / m2) fue de 480, 430 y 435 (sesiones 1, 2 y 3, respectivamente). El riesgo de fracaso fue menor en el grupo MAL + luz del día (RR: 0,18; IC95 %: 0,08-0,41; p = 0,00). En lo referente a la escala de calidad de vida, solo los ítems cinco y 14 del Skindex-29 del grupo MAL + luz solar mostraron diferencias estadísticamente significativas (p<0,05, prueba de Wilcoxon). Cuatro pacientes del grupo MAL + luz solar presentaron eventos adversos, dos de ellos graves no relacionados con el producto (cólico renal y corrección de prolapso genital), y los otros dos no serios (recurrencia de herpes simple y una reacción a la diacereína).

Trabajo 4: Se incluyó un solo estudio con 211 participantes (promedio de edad: 13 años), con dos grupos de tratamiento: uno con etanercept y el otro con placebo. El seguimiento se realizó durante un periodo de 48 semanas. Dado que solo se logró incluir un estudio con numerosas publicaciones, no se pudo realizar un análisis cuantitativo de los resultados (metanálisis). En la semana 12, el 57 % de los pacientes del grupo de etanercept lograron obtener un PASI-75 (RR: 4,95; IC95 %: 2,83-8,65) frente al 11 % del grupo de placebo. La reducción del riesgo absoluto fue del 45 % (IC95 %: 33,95-56,40) y el número necesario a

tratar (NNT) para obtener un beneficio con etanercept fue de dos (CI95 %: 1,77-2,95). Durante el estudio se reportaron tres eventos adversos graves, pero se resolvieron sin secuelas. La muerte u otros eventos como tumores malignos, infecciones oportunistas, tuberculosis o desmielinización, no se dieron durante el estudio.

Trabajo 5: Solo seis publicaciones cumplieron con los criterios de inclusión. El valor global del coeficiente de correlación intraclase fue muy bueno: 0,981 (IC95 %: 0,918- 0,997), y el acuerdo entre los evaluadores fue muy alto. Los dominios mejor puntuados fueron el dominio de alcance, finalidad y claridad en la presentación e independencia editorial; mientras que los peor puntuados correspondieron a los dominios de participación de los implicados, rigor en el desarrollo y aplicabilidad. Solo dos guías (la europea y la de Malasia) se recomendaron sin modificaciones adicionales.

CONCLUSIONES:

- La investigación clínica experimental en Dermatología que se publica en España y Latinoamérica debe mejorar ostensiblemente tanto en su diseño como en su reporte de resultados, para que la investigación dermatológica sea válida, ética, coherente y útil.
- El metil aminolevulinato + dos horas de luz solar, comparado con placebo + dos horas de luz solar, fue eficaz y seguro en adultos con daño actínico facial, con un gran tamaño del efecto y un NNT muy cercano a uno.
- El etanercept parece ser eficaz y seguro a corto plazo para el tratamiento de la psoriasis pediátrica. No obstante, ya que un solo ensayo clínico no aporta evidencia suficiente para recomendar una terapia, se requiere la inclusión futura de otros ensayos clínicos de terapias anti-TNF que permitan confirmar, o no, la eficacia y seguridad de estos tratamientos.
- Aunque se identificaron dos GPC de alta calidad de la terapia del acné, es evidente la necesidad de mejorarla en cuanto al rigor en la elaboración, participación de los interesados y aplicabilidad, así como de emplear el sistema GRADE (*Grading of Recommendations Assessment, Development and Evaluation*) en dichas guías.

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ABSTRACT

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BACKGROUND:

In Dermatology, the huge existing variability in the management of some chronic skin diseases is a clear proof of the uncertainty over the selection of the best therapy. Thus, Evidence-Based Dermatology (DBE) is the best way to integrate and coordinate clinical research with clinical dermatological practice. Among the skin diseases that affect both self-image and quality of life are those damaging visible areas of the skin (face), such as *acne vulgaris* and photodamage, and those that can virtually affect the entire skin surface and that are associated with symptoms (e.g. itching or burning), such as psoriasis.

For the treatment of facial actinic damage there is limited evidence that supports the preferred usage of one of the available therapies. Moreover, moderate to severe forms of pediatric psoriasis are often more difficult to handle due to limitations in the approval of systemic therapies in children, and the uncertainty about biological therapies. Considering that the two epidemiological designs that would allow to determine the real effect of PDT in photodamage and to evaluate the efficacy and safety of anti-TNF in pediatric psoriasis are systematic reviews and randomized clinical trials (RCTs), respectively, the development of such studies in these specific points is of great importance.

Selecting the treatment of *acne vulgaris* (AV) depends on the patient's age and preferences, as well as on the severity of the disorder. There is scientific evidence that supports certain therapies for AV (e.g. oral isotretinoin). However, most acne treatments have been included in clinical practice guidelines (CPGs) worldwide, but no critical appraisal of said guidelines had ever been published until now.

OBJECTIVES OF THE THESIS WORK:

Objective No. 1: To identify and exhaustively and rigorously describe all randomized controlled trials (RCTs) that have been published in dermatological journals in Spanish.

Objective No. 2: To assess the methodological quality of the RCTs published in dermatological journals in Spanish.

Objective No. 3: To determine the clinical efficacy of MAL + two hours of daylight compared to placebo + two hours of daylight in adults with facial photodamage.

Objective No. 4: To evaluate the efficacy and safety of anti-TNF agents in the treatment of pediatric psoriasis.

Objective No. 5: To carry out a critical appraisal of the quality of published clinical practice guidelines of the treatment of *acne vulgaris*.

METHODOLOGY:

The present thesis work has included five publications. In study 1, a thorough search of published RCTs that considered the critical elements of a systematic review was performed. In Study 2, a critical review of all identified RCTs was carried out. In Study 3, a controlled phase II randomized explanatory and double-blind clinical trial was designed and conducted. In Study 4, a Cochrane systematic review was undertaken. Finally, in Study 5, a critical review of the available CPGs about acne treatments was performed.

RESULTS:

Study 1 and 2: Of the 28 journals that met the eligibility criteria, 21 were finally included. A total of 144 RCTs have been identified since 1969. Seventy RCTs were found between 1997 (implementation of the CONSORT) and 2012, of which 73% (51 RCTs) were published in 16 Latin American journals, and 27% (19 RCTs) in five Spanish journals. Overall, most of the studies were considered as "high risk of bias", since the information needed for the evaluation of the quality and the methodological rigour of the study was not provided. A total of 15 studies reported their sources of funding, and only the authors of five studies reported conflicts of interest. Among all the analysed journals only *Actas Dermo-Sifilográficas* complies with the CONSORT standards since 2008 as to instructions to authors.

Study 3: Of the 84 selected patients, 19 did not meet the eligibility criteria and five refused to participate; 60 patients were, therefore, randomized into one of the two groups. All patients were exposed to daylight for 120 minutes. Mean illuminance per session was 82,478, 70,419 and 72,528 lux (sessions 1, 2 and 3, respectively). Mean irradiance (Watts / m2) was 480, 430 and 435 (sessions 1, 2 and 3, respectively). The risk of failure was lower in the group of MAL + daylight (RR: 0.18; CI95% 0.08 to 0.41; p = 0.00). With regard to the quality of life, only the MAL + daylight group showed statistically significant differences in items five and 14 of the Skindex-29 ($p<0.05$, Wilcoxon test). Four patients in the MAL—daylight presented with adverse events, two of them were serious but unrelated to the product (renal colic and correction of genital prolapse), and two non-serious (recurrent herpes simplex and a reaction to diacerein).

Study 4: Only one RCT with two treatment arms was included: one with etanercept and the other one with placebo. The study included 211 participants (average age 13 years) and had a 48-week follow-up. Since only one study was eligible, we were not able to

perform a quantitative analysis of the results (meta-analysis). By week 12, PASI-75 occurred in 57% of patients in the group of etanercept vs. 11% in the group of placebo (RR: 4.95; CI95%: 2.83 to 8.65). The absolute risk reduction was 45% (CI95% 33.95 to 56.40), and the number needed to treat (NNT) to gain benefit with etanercept was two (CI95% 1.77 to 2.95). During the study, three serious adverse events were reported, but they were resolved without sequelae. Death or other events such as malignancies, opportunistic infections, tuberculosis or demyelination did not occur during the trial.

Study 5: Only six publications met the inclusion criteria. The overall value of the intraclass correlation coefficient was very good: 0.981 (CI95%: 0.918 to 0.997; and inter-rater agreement was high. Domains that scored best were scope and purpose, clarity of presentation, and editorial independence. The domains with the lowest scores were stakeholder involvement, rigour in the development and applicability. Only two CPGs, namely the European and Malaysian, were recommended without further modifications.

CONCLUSIONS:

- Experimental clinical research in Dermatology published in Spain and Latin America should significantly improve both in design and publication patterns, in order to be valid, ethical, coherent and useful.

- Methyl aminolevulinate + two hours of daylight in adults with facial photodamage was effective and safe, compared to placebo + two hours of daylight, with a large effect size and a NNT very close to one.

- Etanercept appears to be effective and safe at least in the short-term management of pediatric psoriasis. However, since one single RCT does not provide an adequate body of evidence to recommend a certain therapy, the future inclusion of further RCTs of anti-TNF agents will substantiate or not the efficacy and safety of such treatments.

- Although two high-quality CPGs of the treatment of acne were identified, the following domains still need to be enhanced: rigour of development, participation of stakeholders and applicability. In addition, the GRADE (Grading of Recommendations Assessment, Development and Evaluation) system is imperative.

INTRODUCCION

INTRODUCCIÓN

PLANTEAMIENTO DEL PROBLEMA Y ESTADO DEL ARTE

La importancia de la enfermedad dermatológica a menudo se subestima por su carácter crónico y baja mortalidad, pero su frecuencia es tan alta que se ha determinado que entre el 21 % y 87 % de la población puede padecer algún tipo de trastorno de la piel (1). De hecho, constituyen la cuarta parte de las consultas en atención primaria debido a la importantes limitaciones físicas y psicológicas que comportan (1, 2), lo cual se deba posiblemente a que la autoimagen es un elemento esencial de la personalidad que no solo afecta a la salud mental, sino también a la actitud hacia el entorno (3, 4). Además, se ha descrito que la autoimagen es predictora de la satisfacción general y, por lo tanto, repercute de forma importante en la calidad de vida (5). Se ha reportado que una autoimagen favorable se traduce en emociones positivas, mientras que una autoimagen desfavorable da lugar a ansiedad, temor, ira, depresión y desadaptación social (6).

Entre las enfermedades dermatológicas que más influyen sobre la autoimagen y la calidad de vida se incluyen las relacionadas con las zonas visibles de la piel (la cara) como el acné vulgar y el fotodaño (7), y aquellas que pueden afectar a prácticamente toda la superficie cutánea y que, además, cursan con síntomas como el prurito o el ardor, como es el caso de la psoriasis (7).

El fotodaño facial

El envejecimiento de la piel puede ser intrínseco o extrínseco. El primero se refiere al proceso natural de envejecimiento cronológico que afecta a zonas de la piel tanto expuestas como no expuestas. El segundo se define como el envejecimiento mediado por factores ambientales, como el tabaquismo.

Por otra parte, la exposición a la radiación ultravioleta (RUV) causa alteraciones en la estructura, función y apariencia de la piel, denominadas en su conjunto fotodaño o daño

actínico (8). La gran mayoría de estos efectos perjudiciales de la RUV se puede atribuir al daño en el ADN. La radiación ultravioleta B (UVB) suele ser directamente absorbida por el ADN, y da lugar a la formación de dímeros de pirimidina, los cuales, al no ser adecuadamente reparados por los mecanismos homeostáticos cutáneos, inducen mutaciones y/o muerte celular. Asimismo, aunque la radiación UVA también provoca la formación de estos dímeros, se requieren dosis mucho más altas para obtener los mismos efectos que con la UVB (9, 10). Existen otros mecanismos por los cuales la exposición a la RUV causa daño cutáneo, entre los cuales se incluyen la producción de especies reactivas de oxígeno. Estas pueden aparecer o bien de forma temprana inmediatamente tras la exposición, o como resultado de la respuesta inflamatoria inducida por dosis altas de RUV que se traduce, a su vez, en la alteración de las membranas y proteínas celulares, en la rotura de cadenas de ADN o en cambios mutagénicos de las purinas (11, 12). Por su parte, este ambiente oxidativo origina la expresión del activador de la proteína 1 (AP-1) que interfiere con la expresión de genes para producir colágeno en fibroblastos y, al mismo tiempo, inhibe la expresión de enzimas protectoras como la superóxido dismutasa y la catalasa (11-13).

Todos los cambios moleculares inducidos por la RUV que se han mencionado se manifiestan clínicamente en la piel en forma de cambios en la textura, de arrugas finas y gruesas, hiperpigmentación moteada, color amarillento (cetrino) de la piel y/o telangiectasias. Además, y como consecuencia del carácter acumulativo y crónico de estas las alteraciones moleculares y clínicas enumeradas, aparecen patologías cutáneas específicas como las queratosis actínicas y/o el cáncer de piel (14). Por otra parte, entre los cambios histopatológicos inducidos por la RUV se incluyen: el depósito de material elastótico (fibras elásticas fragmentadas) en el tejido conectivo de la dermis superficial y media, la formación de células epidérmicas atípicas, la atrofia cutánea, el aumento de la melanogénesis (incremento de la producción del pigmento de la piel producido por los melanocitos), el depósito de glicosaminoglucanos excesivo y la disminución del colágeno(15).

Con el creciente conocimiento de los efectos y mecanismos por los cuales la RUV produce daño cutáneo, han surgido nuevos tratamientos para esta patología que causan tanto alteraciones clínicamente visibles en la piel como la disminución en la transformación neoplásica del epitelio cutáneo (16). Tal es el caso de la terapia fotodinámica (TFD), que consiste en la combinación de una fuente de luz que estimula un agente fotosensibilizante, como las porfirinas, en un ambiente rico en oxígeno. Esta modalidad terapéutica destruye selectivamente las células y el tejido dañados mediante la generación de oxígeno singlete muy tóxico después de la activación del agente fotosensibilizante (porfirinas) ocasionada por la luz (17-19).

Ante la posibilidad del uso de estos fotosensibilizantes en el área dermatológica, en 1990 se abrió un abanico de alternativas con la comercialización de precursores tópicos de porfirinas como el ácido 5-aminolevulinico (ALA) o su metil éster (MAL). Ambas formulaciones podían penetrar fácilmente la epidermis y producir fotosensibilización local más corta con una duración de entre 48 a 72 horas, con la ventaja adicional de la ausencia de fotosensibilidad cutánea generalizada. Tanto el 5-ALA como el MAL son precursores de la vía intracelular de la biosíntesis del hemo, e inducen la formación de porfirinas fotoactivas conocidas como la protoporfirina IX (PpIX), que son fotosensibilizadores eficientes que se acumulan en la piel fotodañada (20-25).

El 5-ALA es una molécula hidrofílica que impide atravesar de forma adecuada las barreras biológicas como el estrato corneo de la piel. De esta manera, para alcanzar niveles clínicamente relevantes de PpIX se deben aplicar dosis relativamente altas (al 20 %), y se requiere más tiempo (de 4 a 8 horas) para activar la PpIX y acumularla al máximo. Estas limitaciones fueron las que llevaron a desarrollar un derivado, concretamente, un éster metílico (el 5- metilo aminolevulinato [MAL]) que resultó ser mucho más lipofílico con lo que se consiguió, por lo tanto, una mayor penetración tisular con menores dosis. Además,

su eliminación de la piel es más rápida, lo que implica un menor riesgo de efectos secundarios y una mejor tolerancia por parte de los pacientes, ya que produce menos dolor durante la exposición a la luz (23-25).

La TFD tópica fue aprobada en 1999 en Estados Unidos por la *Federal Drug Administration* (FDA), y en el 2001 en Europa por la *European Medicines Agency* (EMEA) para el tratamiento del carcinoma basocelular superficial, las queratosis actínicas y, recientemente, también para la enfermedad de Bowen (carcinoma escamocelular *in situ*) (22, 26). No obstante, su uso en el tratamiento del fotodaño es más nuevo, de manera que se ha incluido como una indicación no aprobada aún, o lo que en inglés se denomina *off-label*.

En general, los eritemas, edemas y el dolor durante la primera semana postratamiento se encuentran entre los efectos secundarios más frecuentes de la TFD tópica cutánea. El dolor suele limitarse solo al área iluminada, hecho que se atribuye a la estimulación nerviosa local dada por la activación del cromóforo, o por el daño del tejido inducido por la formación de especies reactivas de oxígeno (24, 27).

La TFD requiere una fuente de luz que idóneamente debe ser específica para el cromóforo que se utiliza. Se utilizan diferentes tipos de luz como la roja, azul, el láser de colorante pulsado y la luz intensa pulsada (IPL por sus siglas en inglés) (28). La luz roja ha mostrado tener un efecto profundo en la piel (4 mm) y tiene la ventaja de poder usarse tanto con el 5-ALA como con el MAL (16, 29). Si bien la luz azul es 50 veces más efectiva en la activación de la protoporfirina IV que la luz roja, su profundidad de penetración es más reducida (1-2 mm)(29). La IPL es uno de los tratamientos no ablativos más empleados en el fotorejuvenecimiento. Además, en varios estudios se le ha añadido la TFD y se han obtenido buenos resultados (30, 31).

El mecanismo exacto por el cual la TFD mejora los signos del fotodaño no está claro todavía, pero en estudios moleculares se ha observado un incremento del receptor del factor de crecimiento β tipo II, y un aumento del TGF β que estimula la proliferación de fibroblastos que, a su vez, aumentan la síntesis de colágeno y pro-colágeno tipo I y III en la dermis superior. En consecuencia, se produce una disminución del material elástotico y de las fibras elásticas, además de una reducción importante del infiltrado inflamatorio en la dermis inducido por la RUV crónica (16, 32).

Para el tratamiento del daño actínico se dispone de múltiples procedimientos descritos que incluyen el uso de la quimioexfoliación, los retinoides tópicos, el láser, la IPL, los diodos emisores de luz (LED) y la TFD (33-35). No obstante, y según una revisión sistemática del año 2009, existe limitada evidencia científica que apoye el uso preferencial de alguna de estas terapias (35). De entre todos los procedimientos se destacan las ventajas de la terapia fotodinámica como tratamiento de múltiples lesiones de forma simultánea; es considerada una terapia menos invasiva y presenta buena tolerancia en general (16). Si se tiene en cuenta que el mejor diseño epidemiológico que permitiría determinar el efecto real de la TFD en el fotodaño correspondería a un ECA, entonces es relevante plantear y desarrollar un estudio de este tipo.

La psoriasis

La psoriasis es un trastorno crónico de la piel que puede desarrollarse a cualquier edad y que se asocia a una gran carga tanto física como psicológica. Se estima que este trastorno tiene una prevalencia que oscila entre el 0,5 y 3,8 % en todo el mundo (36-40). Un estudio realizado en el Reino Unido en adultos y niños describe una incidencia de 140 por 100.000 (41).

Al igual que ocurre con otras dermatosis, la desfiguración visible provocada por la enfermedad puede desencadenar reacciones conductuales negativas que explican la mayor parte de la carga psicológica asociada. Asimismo, se ha observado que, de entre numerosas enfermedades crónicas, la psoriasis es de las que inducen una mayor alteración de la calidad de vida por detrás de la depresión y la enfermedad pulmonar obstructiva crónica (42), debido muy posiblemente a los síntomas y signos asociados de prurito, dolor, ardor y sangrado (43). Tal es su impacto que en el año 2013 se consideró como un problema de salud mundial en la Asamblea de la Organización Mundial de la Salud (44). De forma similar, la psoriasis en niños tiene un impacto significativo tanto en los pacientes como en sus familias, principalmente a causa de los síntomas asociados de dolor en las articulaciones, prurito y ardor (45).

Se han descrito seis tipos de psoriasis: la psoriasis en placas (también conocida como *psoriasis vulgaris*); la guttata (gotitas); la inversa, también denominada intertriginosa; la psoriasis pustulosa; psoriasis de las uñas; y, por último, la eritrodérmica, que es una complicación poco frecuente pero muy grave de la psoriasis (46).

Aproximadamente un tercio de las personas con psoriasis la desarrollan antes de los 20 años de edad (38, 47); su manifestación en la infancia no es inusual pero el impacto es mayor debido a la menor disponibilidad de terapias. Al igual que en los adultos, la psoriasis en placas crónica es el subtipo más común y representa entre el 30 y el 60 % de los tipos descritos en la niñez, donde el cuero cabelludo y la cara suelen ser las zonas más dañadas. En comparación con los adultos, la psoriasis guttata y la inversa, que por lo general afecta al área genital en la infancia, son más frecuentes en los niños (48-50).

La patogénesis de la psoriasis aún no se ha dilucidado, pero se piensa que se desarrolla en individuos con predisposición genética, pues entre el 23,4 y 71 % de los niños tiene antecedentes familiares de psoriasis (51). Por otra parte, se ha descubierto que la psoriasis es una enfermedad mediada por células T en la que se han observado niveles elevados de citoquinas pro-inflamatorias como la interleucina-17 (IL-17)(52, 53), el interferón-γ (IFN-γ) (54, 55), el factor de necrosis tumoral alfa (TNF-α) (55), la IL-22 y la IL-23 (52, 54). Precisamente el bloqueo de algunas de estas citoquinas con la terapia biológica ha demostrado ser útil en la psoriasis moderada a grave (55, 56).

La psoriasis leve en los niños no suele presentar dificultades en su manejo. No obstante, las formas moderadas a severas de la enfermedad son, con frecuencia, más difíciles de manejar debido a las limitaciones en la aprobación de terapias sistémicas en niños (50, 57). Los tratamientos utilizados hasta el momento para la psoriasis pediátrica incluyen la ciclosporina, el metotrexate y el acitretin (50). Sin embargo, existe aún incertidumbre acerca del uso de la terapia biológica, por lo que es necesario evaluar la evidencia científica disponible para determinar su eficacia y seguridad en la población pediátrica.

El Acné Vulgar

El acné vulgar (AV) afecta a más del 80 % de las personas en algún momento de su vida (58). Específicamente en Inglaterra se realizan cerca de 3,5 millones de consultas al año por acné, cifra que puede explicarse por la alta morbilidad de esta enfermedad que causa desfiguración, alteración de la calidad de vida, depresión e induce ideas suicidas (58).

El trastorno afecta principalmente a los adolescentes, de los que se ha estimado que hasta el 30 % presentan un grado de severidad suficiente para requerir tratamiento médico (59). Sin embargo, cada vez es más frecuente el inicio tardío de la enfermedad, como en mujeres en la segunda década de su vida en particular.

El acné es el resultado de cambios patológicos en el folículo pilosebáceo, cuyo estrato folicular engrosa y provoca la obstrucción y la acumulación de sebo, el cual se produce inevitablemente en grandes cantidades en la pubertad. Asimismo, el *Propionibacterium acnés* (bacteria comensal de la piel) contribuye a su aparición y severidad al proliferar en los folículos sebáceos ricos en lípidos, y da lugar a la acumulación de metabolitos bacterianos, sebo y detritus celulares que emiten una respuesta inmune inflamatoria. Aunque la predisposición a sufrir acné está influida por factores genéticos, aún no se ha establecido un patrón de herencia determinado (60, 61).

Por lo general, el AV se clasifica como leve, moderado o severo. El acné leve se define como la presencia de pocas lesiones inflamatorias (pápulo-pustulosas) o no inflamatorias (comedones), o ambas. El acné moderado se define como la presencia de lesiones inflamatorias o nódulos ocasionales (o ambos simultáneamente) y cicatrices leves. Por último, el acné severo se define como la manifestación de lesiones generalizadas inflamatorias, nódulos (o ambas de forma concomitante) y cicatrices; o como aquel acné moderado que no mejora con seis meses de tratamiento; o acné de cualquier grado de severidad que esté ocasionando disfunción psicológica grave (62). No obstante, a esta clasificación se le añaden múltiples escalas que se han empleado, si bien solo en algunas se ha determinado la fiabilidad interobservador (63-65). Así, la ausencia de una escala estándar que permita la evaluación objetiva de la respuesta ha repercutido en la eficacia de las intervenciones en esta enfermedad.

Aunque este trastorno es autolimitado, existen dos formas de presentación (acné persistente y acné de inicio tardío) que no suelen resolverse por sí mismas y que generalmente son resistentes a la terapia antibiótica. A los costos inherentes a su terapia (costos directos mayores de tres mil millones de dólares por año) (66), se le añade el gran efecto psicológico que suele ser devastador, y que, en algunos casos, conduce a alteraciones de la conducta (67, 68). Además, su impacto social y emocional se ha

comparado al de enfermedades crónicas incapacitantes como la artritis y epilepsia (69, 70).

Con respecto a la terapia, su selección está determinada por la edad y las preferencias del paciente, así como por la severidad del trastorno. Entre los tratamientos disponibles se encuentran las terapias tópicas y las sistémicas, algunas de las cuales están apoyadas por evidencia científica (ejemplo: isotretinoina oral). No obstante, la mayoría de los tratamientos para el acné han estado influidos por la industria farmacéutica, la calidad metodológica de los estudios, los desenlaces o las variables de resultado que se seleccionan para evaluar el efecto de las intervenciones, así como por la gran variabilidad entre los dermatólogos para seleccionar la terapia. De esta manera, es necesario contar con unos lineamientos terapéuticos basados en la mejor evidencia científica disponible, tal y como lo exige la elaboración de guías de práctica clínica (GPC). Sin embargo, con el aumento de las GPC publicadas ha surgido la preocupación acerca de su calidad, pues muchas carecen de rigor científico para su desarrollo, ejecución e implementación, hecho que repercute de forma negativa en su credibilidad y puede traducirse en una práctica clínica más perjudicial que beneficiosa.

JUSTIFICACION DEL TRABAJO DE TESIS DOCTORAL

JUSTIFICACIÓN DEL TRABAJO DE TESIS DOCTORAL

- La enorme variabilidad que existe en Dermatología respecto al manejo de algunas enfermedades crónicas de la piel es una clara demostración de la incertidumbre que existe a la hora de seleccionar la mejor terapia. Un ejemplo de esto es el ácido fumárico que se ha utilizado durante décadas en Alemania y los Países Bajos dada la evidencia científica de calidad que lo apoya, si bien este tratamiento curiosamente no se usa en otras partes del mundo (71, 72). Por el contrario, a los pacientes con verrugas vulgares se les continúa tratando con crioterapia, a pesar de que no existe evidencia suficiente que garantice que sea más eficaz que el ácido salicílico administrado por el mismo paciente (71, 73). Sin ir más lejos, y considerando que los esteroides tópicos son los medicamentos más recetados por los dermatólogos, el valerato de betametasona suele prescribirse para un uso de dos veces al día, aunque no existe evidencia científica de calidad que pruebe que sea más eficaz que la administración una sola vez al día, lo cual aumentaría la adherencia del paciente al tratamiento y abarataría los costes (71, 74).

- La Dermatología Basada en la Evidencia (DBE) representa la mejor manera de integrar y articular la investigación clínica con la práctica clínica dermatológica. Dado que las preguntas clínicas son innumerables y los recursos limitados, las prioridades de la investigación en esta especialidad deben establecerse mediante criterios explícitos y verificables (71). Por otra parte, los pacientes deben dejar de considerarse convidados de piedra para que la aplicación clínica de los resultados de la investigación se base en sus valores y preferencias (71). No obstante, la realidad de la investigación dermatológica es otra, pues influyen otros aspectos ajenos a los descritos como los intereses económicos (o la falta de interés), dependiendo de si se trata de una enfermedad cutánea rara o de si es más frecuente en países subdesarrollados (71).

- El estudio de la Dermatología difiere de otras especialidades de la Medicina en que la disfunción de un solo órgano (riñón, hígado, etc.) puede causar alrededor de 50-100 enfermedades asociadas, pero en la piel pueden presentarse hasta 2000 (71). A esto se le añade que determinadas enfermedades cutáneas cursan con síntomas severos como el ardor, el prurito o el dolor que alteran las actividades diarias. Además, la necesidad de aplicar algún medicamento tópico durante el día o la noche impide o perturba las actividades normales de un individuo, ya sea en el ámbito laboral o en el recreativo (3, 4). En consecuencia, ha habido un incremento importante en la investigación clínica en Dermatología durante las últimas décadas. No obstante, este auge investigativo no ha sido proporcional al refinamiento metodológico de los estudios, pues se ha observado que los ECAs publicados en Dermatología suelen estar muy por debajo de los estándares aceptables (71, 75, 76).

- Algunos de los muchos aspectos que han influido e influyen negativamente en el diseño y desarrollo de la investigación dermatológica son: la automonitorización de la enfermedad dermatológica por parte del propio paciente, el gran efecto que puede tener el placebo en estos pacientes, los mensajes engañosos y no sustentados científicamente que transmite la publicidad para mejorar la apariencia, la cronicidad de la mayoría de enfermedades cutáneas que dificultan la selección de desenlaces, la abundancia de ensayos clínicos en los que el propio paciente es su control y el gran influjo de la industria farmacéutica en el patrocinio de los ECA en esta especialidad.

- Por otra parte, existen alrededor de mil trastornos poco frecuentes en Dermatología de los que no se ha realizado un solo ensayo clínico con asignación aleatoria, por lo que su tratamiento se selecciona de acuerdo con la pericia del Dermatólogo, o con los casos o series de casos reportados.

PREGUNTAS GENERICAS DEL TRABAJO DE TESIS DOCTORAL

PREGUNTAS GENERICAS DEL TRABAJO DE TESIS DOCTORAL

Según todo lo expuesto, las preguntas de investigación que pretende responder este trabajo de tesis son las siguientes:

Pregunta n. º 1: ¿Cuántos ensayos clínicos controlados con asignación aleatoria y con qué características se han publicado en revistas de Dermatología en Iberoamérica?

Pregunta n. º 2: ¿Cuál es la calidad metodológica de los ensayos clínicos controlados con asignación aleatoria que se han publicado en revistas de Dermatología en español?

Pregunta n. º 3: ¿Cuál es la eficacia y seguridad de la terapia fotodinámica con MAL y luz solar para el tratamiento de pacientes adultos con daño actínico facial?

Pregunta n. º 4: ¿Cuál es la eficacia y seguridad de los agentes anti-TNF en el tratamiento de la psoriasis pediátrica?

Pregunta n. º 5: ¿Cuál es la calidad de las Guías de Práctica Clínica (GPC) publicadas sobre el tratamiento del acné vulgar?

OBJETIVOS DEL TRABAJO DE TESIS

OBJETIVOS DEL TRABAJO DE TESIS

Objetivo general n. º 1: Identificar y describir de manera exhaustiva y rigurosa los ensayos clínicos controlados aleatorizados (ECA) que han sido publicados en revistas de Dermatología en español.

Objetivos específicos:

1.1 Identificar todas las revistas de Dermatología publicadas en español en Latinoamérica y España.

1.2 Identificar todos los ECA publicados en revistas de Dermatología en español en Iberoamérica.

1.2. Describir las características generales de los ECA encontrados.

Objetivo general n. º 2: Evaluar la calidad metodológica de los ensayos clínicos controlados con asignación aleatoria (ECA) que se han publicado en revistas de Dermatología en español.

Objetivos específicos:

2.1. Identificar todos los ECA publicados.

2.2. Evaluar la calidad metodológica de todos los ensayos publicados que reunieron los criterios de un ECA.

Objetivo general n.º 3: Determinar la eficacia clínica del MAL + dos horas de luz solar comparado con placebo + dos horas de luz solar en adultos con daño actínico facial.

Objetivos específicos:

3.1. Identificar los patrones clínicos basales de daño actínico de la piel y postratamiento con MAL + luz solar comparado con placebo + luz solar.

3.2. Cuantificar el dolor que experimentan los pacientes con cada una de las terapias inmediatamente después de la sesión de TFD.

3.3. Determinar los cambios en la escala de fotodaño facial global y específico presentados en ambos grupos de tratamiento un mes después de la tercera sesión.

3.4. Cuantificar la irradiancia y la luminancia durante las dos horas de cada sesión.

3.5. Estimar los efectos adversos durante el desarrollo del estudio y la tolerancia de cada una de las terapias una semana después de cada sesión.

3.6. Cuantificar el impacto que tiene el daño actínico en la calidad de vida de los pacientes mediante la escala validada Skindex-29 en condiciones basales y postratamiento.

Objetivo general n. º 4: Evaluar la eficacia y seguridad de los agentes anti-TNF en el tratamiento de la psoriasis pediátrica.

Objetivos específicos:

4.1. Revisar sistemáticamente la evidencia disponible proveniente de ensayos clínicos aleatorizados que evalúen el efecto de los agentes anti-TNF en los pacientes con psoriasis pediátrica.

Objetivo general n. º 5: Evaluar la calidad de las Guías de Práctica Clínica publicadas sobre el tratamiento del acné vulgar.

Objetivos específicos:

5.1. Identificar las GPC sobre el tratamiento del acné vulgar por medio de una búsqueda sistemática de información.

5.2. Valorar sistemáticamente la calidad de las GPC disponibles.

METODOLOGIA

METODOLOGÍA

Generalidades

Una vez descrito el escenario, este trabajo de tesis doctoral busca generar conocimiento útil que contribuya a un mejor control y tratamiento del fotodaño, la psoriasis pediátrica y el acné vulgar. Para dar fundamento científico a lo anterior, se ha adoptado el enfoque de la Dermatología Basada en la Evidencia, una herramienta fundamental para el ejercicio de la práctica dermatológica partiendo desde lo meramente descriptivo hasta lo analítico.

- Los ensayos clínicos controlados aleatorizados (ECA) realizados de forma rigurosa representan el estándar de referencia para determinar la eficacia y seguridad de una intervención. Debido a que los ECA individuales a menudo tienen un tamaño de muestra pequeño que limita su uso inferencial, o estimaciones precisas de la utilidad de un tratamiento, su compilación, ya sea de forma cualitativa o cuantitativa, es la esencia de las revisiones sistemáticas/los metanálisis que se consideran como el tipo de diseño epidemiológico más útil para guiar la investigación y la práctica clínica (77).
  En la preparación de las revisiones sistemáticas/metanálisis se describen dos etapas:

  - La identificación de las fuentes de información (base de datos).

  - La búsqueda en dichas fuentes de información para recuperar los estudios relevantes.

  Con todo, entre las dificultades inherentes a estas etapas se encuentra la falta de indexación de un número importante de revistas (en Medline o EMBASE) (78), o la falta de indexación de revistas publicadas en idiomas diferentes al inglés. A lo anterior se le suma que muchos ECA figuran mal indexados en Medline, que se incluyen en los libros o CD de resúmenes de congresos que no aparecen en ninguna base de datos y que tan solo la mitad de estos se publican, particularmente los que muestran resultados positivos para el uso de una terapia (79-82). Lo preocupante es que estas

carencias a menudo se traducen en sesgos de selección y de publicación. Inspirados en tal problemática, a comienzos de los años 90 surge una iniciativa mundial, la Colaboración Cochrane (*The Cochrane Collaboration*), con objeto de no solo preparar, mantener y diseminar revisiones sistemáticas actualizadas concernientes a los efectos de una intervención en la salud humana (83-85), sino de promover también la búsqueda manual de la literatura científica para, así, superar los sesgos potenciales de confiar únicamente en la identificación de los ECA en MEDLINE y otras bases de datos electrónicas.

La Colaboración Cochrane se ha propuesto identificar ensayos clínicos desde el año 1948, una tarea que se ha visto entorpecida en todas las áreas de la Medicina (incluyendo la Dermatología), debido a la falta de descripción del diseño del estudio en el título (75). Por este motivo, una de las labores más importantes que ha desarrollado la Colaboración es la búsqueda manual de ensayos clínicos, especialmente en inglés. La necesidad de búsquedas manuales en este idioma cada vez disminuye más, pues ya se han evaluado la gran mayoría de volúmenes antiguos de las revistas. No obstante, se precisa cada vez más contar con búsquedas manuales en idiomas diferentes al inglés (71). De esta manera, y para lograr la identificación de los ECAs de las distintas especialidades médicas en revistas publicadas en español, el Centro Cochrane Iberoamericano (CCIb) inició el proyecto de búsqueda manual de ensayos clínicos. Este programa consiste en la identificación de los ECA en los números de cada volumen de una revista determinada a través de la lectura de todo el contenido, lo que garantiza detectar más ensayos clínicos aleatorizados publicados. Este tipo de trabajo se ha realizado con las revistas de Dermatología publicadas en español, con el fin de aportar a la Colaboración Cochrane la evidencia experimental reportada en español en esta especialidad.

) La calidad en un ECA es un concepto o constructo multidimensional cuyo diseño, desarrollo, análisis, reporte y relevancia clínica definen su pertinencia (71, 86-88). Por otra parte, la validez implica el grado en que los resultados del estudio se acercan a la realidad o "verdad" (71): puede ser externa (¿en qué grado se pueden aplicar mis resultados a mis pacientes?), o interna (¿son ciertos mis resultados?), la cual es un prerrequisito *sine qua non* de la validez externa (71). Además de la conocida escala de Jadad, en la actualidad existen numerosas más que evalúan la calidad de los ensayos clínicos (87, 89). Durante los primeros años de la década del 2000, la Colaboración Cochrane utilizaba algunas de estas que consistían fundamentalmente en listas de comprobación (90). Sin embargo, a partir del año 2005 la Colaboración comenzó a involucrarse en una nueva estrategia para evaluar la calidad de los estudios, la cual se concretó con el diseño de una herramienta, *The Cochrane Collaboration's tool for assessing risk of bias in randomised trials* (91), para determinar la presencia de sesgos en los estudios, y que incluye los siguientes dominios:

- Generación de la secuencia (evalúa el sesgo de selección).
- Ocultamiento de la asignación (evalúa el sesgo de selección).
- Cegamiento de los participantes, el personal (evalúa el sesgo de "performance" o de "evaluación") y/o los evaluadores de los desenlaces (evalúa el sesgo de detección).
- Presencia de datos incompletos (evalúa el sesgo de deserción [retiradas o abandonos]).
- Reporte selectivo de resultados (evalúa el sesgo de reporte).
- Otras posibles fuentes de sesgo (evalúa cualquier otro tipo de sesgo).

Hemos empleado esta herramienta en la evaluación de la calidad metodológica de los estudios encontrados, con el objetivo de contribuir al esfuerzo de la Colaboración Cochrane y del CCIb, y de hacer un diagnóstico de la calidad metodológica encontrada

en la evidencia experimental publicada en la literatura iberoamericana de Dermatología.

- Los ensayos clínicos son estudios experimentales en los que el investigador deja de ser un mero observador y se convierte en quien manipula o asigna una exposición o intervención a los individuos del estudio. Este tipo de diseño es siempre de carácter prospectivo en el que se compara el efecto y/o beneficio de una intervención con respecto a otra o a un control (92).

  Un ensayo clínico controlado con asignación aleatoria (ECA) que sea pertinente, viable, y que esté bien diseñado y correctamente ejecutado proporciona la mejor evidencia científica para determinar el efecto de una intervención en salud (93). En este sentido, los tres ítems que más se relacionan con alterar la estimación del efecto en un ensayo clínico son (71, 88): 1- el método con el cual se generó la secuencia aleatoria y su enmascaramiento; 2- el cegamiento de los pacientes y de los evaluadores de desenlaces y 3- el análisis por intención de tratar (ITT). No obstante, otras características especialmente importantes que permiten determinar la calidad de estos estudios en cualquier ámbito, pero en el dermatológico en particular, son (71): una clara y precisa definición de la enfermedad; grupos equilibrados con respecto a variables predictoras de los desenlaces; la descripción anticipada (*a priori*) de los desenlaces a evaluar; la pertinencia de los desenlaces tanto para los pacientes como para los investigadores clínicos; el uso de pruebas estadísticas adecuadas para el análisis y la comparación de los elementos; el análisis de subgrupos definido *a priori* (94); el no confundir entre la falta de evidencia acerca de un efecto con la evidencia de una falta de efecto; la evaluación completa de los pacientes de ambos grupos y la medición por igual de los desenlaces; la descripción de las fuentes de financiación del estudio y la detección de la posible injerencia del patrocinador en los resultados del estudio; y por último, si el ECA fue adecuadamente difundido según la normativa CONSORT.

Ante la incertidumbre reinante acerca del uso de la terapia fotodinámica en el fotodaño facial, es preciso dar respuesta a preguntas no resueltas mediante el diseño y la ejecución de un ECA que siga los lineamientos y el rigor científico característicos de estos estudios.

Un ensayo clínico en este campo se basa en el hecho de que, aunque la terapia fotodinámica con MAL ya haya sido aprobada en Europa y Estados Unidos para el tratamiento del carcinoma basocelular superficial y de las queratosis actínicas, hay que evaluar su efecto en una indicación diferente.

- Una revisión sistemática (RS) es una herramienta científica utilizada para evaluar, resumir y comunicar los resultados e implicaciones de la investigación clínica. Son de gran utilidad para los prestadores y proveedores de servicios sanitarios y para los tomadores de decisiones en la valoración de tecnologías existentes o innovadoras. Dichas revisiones sistemáticas pueden o no incluir una síntesis estadística de la evidencia encontrada (metanálisis), dependiendo de si existe un número suficiente de estudios y de si son lo suficientemente homogéneos como para permitir una combinación de los resultados. Debido al impacto que tiene la psoriasis en un individuo (máxime si se trata de un niño), a la escasez de la evidencia publicada y a la necesidad de conocer alternativas eficaces y seguras para el manejo de la psoriasis pediátrica, sería muy útil llevar a cabo una revisión sistemática que pudiera llenar este vacío en el conocimiento. Lo idóneo sería una RS basada en y guiada por los principios metodológicos de la Colaboración Cochrane mundial y, específicamente, por el Grupo Cochrane de Piel (Cochrane Skin Group [CSG]), que publica las RS de mayor calidad e impacto en la práctica dermatológica a nivel mundial.

- Las GPC están basadas en la mejor evidencia disponible. Se desarrollan de forma rigurosa y sistemática y les sirven de ayuda a los prestadores de servicios sanitarios y

a los pacientes en la toma de decisiones ante circunstancias y escenarios clínicos específicos (95).

Las GPC han surgido a raíz de la gran variabilidad existente en la práctica clínica entre los prestadores y/o las entidades proveedoras de servicios sanitarios locales o de diferentes áreas geográficas que conducen a una inequidad en la utilización de los recursos o en la selección inadecuada de tratamientos (96) (97) o métodos diagnósticos. Dichas guías permiten justificar la selección de una terapia con base en sus beneficios, daños y costes y en las preferencias de los pacientes (98).

Según lo anterior, la elaboración de una GPG *de novo* constituye una ardua y costosa tarea, lo que explica la escasez de GPC publicadas en Dermatología. Las pocas que existen en algunos países como España han sido elaboradas por personal de Atención Primaria (99).

Tal dificultad en la elaboración de una GPC supone que en ocasiones sea más costo-efectivo adaptar una de alta calidad que haya sido elaborada y desarrollada en otro país. De ahí surge la GIN (*Guidelines International Network)* como una iniciativa global que busca aunar esfuerzos para evitar duplicaciones, y establece, así, criterios específicos protocolizados y estandarizados para la elaboración de guías (100). De hecho, incluso entre las mismas guías sobre un tema específico también puede haber variabilidad con respecto al método de diseño y desarrollo, lo cual sirvió de motivo en los años noventa para la creación de una herramienta para le evaluación de GPC denominada el instrumento AGREE (101), cuyo objetivo primordial es la valoración de la validez, reproducibilidad y fiabilidad de las GPC (96, 102). Desde sus inicios y hasta la fecha, el instrumento AGREE se ha perfeccionado para obtener una versión mejorada, el AGREE II (103).

Si tenemos en cuenta que, según lo analizado, no existe ninguna publicación que revise de manera crítica las GPC de acné vulgar, es patente la necesidad de identificar las guías de mejor calidad para una enfermedad dermatológica de gran impacto y altos costes de tratamiento, con el fin de determinar qué guías pudieran ser susceptibles de una posterior adaptación en entornos específicos.

A continuación se presenta un resumen de la metodología utilizada en cada trabajo para responder la respectiva pregunta formulada y para cumplir los objetivos de cada investigación. En cada una de las publicaciones (ver apartado de «Resultados») se aportan más detalles.

METODOLOGÍA DEL TRABAJO N. º 1

Título: Búsqueda e identificación de ensayos clínicos en revistas de Dermatología publicadas en español entre 1969 y 2012.

Diseño: Revisión de la literatura que consideró los elementos críticos de una revisión sistemática: búsqueda exhaustiva de los ECAs publicados.

Identificación de las revistas

La identificación de las revistas se realizó en el marco del proyecto liderado por el Centro Cochrane Iberoamericano (CCIb) (Barcelona, España), a través del cual se identifican revistas biomédicas de países de lengua española.

Estas búsquedas se complementaron con bases de datos como el Índice Bibliográfico Español en Ciencias de la Salud (IBECS), EMBASE e IMBIOMED, MEDLINE, y con la búsqueda en internet de las diferentes asociaciones de Dermatología de cada país latinoamericano hispanohablante. Asimismo, se contactó con los comités editoriales y especialistas en Dermatología y, como último recurso, se realizó una búsqueda libre a través de Google.

Las revistas debían publicar artículos originales y se debía disponer del texto completo (impreso o digital). Se excluyeron las revistas de Dermatología pediátrica, las ya incluidas en las búsquedas de otras especialidades, aquellas que no publicaran ECA y, por último, aquellas de las que no se pudo obtener el texto completo.

La revisión de cada revista se hizo de forma retrospectiva desde el año 2012 hasta el inicio del periodo de publicación de la revista, o hasta donde fuera posible recuperar el texto completo. Si en cinco años consecutivos no se encontraban ECA, la búsqueda manual para la respectiva revista se detenía. En las publicaciones en las que había acceso a más números, la búsqueda se extendió hasta terminar lo que se tenía disponible.

Además, se determinó qué revistas incluían la herramienta CONSORT (CONsolidated Standards Of Reporting Trials) dentro de su normativa de publicación, y la indexación en MEDLINE o EMBASE.

Búsqueda manual de ensayos clínicos:

Los revisores recibieron información en cuanto al Protocolo de Búsqueda Manual de Ensayos Clínicos del CCIb (disponible en http://www.cochrane.es/~cochrane/?q=es/node/140).

Búsqueda electrónica de ensayos clínicos:

Para determinar las diferencias con el número de estudios identificados por búsqueda manual, se realizó una búsqueda electrónica en MEDLINE (a través de PubMed), EMBASE, LILACS e IBECS.

Criterios de inclusión para la identificación de los ensayos clínicos

Para ser considerados como un ECA, los artículos debían cumplir los siguientes criterios: 1- comparar tratamientos en seres humanos; 2- ser prospectivo; 3- comparar dos o más intervenciones entre sí; 4- el método de asignación a los tratamientos debía ser aleatorio,

cuasi-aleatorio y/o enmascarado (simple/doble ciego). Las unidades de aleatorización podían ser individuos, grupos (hospitales, comunidades) o partes del cuerpo humano (ej.: hemicaras, extremidades, etc.).

Evaluación de la información e identificación de los ECA

Durante la lectura de las revistas cada revisor registraba la cantidad de artículos encontrados. Posteriormente, dos evaluadores con formación en epidemiología clínica seleccionaron los ECA tras la lectura del texto completo del artículo.

Plan de análisis

Se realizó un análisis descriptivo de la información. Las variables continuas se presentaron con las medidas de resumen apropiadas; y las cualitativas se expresaron con frecuencias absolutas y relativas, y en porcentajes. Para el almacenamiento de la información se utilizó una base de datos de Excel (Microsoft Office®, versión 2010, Redmond, WA, Estados Unidos). Para los análisis estadísticos se empleó el programa IBM® *SPSS*® Statistics versión *19 (New York, NY, Estados Unidos)*.

METODOLOGÍA DEL TRABAJO N. º 2

Título: Evaluación de la calidad de los ensayos clínicos publicados en revistas de Dermatología publicadas en español entre 1997 y 2012.

Diseño: Se realizó una revisión crítica de los ensayos clínicos encontrados.

Identificación de las revistas. Búsqueda manual y electrónica

Los métodos utilizados para la detección de ECA en revistas de Dermatología publicadas en español ya han sido descritos en la metodología del trabajo 1.

Extracción de datos

Se creó una base de datos para registrar los ECA identificados y para seguir el progreso de búsqueda manual de cada revista.

Evaluación de la calidad y riesgos de sesgo

Para la evaluación del rigor científico y la calidad metodológica se incluyeron solo los ECAs identificados entre el año 1997 (implementación del CONSORT) y 2012. Esta evaluación se realizó por duplicado y un tercer evaluador resolvió las discrepancias. Para la evaluación del riesgo de sesgo se utilizó la herramienta proporcionada por la Colaboración Cochrane. Tanto la evaluación como las puntuaciones de ambos aspectos se registraron en el programa *Review Manager* versión 5.2 (Copenhagen, The Nordic Cochrane Centre, The Cochrane Collaboration, 2012). Por último, se determinó la fuente de financiación de los estudios y el reporte de conflictos de interés de los autores.

Análisis estadístico

Se realizó un análisis descriptivo de la información recogida evaluando las frecuencias mediante el análisis univariado de las variables. En las variables continuas se calcularon las medidas de resumen apropiadas; en las cualitativas se determinaron las frecuencias absolutas y relativas, y los respectivos porcentajes. Para el almacenamiento de la información, aparte de *Review Manager*, se utilizó una base de datos de Excel (Microsoft Office®, versión 2010, Redmond, WA, Estados Unidos). Para los análisis estadísticos se usó el programa IBM® *SPSS®* Statistics versión *19 (New York, NY, Estados Unidos).*

METODOLOGÍA DEL TRABAJO N. º 3

Título: Ensayo clínico controlado con asignación aleatoria de la eficacia del metil aminolevulinato (MAL) + luz solar frente a placebo – luz solar en la mejoría del daño actínico facial.

Diseño: Experimento clínico controlado, de fase II, con asignación aleatoria, de tipo explicativo y con evaluación del efecto en doble-ciego.

Población: Adultos entre 35 y 75 años de edad con daño actínico facial global crónico tipo 2 a 4 según la clasificación de Dover y cols. (33), que acudieron a la consulta dermatológica de la IPS universitaria de la Universidad de Antioquia en Medellín, Colombia.

Unidad de Análisis: Cada cara.

Criterios de inclusión: Adultos sin distinción de sexo entre 35 y 75 años de edad; adultos con simetría bilateral facial en el grado de daño solar; adultos con daño actínico facial entre 2 y 4 según la escala de Dover y cols. (33); adultos que quisieron participar y que firmaron un consentimiento informado antes del inicio del estudio.

Criterios de exclusión: Mujeres embarazadas o lactando; patologías fotodependientes; pacientes con enfermedades infecciosas activas en la piel de la región a tratar; antecedentes de herpes simple en la zona en cuestión; tratamientos para el fotoenvejecimiento en los seis meses anteriores; tratamiento sistémico con isotretinoina por vía oral un año antes; tratamiento tópico con derivados de la vitamina A 15 días antes del inicio del estudio; presencia de alguna enfermedad u otro trastorno dermatológico que hubiese requerido de tratamiento tópico o sistémico que interfiriera con los medicamentos a estudio; hipersensibilidad a los medicamentos o a alguno de los componentes de las fórmulas; probabilidad de exposición solar intensa durante las primeras 48 horas después del tratamiento; sospecha clínica de enfermedad maligna sistémica, premaligna o maligna local.

Asignación del tratamiento: Un estadístico independiente de la Universidad de Antioquia generó la secuencia de asignación aleatoria, para la cual se utilizó el Software Estadístico R versión 2 o 3 (AT&T, Estados Unidos).

La distribución de la asignación aleatoria de las caras y la rotulación de los tubos se llevaron a cabo por la Química Farmacéutica del centro (IPS Universitaria), según lo estipulado en la

secuencia previamente obtenida. Una enfermera capacitada por los dermatólogos aplicó la terapia y evaluó únicamente la escala de dolor al término de cada sesión.

Antes de aplicar las cremas en la cara se practicó la asepsia, el lijado de la piel y se aplicó un protector solar. Posteriormente, se les administró 1 gramo de Metvixia/placebo y se expusieron a la luz solar durante dos horas. Se siguió el mismo procedimiento en la segunda y tercera sesión entre dos y cuatro semanas después de la primera.

Todos las pacientes fueron evaluados por los dermatólogos, quienes desconocían completamente la asignación de las terapias.

Plan de recolección, manejo y almacenamiento de datos

Formato de recolección de la información: Se realizó mediante un cuestionario que incluyó información demográfica, las características basales y todas las escalas de daño actínico antes y después de la terapia, así como la cuantificación de la escala de dolor tras cada sesión y los efectos adversos según el formato establecido por el Invima (ente de control colombiano). Esta información se almacenó en una base de datos de Access® (Microsoft Office XP 2010, Estados Unidos).

Desenlace primario

Mejoría del daño actínico global con el uso de MAL y dos horas de exposición a la luz solar frente a placebo y dos horas de exposición a la luz solar. La falta de mejoría se definió como la permanencia en la misma escala tras la terapia. La mejoría se estableció en el paso a la siguiente escala de mejoría, y el éxito total se fijó en llegar a la escala 0 después del tratamiento, o en mejorar dos escalas. La evaluación del desenlace principal se realizó un mes después de la tercera sesión de TFD.

Desenlaces secundarios

Dolor experimentado por el paciente: Se evaluó con la escala visual análoga de dolor inmediatamente después de cada sesión.

Mejoría/falta de mejoría del fotodaño específico para arrugas finas, pigmentación moteada, color amarillento de la piel, textura, arrugas gruesas y eritema facial un mes después de la tercera sesión.

Cuantificación de la dosis de luz solar: La luminancia y la irradiancia se midieron cada 15 minutos con un instrumento multifunción con sensores para radiación ultravioleta (DeltaOHM, Padova, Italia).

Evaluación de efectos adversos/secundarios: Se evaluaron de acuerdo con el formato de efectos adversos del Invima. El manejo del dolor se realizó con 500 mg de acetaminofén cada seis horas.

Evaluación de la tolerancia: Se evaluó a la semana después de cada sesión.

Estimación de la calidad de vida: Se evaluó mediante la versión colombiana validada del Skindex-29, antes del tratamiento y un mes después de la tercera sesión.

Consideraciones bioestadísticas

Tamaño de muestra: El objetivo era probar una mejoría del daño actínico facial según la escala de Dover y cols., con Metvix®+ luz solar de 70 % frente a 30 % con el placebo un mes después de la tercera sesión, lo cual arrojó un ***n*** corregido de 58 pacientes (error alfa de 0,05; poder 80 % para cada grupo [placebo/intervención activa]). (Epidat, programa para análisis de datos tabulados, versión 3.1, Organización Panamericana de la Salud). Dicho cálculo se basó en los resultados obtenidos en un ensayo clínico realizado localmente con la misma intervención como fotosensibilizante pero con luz roja.

Plan de análisis estadístico: Se realizó un análisis univariado de las variables para conocer sus frecuencias. Las variables continuas se presentaron con las medidas de resumen apropiadas. Las variables ordinales y categóricas se presentaron con frecuencias absolutas y relativas, y en porcentajes. La distribución normal de las variables cuantitativas se evaluó con la prueba de Kolmogorov Smirnov. Las diferencias entre las proporciones obtenidas en la escala de fotodaño global y de tolerancia en ambos grupos al mes de la tercera

sesión se determinaron con la prueba de Chi^2 o de Fisher. Para estimar las diferencias en la escala de dolor entre todas las sesiones se utilizó la prueba U de Mann Whitney. Para medir la eficacia clínica del MAL con luz solar frente al placebo con luz solar en el daño actínico facial global se calculó el riesgo relativo (RR) y su respectivo IC95 %. La significación se definió como un $\Im<0.05$ y el estudio fue bilateral. Los análisis se realizaron con el programa SPSS, versión 19.

Financiación: Este estudio fue financiado y ejecutado por la Fundación Dermabase (entidad sin ánimo de lucro cuyo objeto es el diseño, la ejecución y promoción de la investigación en Dermatología). Tanto el medicamento activo (Metvix®) como el placebo y el protector solar, fueron proporcionados por Laboratorios Galderma.

METODOLOGÍA DEL TRABAJO N. º 4

Título: Agentes anti-TNF para la psoriasis pediátrica.

Diseño: Se realizó una revisión sistemática.

Criterios de elegibilidad de estudios primarios

Tipos de estudios: Todos los ensayos controlados aleatorios (ECA) que hubiesen evaluado la eficacia y seguridad de los agentes anti-TNF para el tratamiento de la psoriasis crónica vulgar en individuos menores de 18 años de edad.

Tipos de intervenciones: Cualquier terapia anti-TNF (o cualquier medicamento que actuara para bloquear la actividad biológica del TNF-α) en cualquier dosis y administrada por vía oral, subcutánea o intravenosa, y como medicamento único o en combinación con otras terapias.

Tipos de medidas de resultado

Desenlaces primarios: 1- mejoría de la psoriasis evaluada por el investigador como la proporción de participantes que alcanzó PASI 75; 2- mejoría en la calidad de vida evaluada por medio de un instrumento dermatológico reconocido (genérico o específico); 3- proporción de participantes con efectos adversos menores o mayores.

Desenlaces secundarios: 1- proporción de participantes que alcanzaron el PASI 50, PASI 90 o ambos. 2- evaluación global del médico (Physician Global Assessment); 3- superficie de área corporal afectada (Body Surface Area [BSA]); 4- evaluación global del paciente (Patient Global Assessment). Además, se consideraron la remisión, la recurrencia y los costos del tratamiento de la psoriasis, en caso de estar disponibles o de haberse incluido en los estudios.

Métodos de búsqueda para la identificación de estudios*:* Se identificaron todos los ECA relevantes, independientemente del estado de publicación (publicado, no publicado, en prensa o en curso).

Búsquedas electrónicas: Se realizaron búsquedas en el registro especializado del Grupo Cochrane de Piel; el Registro Cochrane Central de Ensayos Controlados (CENTRAL) 2013, número 8; MEDLINE vía OVID (desde 1946); EMBASE vía OVID (desde 1974); y LILACS (a partir de 1982).

Búsqueda de otros recursos: Se efectuaron búsquedas en los registros de ensayos clínicos mundiales para identificar estudios relevantes. Se revisaron las referencias bibliográficas de los estudios incluidos. Se buscaron también artículos de revisión y se evaluaron sus referencias.

Literatura no publicada: Tratamos de obtener información sobre los ensayos no publicados o en curso a través de la correspondencia con los autores del ensayo y con las siguientes compañías farmacéuticas: Abbott, Amgen Inc, Wyeth, Pfizer, UCB Inc y Janssen-Cilag.

Eventos adversos: Se consultaron los informes de la FDA y del EMA para obtener información acerca de la seguridad de los medicamentos. También se tuvieron en cuenta los efectos adversos reportados tanto en los estudios incluidos como en los excluidos.

Recopilación y análisis de datos

Selección de los estudios: Dos autores verificaron los títulos y los resúmenes, y una tercera autora resolvió las diferencias.

Extracción de los datos: Dos autores recopilaron los datos y un revisor introdujo los datos finales en Review Manager (RevMan). Los dominios relevantes se evaluaron de acuerdo con la herramienta de evaluación de sesgos de este programa.

Medidas del efecto del tratamiento: El éxito del tratamiento se definió según la proporción de participantes que alcanzaron PASI 75. Los resultados se expresaron en riesgos relativos (RR) con sus respectivos intervalos de confianza del 95 % (IC) para los resultados dicotómicos, y se estimó el número necesario a tratar. Para las variables cuantitativas se calculó la diferencia de medias.

Análisis de datos: Los resultados se reportaron de manera descriptiva y cualitativa. No fue posible combinar los resultados de manera cuantitativa por haber encontrado solo un estudio publicado.

METODOLOGÍA DEL TRABAJO N. º 5

Título: Guías de práctica clínica para el tratamiento del *acne vulgaris*: evaluación crítica con el instrumento AGREE II.

Diseño: Se realizó una revisión crítica de las GPC disponibles acerca de la terapia para el acné.

Búsqueda

Se realizó una búsqueda de GPC sobre el tratamiento del acné vulgar publicadas entre julio de 2002 y julio de 2012. Se completó la búsqueda en MEDLINE (a través de PubMed), y también se examinaron las referencias bibliográficas de los artículos incluidos. Dicha búsqueda se limitó al inglés, francés, alemán y español.

Criterios de elegibilidad

Criterios de inclusión: Se consideraron las guías desarrolladas sistemáticamente. Los criterios para la inclusión fueron los siguientes: (1) un documento explícito identificado como una ''guía''; (2) un documento producido a nivel nacional o internacional de asociaciones médicas u organismos gubernamentales; (3) documentos con recomendaciones relacionadas con el *acne vulgaris* y su terapia; y (4) los documentos que incluyeran una revisión sistemática de la evidencia en el tratamiento del *acne vulgaris*.

Criterios de exclusión: Se excluyeron los documentos de consenso, los que no se basaran en una revisión sistemática de la evidencia, las guías relacionadas con el acné hormonal y de tratamientos con un solo medicamento.

La selección de guías de práctica clínica: Dos revisores examinaron los títulos y los resúmenes; los desacuerdos se resolvieron mediante discusión con un tercer revisor.

Evaluación de la calidad metodológica de las guías de práctica clínica seleccionadas:

Para la evaluación de la calidad de las GPC se utilizó el instrumento AGREE II (104, 105). La guía se clasificaba en alguna de las siguientes tres categorías: “no recomendada”, “recomendada con modificaciones” o “fuertemente recomendada”.

Inicialmente se realizó una prueba piloto de la evaluación de GPC con los tres revisores (un dermatólogo, un pediatra y un médico de Medicina General con formación en epidemiologia clínica).

Para determinar la calidad de cada GPC se calculó el puntaje estandarizado expresado en porcentaje:

(Puntuación obtenida – puntuación mínima posible) x 100. (Puntuación máxima posible – puntuación mínima posible).

Posteriormente, se realizó la estandarización de la siguiente manera:

$$\frac{pi \quad \acute{o}n\ o\acute{l} \quad - pi \quad \acute{o}n\ m\acute{i}ni \quad p}{pi \quad \acute{o}n\ m\acute{a}xi \quad p \quad - pi \quad \acute{o}n\ m\acute{i}ni \quad p}$$

Las puntuaciones obtenidas fueron validadas por cada evaluador a través del link de evaluación de las guías de práctica (Disponible en: http://www.agreetrust.org/resource-centre/).

Se seleccionó un umbral de puntuación del 60 %.

El análisis estadístico

Se realizó un análisis estadístico descriptivo para cada dominio. Los valores descriptivos incluyeron la media, la desviación estándar, el mínimo y el máximo. Las variables categóricas se calcularon con el número de casos y los porcentajes correspondientes. El acuerdo entre los tres revisores se determinó mediante el coeficiente de correlación intraclase (CCI) con su respectivo IC95 %. Asimismo, se calculó un puntaje estandarizado por separado para cada uno de los seis dominios. El grado de acuerdo se clasificó de la siguiente manera conforme a la escala de Landis y Koch: pobre (\ 0,00), ligero (entre 0,00 y 0,20), justo (desde 0,21 hasta 0,40), moderado (desde 0,41 hasta 0,60), sustancial (0,61-0,80) y muy bueno o casi perfecto (0,81-1,00) (106). Todos los análisis se realizaron con la versión 19 del paquete estadístico SPSS (paquete estadístico para las ciencias sociales, Chicago, IL, EE.UU.).

Topical tacrolimus for atopic dermatitis.
Efficacy and Safety of 308-nm Monochromatic Excimer Lamp Versus Other Phototherapy Devices for Vitiligo: A Systematic Review with Meta-Analysis.

RESULTADOS

RESULTADOS

A continuación se presentan brevemente los resultados de cada uno de los cinco trabajos y su respectiva publicación.

Publicación 1: Búsqueda e identificación de ensayos clínicos en revistas de Dermatología publicadas en español entre 1969 y 2012 (Sanclemente, G; Pardo, H; Sánchez, S; Bonfill, X. *Identifying randomized clinical trials in Spanish-language dermatology journals*. Actas Dermosifiliogr. 2015 Jun; 106(5):415-22)
(Source Normalized Impact per Paper (SNIP): 0.836; SCImago Journal Rank (SJR): 0.388).

De todas las revistas de Dermatología evaluadas la única actualmente indexada en MEDLINE y EMBASE es *Actas Dermo-Sifiliográficas*, y cuatro lo están solo en EMBASE.

Revistas incluidas y excluidas

De las 28 revistas que reunieron criterios de elegibilidad finalmente se incluyeron 21. Solo *Actas Dermo-Sifiliográficas* requiere y promueve el uso de la normativa CONSORT.

Detección de ensayos clínicos

Desde el año 1969 se identificaron un total de 144 ECA: el 54 % (78) en 16 revistas latinoamericanas, y el 46 % (66) en cinco revistas españolas.

Entre las enfermedades cutáneas estudiadas entre las revistas españolas predominaron la psoriasis (11 ECA), las micosis (9 ECA) y el acné vulgar (8 ECA); y en las latinoamericanas las verrugas vulgares (9 ECA), las micosis (8 ECA), el acné vulgar (7 ECA) y las úlceras de miembros inferiores (6 ECA).

En la búsqueda electrónica en MEDLINE se encontraron 3997 registros, de los cuales 669 correspondieron a *Actas Dermo-Sifilográficas*. Dos de estas referencias no eran ECA, pero cuatro sí e incluían en el título el término *randomized*. Todas estas referencias se hallaron mediante búsqueda manual.

En EMBASE se detectaron inicialmente 9584 registros, entre los cuales se identificaron 16 referencias a ECAs. De estas 16 referencias, ocho correspondieron a seis ECAs ya previamente identificados y a dos de la Revista Dermatología Mexicana que no se habían encontrado en la búsqueda manual porque en, un principio, no se disponía de la tabla de contenidos, ni del formato impreso o electrónico de los volúmenes 46 y 48 (números 6 y 2, respectivamente). En la búsqueda electrónica a través portal de la BVS se detectaron inicialmente un total de 5140 registros. En comparación con la búsqueda manual se identificaron solo 28 ECA de los 144 (19,5 %) hallados con anterioridad.

Las siguientes revistas que no se lograron evaluar de forma completa debido a la imposibilidad de obtener la totalidad de los volúmenes y números: Dermatología Revista Mexicana, Dermatología Venezolana, Revista Argentina de Dermatología, Archivos Argentinos de Dermatología, las dos revistas ecuatorianas, la dominicana y la Revista Fontilles.

PUBLICACIÓN 1

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Actas Dermosifiliogr. 2015;106(5):415–422

ACTAS Dermo-Sifiliográficas

Full English text available at www.actasdermo.org

ORIGINAL ARTICLE

Identifying Randomized Clinical Trials in Spanish-Language Dermatology Journals☆

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KEYWORDS
Randomized clinical trial;
Manual literature search;
Dermatology journals

Abstract

Background: The necessary foundation for good clinical practice lies in knowledge derived from clinical research. Evidence from randomized clinical trials (RCTs) is the pillar on which decisions about therapy are based.

Objective: To search exhaustively and rigorously to identify RCTs in dermatology journals published in Spanish.

Methods: We located dermatology journals through the following search engines and indexes: PubMed, LILACS, SciELO, Periódica, Latindex, Índice Médico Español, C-17, IBECS, EMBASE, and IMBIOMED. We also sought information through dermatology associations and dermatologists in countries where Spanish was the usual language of publication, and we searched the Internet (Google). Afterwards we searched the journals electronically and manually to identify RCTs in all available volumes and issues, checking from the year publication started through 2012.

Results: Of 28 journals identified, we included 21 in the search. We found a total of 144 RCTs published since 1969; 78 (54%) were in Latin American journals and 66 (46%) were in Spanish journals. The most frequent disease contexts for RCTs in Spanish journals were psoriasis, mycoses, and acne vulgaris. In Latin American journals, the most frequent disease contexts were common warts, mycoses, acne vulgaris, and skin ulcers on the lower limbs. Manual searches identified more RCTs than electronic searches.

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Conclusions: Manual searches found a larger number of RCTs. Relatively fewer RCTs are published in Spanish and Latin American journals than in English-language journals. Internet facilitated access to full texts published by many journals; however, free open access to these texts is still unavailable and a large number of journal issues are still not posted online.
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PALABRAS CLAVE
Ensayo clínico aleatorizado;
Búsqueda manual;
Revistas dermatológicas

Identificación de ensayos clínicos en revistas dermatológicas publicadas en español

Resumen
Introducción: Para asegurar una práctica adecuada se hace necesario incorporar el conocimiento derivado de la investigación clínica, en la que los ensayos clínicos con asignación aleatoria (ECA) son el pilar fundamental para la decisión de una terapia.
Objetivo: Buscar e identificar de manera exhaustiva y rigurosa los ECA publicados en revistas dermatológicas en español.
Métodos: Se detectaron las revistas dermatológicas mediante búsquedas en PubMed, LILACS, SciELO, Periódica; Latindex; Índice Médico Español; el C-17; el IBECS, EMBASE e IMBIOMED; y/o por el contacto con las asociaciones de dermatología/especialistas de cada país y la búsqueda libre por Google. Posteriormente se realizó tanto una búsqueda manual como electrónica de los ECA en los volúmenes y números disponibles. La revisión de cada revista se realizó en cada volumen y número desde su publicación hasta el año 2012.
Resultados: De las 28 revistas encontradas se incluyeron 21. Desde 1969 se identificaron 144 ECA, 54% (78) en las revistas latinoamericanas y 46% (66) en las españolas. Entre las enfermedades estudiadas predomina la psoriasis, las micosis y el acné vulgar entre las revistas españolas, mientras que entre las latinoamericanas prevalecen las verrugas vulgares, las micosis, el acné vulgar y las úlceras de los miembros inferiores. La búsqueda manual identificó más ECA de los detectados por búsqueda electrónica.
Conclusiones: La búsqueda manual permitió una alta detección de ECA. El número de ECA identificados en revistas dermatológicas iberolatinoamericanas es bajo comparado con las revistas publicadas en inglés. Internet facilitó el acceso al texto completo de muchas revistas, pero se carece aún de un acceso libre al texto completo y de un volumen importante de números publicados por esta vía.
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Introduction

An individual clinician's experience is an important source of knowledge in dermatology. However, when such knowledge becomes the sole basis for clinical decision-making, therapeutic effects are often overestimated. Compounding this problem is the physician's tendency to rely on knowledge acquired during residency training or to find it difficult to incorporate current evidence into routine practice, especially if new information calls beliefs and previous experience into question.[1–3] Clinical trials follow an experimental design in which a researcher manipulates exposure to 1 or more treatments in order to compare effects.[4,5] The main purpose of this type of study is to assess the efficacy and safety of an intervention that seeks to prevent or cure a health condition or to speed recovery.[4,5]

Given the importance of randomized clinical trials (RCTs), it might be supposed that they would be easily available to both treating physicians and researchers. Problems arise, however, when health care professionals seek to locate and use information from RCTs. Among the difficulties that have been reported are 1) the novelty of the terminology itself, 2) the underuse of descriptors when trials are indexed in databases, and 3) the high percentage of journals that do not post articles online.[6–8] Problems that further interfere with physicians' use of RCTs are lack of time for reading these articles and the lack of access to the publishing journals.[9,10]

To help identify RCTs published in the Spanish language in several medical specialties, the Cochrane Collaboration undertook a project to search for them manually. Searching in databases alone reportedly fails to find a significant number of RCTs in the specialties of ophthalmology, public health, anesthesiology and critical care, and general and internal medicine.[8,11–14] In addition, online MEDLINE searches can fail to return up to 25% of RCTs available, mainly when the authors have not included the search terms *randomized controlled trial* or *controlled clinical trial* in the titles.[15]

We present the results for dermatology journals included in the Cochrane Collaboration's project on hand searching for RCTs in Spanish, as these findings complement the important earlier work of González-Castro et al.[7,16] in identifying trials reported in *Actas Dermo-Sifiliográficas* between 1948 and 2000 and *Medicina Cutánea Ibero-Latino-Americana* between 1970 and 2000.

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Aim of This Study

We sought to exhaustively and rigorously search for RCTs in dermatology journals published in the Spanish language.

Material and Methods

Identification of Journals

We identified journals within the framework of a project led by the Iberoamerican Cochrane Centre (IbCC) in Barcelona, Spain, to find biomedical journals in countries where Spanish is spoken. An IbCC-trained researcher, who was responsible for managing and coordinating the study, carried out the journal search and sent the results to the IbCC collaborators in each country. The collaborators were charged with confirming that the journal information was complete and accurate. Any other sources that might help us find these journals, such as national library catalogs and collections, were also searched.

Appropriate databases (IBECS [the Spanish health sciences index], EMBASE [Excerpta Médica dataBASE], and IMBIOMED) and the web pages of dermatology associations in Latin American countries where Spanish is spoken were included in the search. We also made direct contact with journals' editorial boards and specialists in dermatology, and as a last resort we searched for candidate journals in Google.

Journals were eligible if they published original research articles and made full texts available to researchers in print or online. Journals were excluded if they focused on pediatric dermatology, covered areas already included in the project under another specialty (for example, infectious diseases), or published only reviews or case reports in dermatology. If a journal's full texts could not be obtained by any means, it was likewise excluded.

Each journal was searched in reverse chronological order from 2012 to the first issue published (provided full texts were still available). If no RCTs were found for 5 consecutive years, the manual search was halted, unless we had ready access to issues, in which case we extended the search.

Additionally, we checked whether these journals instructed authors to follow the CONSORT (Consolidated Standards of Reporting Trials) guidelines and whether they were indexed in MEDLINE or EMBASE.

Hand Search Method

We asked 40 undergraduate and postgraduate students in the health sciences to carry out the systematic hand searches. Each student did a test search of a journal for a period the IbCC had already assessed. The searchers' training was based on the IbCC's hand RCT search protocol for Spanish articles (available from http://www.cochrane.es/~cochrane/?q=es/node/140). That protocol was based on the Cochrane Collaboration's *Training Manual for Handsearchers*.

Once training and the pilot search had been completed, the searcher was assigned volumes in which to find RCTs by 1) reading the tables of contents, 2) locating key terms for RCT-associated concepts in Spanish (*aleatorizado, prospectivo, comparación*, etc.) in titles and abstracts, and 3) reading the patients and methods sections of the full texts. Afterwards, the searcher filled in the form for recording the results of hand searches of journals or updates.

Electronic Search Method

So that we could compare electronic and hand-searching results, we conducted RCT searches in MEDLINE (through PubMED), EMBASE, LILACS (Latin American index of scientific and technical literature) and IBECS. Validated combinations of descriptors were used in multiterm combinations, along with free-text terms.[1,2] (See Appendix 1, online supplementary material.) These searches were updated in November 2014 to check for RCTs published between 2012 and 2014.

RCT Inclusion Criteria

We followed the Cochrane Collaboration criteria for defining RCTs. Thus, we included 1) trials comparing treatments in humans; 2) trials designed to gather data prospectively; 3) clinical comparisons of 2 or more interventions (1 of which could be a control treatment) of any type (medications, operations, diagnostic or educational procedures, rehabilitation therapies, management systems, or other); and 4) trials using random, or quasi-random, assignment of treatments, and/or use of double blinding. The randomization units could be individuals, clusters (hospitals, communities), or parts of the body (such as split faces or different limbs).

Classification of Information and Identification of RCTs

Each searcher recorded the number of RCTs found while reading the assigned issues. Later, 2 evaluators who had formal training in clinical epidemiology (G. S. and H. P.) read the full texts in order to confirm that each RCT met the selection criteria.

Planned Analysis

Descriptive statistics were compiled. Continuous variables were summarized in appropriate measures. Qualitative variables were reported as absolute and relative frequencies and percentages. Data were stored in a spreadsheet (Excel, version 2010, Microsoft Office, Redmond, WA, USA). SPSS software (IBM, version 19 (Armonk, NY, USA) was used to analyze the data.

Results

The only dermatology journal we found to be indexed in both MEDLINE and EMBASE at this time is *Actas Dermo-Sifiliográficas*. The journals indexed only in EMBASE are *Dermatología Revista Mexicana*, *Revista Argentina de Dermatología*, *Medicina Cutánea Ibero-Latino-Americana*, and *Piel*.

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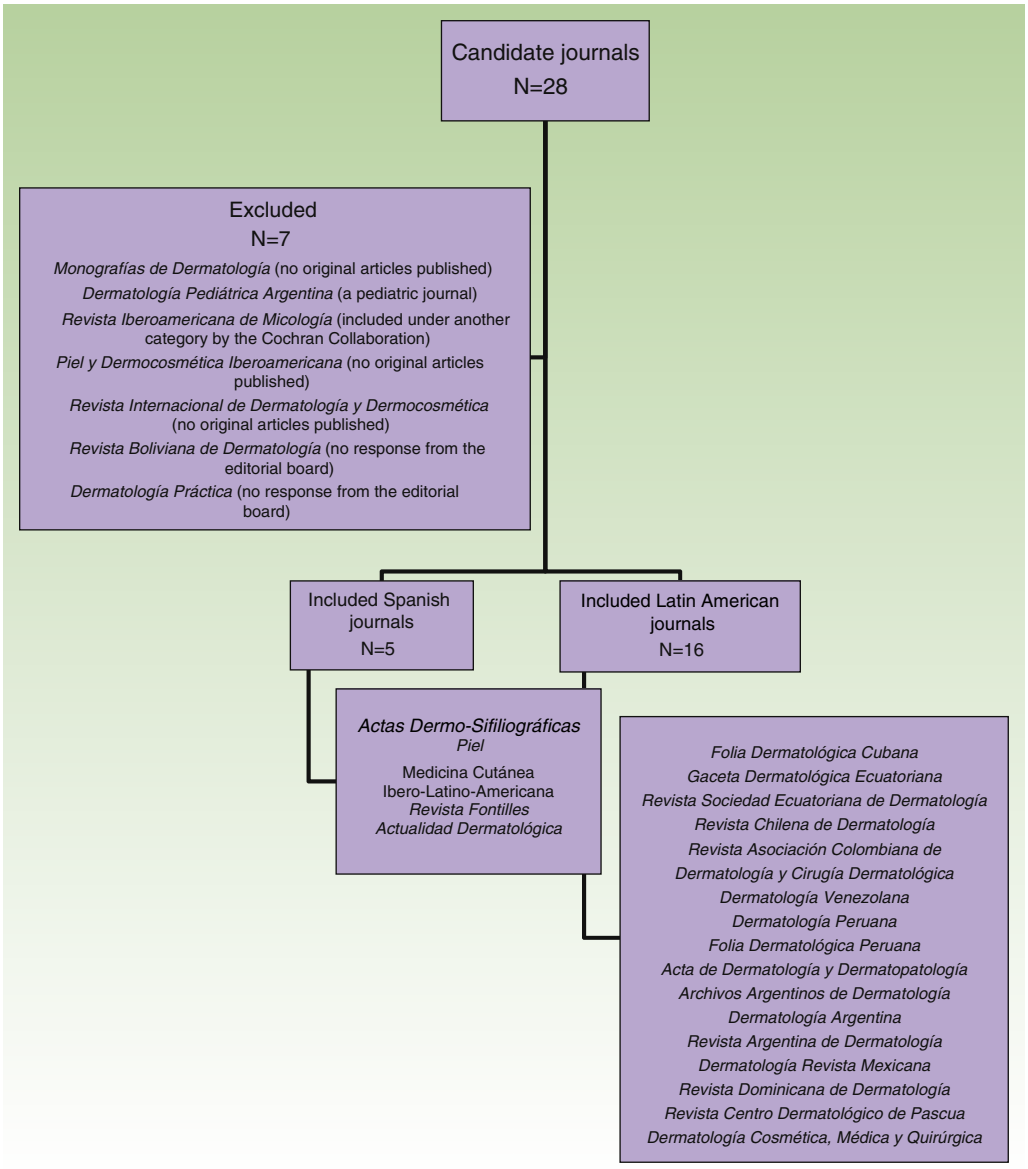

Figure 1 Flow chart of the dermatology journal search process and the selection of included and excluded journals.

Included and Excluded Journals

Of the 28 candidate journals, 21 were included. All 28 journals and the reasons for exclusions are shown in Fig. 1.

Actas Dermo-Sifiliográficas is the only journal included in this study that specifies and promotes the use of the CONSORT guidelines.[17]

RCTs Identified

A total of 144 RCTs published since 1969 were found in the 21 included journals (Table 1). Seventy-eight (54%) of the RCTs were published in the 16 Latin American journals searched, and 66 (46%) were found in the 5 Spanish journals (Table 1, which also shows the number of RCTs found in each journal). A large number of the RCTs found in *Actas Dermo-Sifiliográficas* and *Medicina Cutánea Ibero-Latino-Americana* were previously gathered and described in 2 earlier publications.[7,16]

Analysis by 5-year intervals shows that many of the RCTs (89 in total) were published in the last 20 years (from 1993 to 2012). The 25 preceding years (from 1992 to 1968) saw 55 RCTs published (Fig. 2).

The most frequently studied skin diseases in the Spanish trials were psoriasis (11 RCTs), mycoses (9), and acne vulgaris (8). The most frequent disease contexts in the Latin American trials were common warts (9 RCTs), mycoses (8), acne vulgaris (7), and lower-limb ulcers (6). Details of the RCTs found are listed in Appendix 2 of the online supplementary material.

The MEDLINE search identified 3997 entries, 669 of which were in *Actas Dermo-Sifiliográficas*. Two of these entries

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Table 1 Included Dermatology Journals.

No.	Journal Name	Period Searched	First Year of Publication	Periods Not Searched[a]	No. of RCTs Found
	Latin America				
1	*Dermatología Revista Mexicana*	1981–2012	1956	1969–1980, 1984, 1987	21
2	*Dermatología Venezolana*	1984–2012	1957	1969–1983	13
3	*Dermatología Peruana*	1996–2012	1996	–	9
4	*Revista Asociación Colombiana de Dermatología*	1991–2012	1991	–	8
5	*Revista Chilena de Dermatología*	1985–2012	1985	–	8
6	*Dermatología Cosmética, Médica y Quirúrgica*	2003–2012	2003	–	4
7	*Revista del Centro Dermatológico Pascua*	1999–2012	1999	–	4
8	*Revista Argentina de Dermatología*	1981–2012	1908	1969–1980	4
9	*Folia Dermatológica Peruana*	1986–2012	1986	–	2
10	*Dermatología Argentina*	1995–2012	1995	–	2
11	*Folia Dermatológica Cubana*	2007–2012	2007	–	2
12	*Archivos Argentinos de Dermatología*	1983–2012	1951	1969–1982	1
13	*Actas de Dermatología y Dermatopatología*	2001–2009	2001 (publication ceased in 2009)	–	0
14	*Revista Dominicana de Dermatología*	2010–2012	1971	1971–2009	0
15	*Revista Sociedad Ecuatoriana de Dermatología*	2003–2010	1991	1991–2002, 2005, 2008, 2009, 2011, 2012	0
16	*Gaceta Dermatológica Ecuatoriana*	1998	1998	1997–2012	0
Total RCTs in Latin American journals					**78**
	Spain				
17	*Actas Dermo-Sifiliográficas*	1969–2012	1909	–	30
18	*Medicina Cutánea Ibero-Latino-Americana*	1969–2012	1966		25
19	*Piel*	1986–2012	1986	–	10
20	*Actualidad Dermatológica*	1974–2008	1962	1969–1973,	1
21	*Revista Fontilles*	2008–2012	1932	1969–2002	0
Total RCTs in Spanish journals					**66**

Abbreviation: RCT, randomized clinical trial.

[a] These years could not be searched because neither print nor digital content was available.

were initially considered candidates for inclusion, but were not in fact RCTs, and 4 were. These 4 articles included the word *randomized* in their indexed title. All these RCTs had also been found by hand searching (Fig. 3).

The EMBASE search initially yielded 9584 entries (Fig. 3); 16 of these were for RCTs. Of these, 6 had been previously identified by hand searching and 2 were newly identified ones from the *Dermatología Revista Mexicana*. These 2 articles had not been found during earlier hand searching because neither print nor digital versions of the table of contents could be found for issue 6 of volume 56 or issue 2 of volume 48 (Fig. 3).

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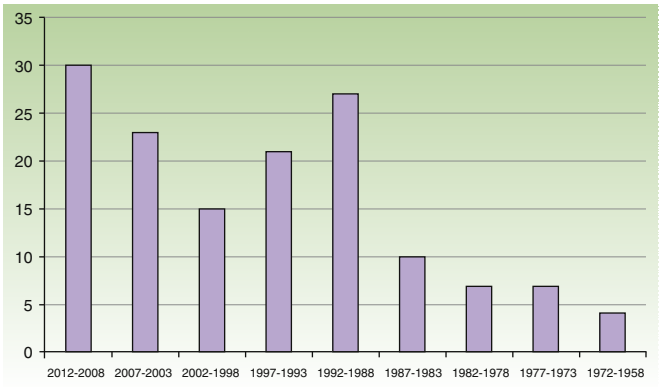

Figure 2 Number of randomized clinical trials published in 5-year periods.

The search of indexes on the Spanish language Virtual Health Library (BVS) initially returned 5140 entries (Fig. 3). After filtering for dermatology, 30 candidates were identified; 2 of these were not RCTs. Thus, the digital searches found only 28 (19.5%) of the 144 RCTs that had already been found by hand searching (Fig. 3).

We were unable to hand search all of the following journals because of missing volumes or issues: *Dermatología Revista Mexicana*, *Dermatología Venezolana*, *Revista Argentina de Dermatología*, *Archivos Argentinos de Dermatología*, the 2 Ecuadoran journals, the single journal published in the Dominican Republic, and *Revista Fontilles* (Table 1).

Discussion

RCTs are the principal units of analysis for systematic reviews, clinical practice guidelines, and other documents that synthesize knowledge. Regulatory agencies also require them before medicines can be approved for use in humans.

Hand searching identified about 80% more RCTs than database searching. This finding is consistent with previous reports for our own field, in which journals like *Archives of Dermatology*[18] and *Actas Dermo-Sifiliográficas*[7,19] were searched. It is also consistent with reports for other medical specialties.[8] These results underline the importance of manually checking dermatology journals, as many of the RCTs we found could not have been otherwise identified, possibly because MEDLINE and EMBASE are not sensitive to search terms in Spanish.[11,19–22] Alternatively, the reason may be that *Actas Dermo-Sifiliográficas* is the only Spanish language dermatology journal indexed in MEDLINE or that EMBASE does not index all of the other Spanish journals. Compounding the problem is the inherent difficulty of electronic searching in any language other than English. Searches in other languages have returned 37% fewer entries than searches in English.[15]

Dermatología Revista Mexicana and *Dermatología Venezolana* were the Latin American journals that published the largest number of RCTs. In Spain, *Actas Dermo-Sifilográficas* published the most. We offer no explanation for these observations, but we think it may be that more funding is available for conducting RCTs in the countries where these journals are published. It is also possible that these journals have less stringent policies governing the RCTs they publish than other Latin American journals do.

Our findings showed an increase in the number of RCTs published in Spanish in recent decades. The reason for the increase may lie in the importance currently placed on evidence-based medicine, an approach that obliges researchers to value this type of study above others because it provides more and stronger evidence.

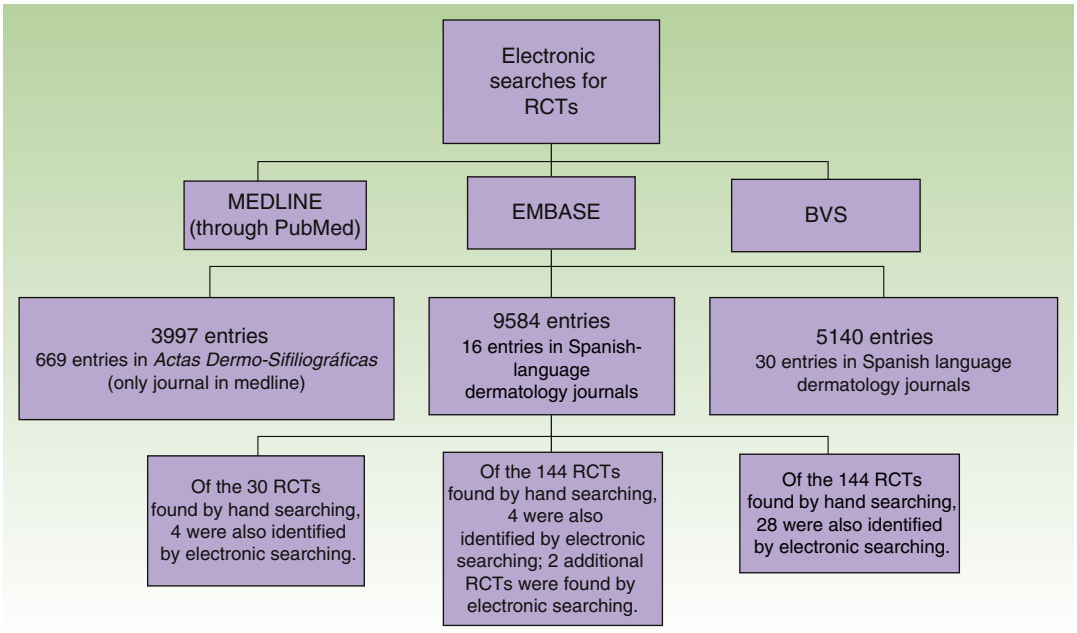

Figure 3 Flow chart of the digital search process for each database searched and the selection of randomized clinical trials (RCTs). BVS refers to the Biblioteca Virtual de la Salud (Virtual Health Library).

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We found 78 Spanish-language RCTs in Latin American journals and 66 in Spanish ones published over the course of 44 years. On average, RCTs were published at a rate of 1 to 2 per year, a statistic that is in sharp contrast with the rate of RCT publication in English. Up to 11 RCTs per year are published by *Archives of Dermatology* alone, for example.[18]

The CONSORT reporting guidelines were established in 1996 to standardize the way clinical trials are reported in different journals.[17] These standards indirectly encourage greater methodological rigor by obliging the researcher to describe the design explicitly and fully. Only 1 journal in this study, namely *Actas Dermo-Sifilográficas*, requires authors to follow the CONSORT guidelines. There seems to be a need, therefore, not only to promote the design of RCTs but also to encourage journals to require CONSORT-guided reporting, just as the important English-language dermatology journals do.

That both Spanish and Latin American researchers showed interest in psoriasis, mycoses, and acne was noteworthy. The attention is probably attributable to the greater impact of these diseases among patients, given that clinical importance would drive an effort to identify effective therapies; alternatively, the pharmaceutical industry may be more interested in funding RCTs in these areas.[23,24]

This study identified Spanish-language dermatology journals. Their full texts proved impossible to find in only a few cases once we applied various means to locate them. This experience underlines the importance of posting full texts online because this strategy not only facilitates the identification of RCTs for systematic reviews but also contributes to making knowledge available worldwide and enhancing the visibility of Spanish-language publications.

One of the strengths of this study is the large number of journals, volumes, and issues we searched exhaustively and systematically. A total of 28 dermatology journals were initially identified. Electronic searching found nearly all the RCTs that had been identified manually. Two references were found by database searching but not by hand searching, since print copies of the issues in question were unavailable. A limitation of our study is our lack of access to all of the articles published from the start of publication (Table 1). However, those early issues probably did not contain RCTs, since this design was little used before the 1970s. Another limitation is that we excluded relevant RCTs that were published in journals that focus on other specialties or in dermatology journals published in other languages. Furthermore, we did not evaluate the quality of the RCTs for this report, although we have recently been working on that task and plan to publish the results shortly.

In conclusion, manual searches identified a large number of RCTs in dermatology journals in Spain and Latin America. However, these journals publish far fewer RCTs than English-language dermatology journals do. Finally, ready access to these RCTs and a large number of other articles of interest is still lacking.

Ethical Disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this investigation.

Data confidentiality. The authors declare that no private patient data are disclosed in this article.

Right to privacy and informed consent. The authors declare that no private patient data are disclosed in this article.

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Conflicts of Interest

The authors declare that they have no conflicts of interest.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.adengl.2015.04.010.

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Publicación 2: Sanclemente G, Pardo H, Sánchez S, Bonfill X. Analysis of the Quality of Clinical Trials Published in Spanish-Language Dermatology Journals Between 1997 and 2012. Actas Dermosifiliogr. 2015 Nov 3. pii: S0001-7310(15)00344-0. doi: 10.1016/j.ad.2015.07.008.
(Source Normalized Impact per Paper (SNIP): 0.836; SCImago Journal Rank (SJR): 0.388).

El total de revistas incluidas y excluidas, junto con la respectiva justificación, y la inclusión en MEDLINE y en EMBASE se han descrito previamente en el Trabajo 1.

Se han identificado 70 ECA desde el año 1997 (implementación del CONSORT) hasta el 2012. El 73 % (51 ECA) se publicó en las 16 revistas latinoamericanas, y el 27 % (19) en las cinco revistas españolas. Las revistas latinoamericanas que más ECA publicaron fueron: Dermatología Revista Mexicana (16), Dermatología Peruana (9) y Revista Chilena de Dermatología (5); y Actas Dermo-Sifiliográficas y Piel en el caso de las españolas, con 8 ECA cada una.

En términos generales, la mayoría de los estudios se clasificaron como de "alto riesgo de sesgo" porque no proporcionaron la información necesaria para evaluar la calidad y el rigor metodológico del estudio. Por otra parte, un pequeño porcentaje de estudios presentó bajo riesgo de sesgo en los ítems evaluados, lo cual es preocupante.

Un total de 15 estudios señalaron sus fuentes de financiación, pero solo dos lo hicieron de forma adecuada. Los autores de cinco estudios reportaron los conflictos de interés, pero solo uno lo hizo conforme a los estándares aceptados. De todas las revistas evaluadas, únicamente *Actas Dermo-Sifilográficas* se adhiere desde el año 2008 a la normativa CONSORT en relación con las instrucciones para autores, si bien en el cuerpo de los artículos no se indica la utilización de dicha herramienta como guía para publicar el estudio.

PUBLICACIÓN 2

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ORIGINAL ARTICLE

Analysis of the Quality of Clinical Trials Published in Spanish-Language Dermatology Journals Between 1997 and 2012☆

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KEYWORDS
Randomized clinical trial;
Bias;
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Dermatology journals;
Spanish

Abstract

Introduction: The value of randomized clinical trials (RCTs) undertaken to identify an association between an intervention and an outcome is determined by their quality and scientific rigor.

Objective: To assess the methodological quality of RCTs published in Spanish-language dermatology journals.

Methods: By way of a systematic manual search, we identified all the RCTs in journals published in Spain and Latin America between 1997 (the year in which the CONSORT statement was published) and 2012. Risk of bias was evaluated for each RCT by assessing the following domains: randomization sequence generation, allocation concealment, blinding of patients and those assessing outcomes, missing data, and patient follow-up. Source of funding and conflict of interest statements, if any, were recorded for each study.

Results: The search identified 70 RCTs published in 21 journals. Most of the RCTs had a high risk of bias, primarily because of gaps in the reporting of important methodological aspects. The source of funding was reported in only 15 studies.

Discussion and conclusions: In spite of the considerable number of Spanish and Latin American journals, few RCTs have been published in the 15 years analyzed. Most of the RCTs published had serious defects in that the authors omitted methodological information essential to any evaluation of the quality of the trial and failed to report sources of funding or possible conflicts of interest for the authors involved. Authors of experimental clinical research in dermatology published in Spain and Latin America need to substantially improve both the design of their trials and the reporting of results.

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PALABRAS CLAVE
Ensayo clínico aleatorizado;
Sesgos;
Metodología;
Revistas dermatológicas;
Español

Análisis de la calidad de los ensayos clínicos publicados en revistas dermatológicas publicadas en español entre 1997 y 2012

Resumen

Introducción: La relevancia del ensayo controlado con asignación aleatoria (ECA) para determinar si existe una asociación entre una intervención y un desenlace está determinada por su calidad y rigor científico.

Objetivo: Evaluar la calidad metodológica de los ECA publicados en revistas dermatológicas en español.

Métodos: Se realizó una búsqueda manual y sistemática de los ECA publicados en las revistas de Dermatología españolas y latinoamericanas entre 1997 (publicación de los criterios CONSORT) y 2012. Se determinó el riesgo de sesgo de cada ECA, evaluando los siguientes dominios: generación de la secuencia aleatoria, ocultamiento de la asignación, cegamiento de los pacientes/evaluadores de desenlaces, datos faltantes y seguimiento de pacientes. Se identificaron la fuente de financiación de los estudios y el reporte de conflictos de interés.

Resultados: Se identificaron 70 ECA publicadas en 21 revistas. La mayoría de los ECA tuvo un alto riesgo de sesgo, principalmente por falta de reporte de los aspectos metodológicos importantes. Solo 15 estudios declararon fuentes de financiación.

Discusión y conclusiones: A pesar del número considerable de revistas existentes en España y Latinoamérica, en los 15 años estudiados se han publicado pocos ECA. La mayoría de los estudios presentó problemas de calidad importantes, al carecer de información metodológica que permitiera evaluar su calidad y a las falencias en el reporte de las fuentes de financiación y de los conflictos de interés de los autores. La investigación clínica experimental dermatológica que se publica en Ibero-Latinoamérica debe mejorar ostensiblemente tanto en su diseño como en su reporte de resultados.

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Introduction

The randomized controlled trial (RCT) is the most rigorous type of methodological design and the best way of determining whether a cause-effect relation exists between an intervention and the result or outcome being assessed. RCTs also provide the raw material for systematic reviews and meta-analyses. However, the value of such studies depends on the quality and methodological rigor of their design and implementation.

In recent decades, the field of dermatology has seen a substantial increase in experimental clinical research. However, this upturn in the volume of research has not been accompanied by a corresponding improvement in trial design and methodology. Several studies have reported that the RCTs published in the dermatology literature tend to fall below acceptable standards.[1–4]

The Consolidated Standards of Reporting Trials (CONSORT) statement was first published in 1996 to improve the quality of reporting of clinical trials worldwide.[5] The CONSORT statement includes a checklist designed to improve the reporting of RCTs, which also, indirectly, throws light on the study's quality and scientific rigor.

An improvement in the scientific quality and reporting of RCTs might have been expected following the implementation of CONSORT and the publication of the Medical Research Council Guidelines for Good Clinical Practice in Clinical Trials (available from: http://www.fda.gov/downloads/Drugs/Guidances/ucm073122.pdf and http://www.mrc.ac.uk/documents/pdf/good-clinical-practice-in-clinical-trials/). However, the evidence reveals the continued presence after 1997 of serious flaws in the design and reporting of clinical trials.[6] The problem has also been observed in trials in the Spanish-language dermatology literature published after 1997. A study carried out in Spain found that only 6 (25%) of the 24 clinical trials found in the dermatology journal with the highest impact in that country—ACTAS DERMO-SIFILIOGRÁFICAS–were classified as being of high quality.[3]

In this context, the aim of the present study was to assess the methodological quality of the experimental clinical research in dermatology published in Spanish to facilitate an analysis of the strengths of these studies and the challenges that must be overcome. We analyzed the RCTs identified by a recent study that handsearched Spanish-language dermatology journals.[7]

The present study complements that work by analyzing the methodological quality of the RCTs published between 1997 and 2012 using the appropriate Cochrane Collaboration tools and a review of the reporting of conflicts of interest and funding sources.

Objective

To assess the methodological quality of the RCTs published in Spanish-language dermatology journals between 1997 and 2012.

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Materials and Methods

Journal Identification: Manual and Electronic Search

The methodology used to identify the RCTs published in Spanish-language dermatology journals has already been described in an earlier article.[7]

In a preliminary phase, all eligible journals were identified in the framework of a project led by the Iberoamerican Cochrane Centre (IbCC) in Barcelona, Spain. Using the IbCC protocol, journals were located through the following search engines and databases: MEDLINE (through PubMED), EMBASE, LILACS (Latin American Index of Scientific and Technical Literature), SciELO, Periódica, Latindex, Índice Médico Español, Catálogo Nacional de Publicaciones Periódicas en Ciencias de la Salud Españolas (C-17), as well as in other catalogues of health sciences publications in Spain. This initial search strategy was then complemented by a search of the Spanish health sciences indexes (IBECS and IMBIOMED), by free-text Internet searches using Google, by contacting the Dermatology societies in each of the countries studied, and through direct contact with dermatologists.

Each journal identified was then handsearched to identify all the RCTs published. This retrospective review was carried out in accordance with the Cochrane Collaboration's manual for handsearching archives and identifying clinical trials (available from http://www.cochrane.es/~cochrane/?q=es/node/140). Each journal was searched from 2012 back to the first issue published (provided full texts were still available).[7]

In addition to handsearching for RCTs, we also conducted an electronic search of MEDLINE (using PubMed),EMBASE, LILACS and IBECS, as well as the search engines of the Biblioteca Virtual en Salud hosted by the Latin American and Caribbean Center on Health Sciences Information (Bireme), the Pan American Health Organization, and the World Health Organization.

Data Extraction

A database was created to store each of the RCTs retrieved, to facilitate the handsearch of each journal, and to ensure that data was gathered and processed in an organized and systematic manner. We also identified journals specifying CONSORT reporting in their instructions to authors and journals indexed on MEDLINE or EMBASE.

Analysis of Quality and Risk of Bias

Only RCTs published between 1997 (the first year the CONSORT statement was implemented) and 2012 were included in the review of scientific rigor and methodological quality. The appraisal was performed twice, and any resulting discrepancies were resolved by a third assessor. The review was carried out using the Cochrane Collaboration tool for assessing risk of bias (high/medium/low).[8] This tool assesses the methodological aspects of clinical trials, including sequence generation, concealment of the sequence of patient allocation to the different arms of the study, blinding of participants and outcome assessors, incomplete data, and patient follow-up. The reviewer assesses each one of these domains and assigns one of the following answers: ''yes'', ''no'', or ''unclear/not reported''.

Studies were categorized as having a ''high risk of bias'' if they had 1 flaw that affected the generation of the allocation sequence or had more than 1 flaw affecting any of the other methodological aspects analyzed. If the necessary information was unavailable, the study was categorized as ''unclear risk/not reported''. The results of the assessment and scoring of these methodological aspects were recorded using version 5.2 of the application Review Manager (Copenhagen, the Nordic Cochrane Centre, The Cochrane Collaboration, 2012). Information on sources of funding and the reporting of potential conflicts of interest on the part of authors were also logged.

Statistical Analysis

Descriptive statistics of the resulting information were compiled, using univariate analysis to determine the frequencies of the variables. Appropriate summary measures were calculated for the continuous variables. Absolute and relative frequencies and their percentages were determined for qualitative variables. When appropriate, the confidence interval was calculated for proportions. The data were recorded on Review Manager and also in an Excel spreadsheet (Microsoft Office 2010). The software package SPSS (version 19, IBM) was used to analyze the data.

Results

Of the 28 journals that fulfilled the criteria for eligibility, 21 were eventually included in the study: 5 from Spain and 16 from Latin American countries. Of these 21 journals only ACTAS DERMO-SIFILIOGRÁFICAS is currently indexed on both MEDLINE and EMBASE. Four others are indexed on EMBASE: *Dermatología Revista Mexicana*, *Argentina de Dermatología*, *Medicina Cutánea Ibero Latinoamericana* and *Piel*.[7]

The total number of journals included and excluded, and the reasons for the choices made have been described in an earlier article (Fig. 1).[7]

Identification of Clinical Trials

Seventy RCTs published between 1997 and 2012 were identified in the 21 journals studied: 73% (51) in the 16 Latin American journals and 27% (19) in the 5 Spanish journals (Table 1) (Appendix 1). The Latin American journals that published the largest number of RCTs were *Dermatología Revista Mexicana* (16), *Dermatología Peruana* (9), and *Revista Chilena de Dermatología* (5) (Table 1). The Spanish journals that published the most RCTs were ACTAS DERMO-SIFILIOGRÁFICAS and *Piel*, with 8 each (Table 1).

Most of the trials reviewed were classified as having a high risk of bias because the authors failed to report the information needed to assess the quality and methodological rigor of the trial (Table 2). A small percentage of trials had a low risk of bias in the domains assessed (Table 2) (Fig. 2).

The authors of 15 RCTs reported sources of funding and only 2 did so in the required manner (Ramirez-Bosca et al. and Pinto et al.) (Appendix 1). The authors of 5 studies

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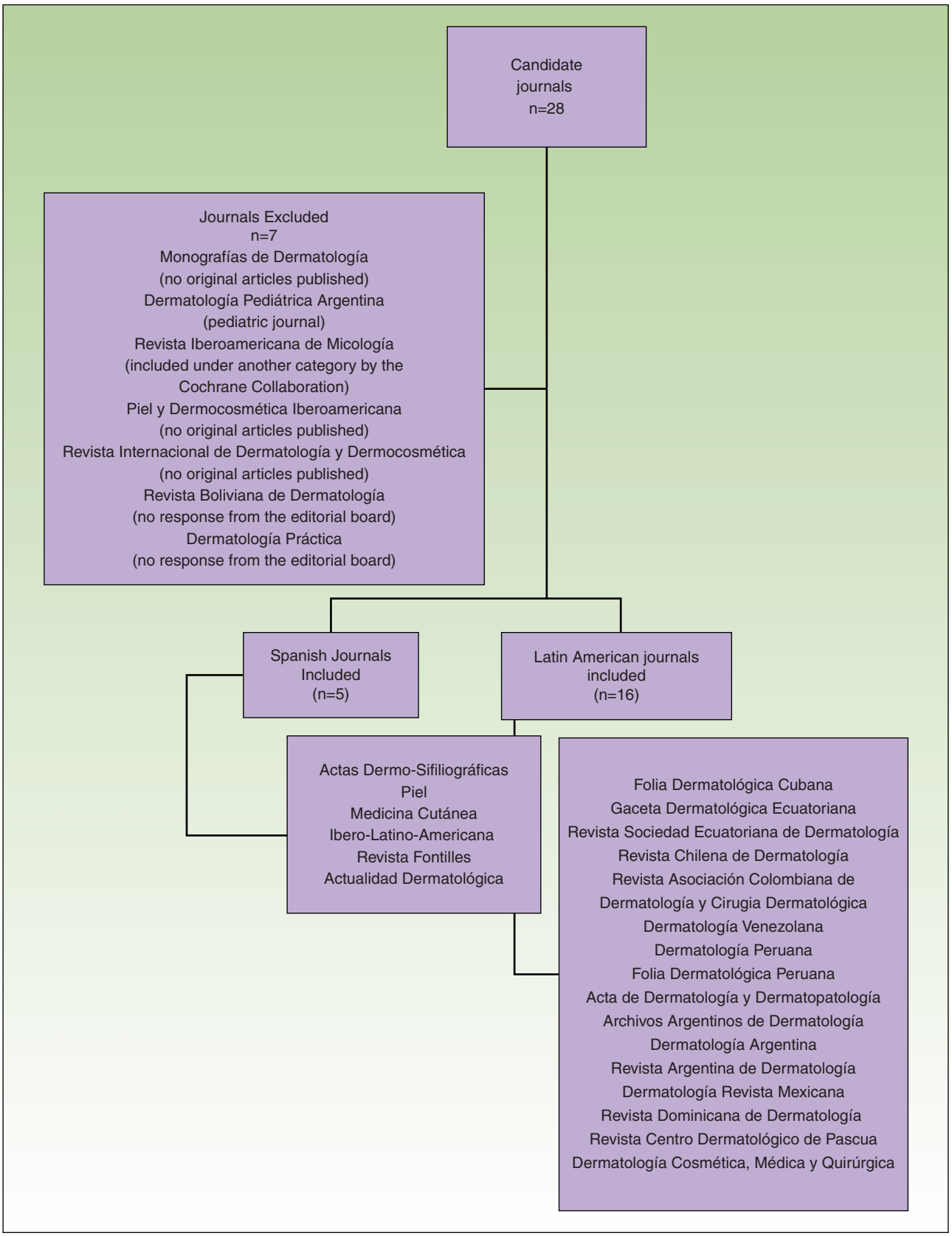

Figure 1 Flow chart showing the process used to select dermatology journals according to inclusion and exclusion criteria. Source: Sanclemente G, Pardo H, Sánchez S, Bonfill X. Identificación de ensayos clínicos en revistas dermatológicas publicadas en español. Actas Dermosifiliogr. 2015;106:415-422).

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Table 1 Randomized Controlled Trials (RCTs) Identified in Spanish and Latin American Dermatology Journals.

	Journal Name	Periods Not Assessed Because No Copies (Print or Electronic) Available	Number of RCTs Identified
1	*Dermatología Revista Mexicana*	–	16
2	*Dermatología Peruana*	–	9
3	ACTAS DERMO-SIFILIOGRÁFICAS	–	8
4	*Piel*	–	8
5	*Revista Chilena de Dermatología*	–	5
6	*Dermatología Cosmética, Médica Y Quirúrgica*	–	4
7	*Revista del Centro Dermatológico Pascua*	–	4
8	*Revista Asociación Colombiana de Dermatología*	–	4
9	*Medicina Cutánea Ibero-Latino-Americana*	–	3
10	*Folia Dermatológica Peruana*	–	2
11	*Dermatología Argentina*	–	2
12	*Folia Dermatológica Cubana*	–	2
13	*Dermatología Venezolana*	–	2
14	*Revista Argentina de Dermatología*	–	1
15	*Archivos Argentinos de Dermatología*	–	0
16	*Actas de Dermatología y Dermatopatología*	–	0
17	*Revista Dominicana de Dermatología*	1997-2009	0
18	*Revista Sociedad Ecuatoriana de Dermatología*	1997-2002, 2005, 2008, 2009, 2011, 2012	0
19	*Gaceta Dermatológica Ecuatoriana*	1999-2012	0
20	*Actualidad Dermatológica*	–	0
21	*Revista Fontilles*	1997-2002	0
Total			70

reported conflicts of interest, but only 1 of these reports conformed to accepted standards (Ramirez-Bosca et al.) (Appendix 1). Of all the journals assessed, only ACTAS DERMO-SIFILIOGRÁFICAS,since 2008, requires authors to report trials in accordance with the CONSORT guidelines; however, none of the authors reported in the body of the article whether or not the CONSORT checklist had been used to guide the reporting of the study.

Figure 2 is a summary of the risk of bias for the RCTs identified.

Discussion

The objective of this study was to assess the methodological quality of the RCTs published in Spanish-language dermatology journals between 1997 and 2012. Our findings

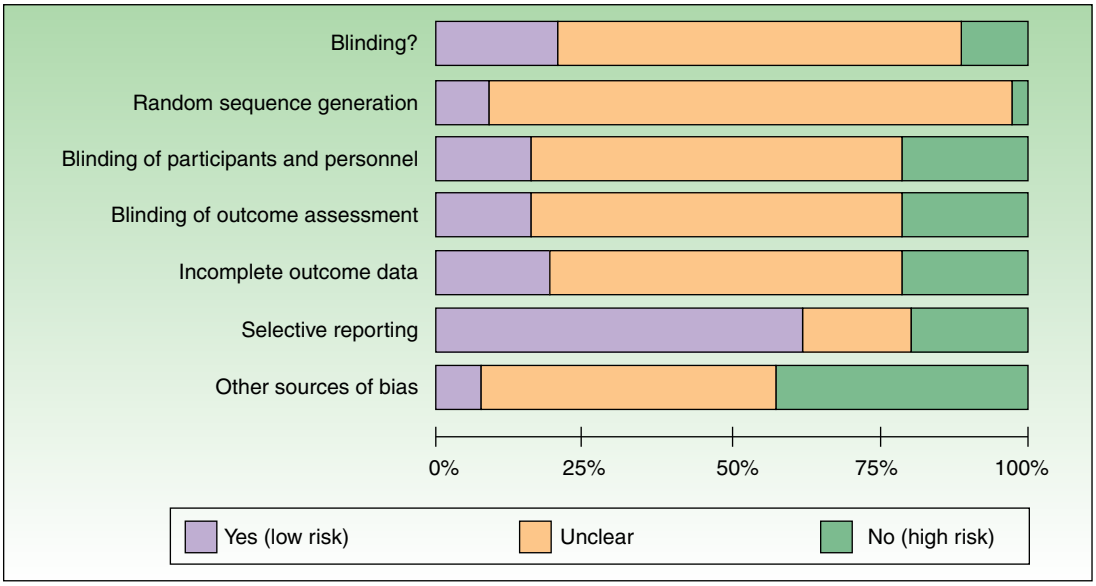

Figure 2 Risk of bias of the RCTs analyzed (graphic designed using Review Manager, version 5.2, Copenhagen, The Nordic Cochrane Centre, The Cochrane Collaboration, 2012).

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Table 2 Assessment of Methodological Aspects of Randomized Controlled Trials (RCTs) Published in Spanish and Latin American Dermatology Journals.

Methodological Aspect	No. (%)	95% CI
Allocation concealment		
Unclear/Not reported	48 (68.6)	57.73%-79.47%
Yes	14 (20)	10.63%-29.37%
No	8 (11.4)	3.95%-18.85%
Unclear/Not reported	62 (88.6)	81.15%-96.05%
Yes	6 (8.6)	2.03%-15.17%
No	2 (2.8)	−1.06%-6.66%
Unclear/Not reported	44 (62.8)	51.48%-74.12%
Yes	11 (15.7)	7.18%-24.22%
No	15 (21.5)	11.88%-31.12%
Unclear/Not reported	44 (62.8)	51.48%-74.12%
Yes	11 (15.7)	7.18%-24.22%
No	15 (21.5)	11.88%-31.12%
Unclear/Not reported	42 (60)	48.52%-71.48%
Yes	13 (18.5)	9.4%-27.6%
No	15 (21.5)	11.88%-31.12%
Unclear/Not reported	12 (17.2)	8.36%-26.04%
No	44 (62.8)	51.48%-74.12%
Yes	14 (20)	10.63%-29.37%
Unclear/Not reported	35 (50)	38.29%-61.71%
No	5 (7, 15, 8)	7.26%-24.34%
Yes	30 (42.9)	31.31%-54.49%
Not reported	55 (78.6)	68.99%-88.21%
Reported	15 (21.4)	11.79%-31.01%
Not reported	65 (92.8)	86.74%-98.86%
Reported	5 (7.2)	1.14%-13.26%

show that the risk of bias was high in the clinical trials published in the Spanish-language dermatology literature in that period, primarily because authors failed to report on important methodological aspects of their work. Although this shortcoming had already been described in earlier studies focusing on specific dermatology journals in Spanish,[9] this is the first comprehensive analysis that covers all the dermatology journals publishing RCTs in Spain and Latin America. Our findings are similar to those of authors who studied RCTs in the English-language dermatology literature or RCTs on diseases such as perioral dermatitis and atopic dermatitis.[4,10,11]

The presence of such flaws in RCTs is of particular concern because this type of study is considered to be a gold standard for the assessment of the efficacy and safety of an intervention. Consequently, the implication is that dermatological practice today (at least that predicated on evidence from the studies assessed) may be based on information gathered in a non-systematic manner or on clinical experiments lacking control groups.[12] We also detected a mismatch between the outcomes typically assessed and those that might interest patients. For example, many dermatology studies now incorporate variables relating to quality-of life because of the considerable interest of patients in this outcome in relation to dermatological treatments.[13–15] However, it is striking that quality-of-life was assessed in only 1 of the 70 RCTs identified.

The methodological aspects least often reported were random sequence generation and allocation concealment; authors also failed to report on sources of funding and possible conflicts of interest. Our findings, which are similar to those observed by other authors in journals that endorse CONSORT reporting as well as in those that do not,[6,16,17] highlight shortcomings in the scientific rigor with which the

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RCTs were designed and reported. In the future, experimental clinical research published in Spain and Latin America in the field of dermatology needs to be considerably improved both in the design and the reporting of results (endorsement and application of the CONSORT guidelines).

The starting point for an unbiased study is the use of a mechanism that ensures that all the patients have the same probability of belonging to one group or the other, and that adequate concealment of the allocation sequence prevents selective recruitment of patients according to prognostic factors (guidelines available from http://handbook.cochrane.org/). In fact, it has been shown that inadequate random sequence generation in an RCT can result in an overestimation of the effect of the treatment of up to 12%,[18] while inadequate allocation concealment may increase the effect up to 18%. Furthermore, the fact that a clinical experiment is classified as randomized does not, in and of itself, guarantee that the study fulfils the methodological standards associated with this type of study.[19]

The only journal included in this study that requires authors to comply with the CONSORT statement when reporting clinical trials is ACTAS DERMO-SIFILIOGRÁFICAS. This endorsement may explain the higher methodological quality of the RCTs published recently by that journal. However, it has been observed that, despite improvements in reporting of RCTs when this tool is used, the completeness of reporting of trials continues to be suboptimal in terms of ensuring a better quality of study.[6]

Of note is the fact that almost none of the trials identified provided any information on sources of funding or conflicts of interest. Complete reporting of both of these aspects is essential since the results of the trial may be affected by the personal interests of the researcher or the funder of the study (very often a pharmaceutical company).[20–22] Transparency is important because it is common in the dermatology literature to find selective reporting of endpoints, a practice which in most cases leads to the overestimation of positive outcomes.[23] This practice may be associated with the presence of conflicts of interest. Therefore, in the future careful assessment of these characteristics will be essential in the studies published in Spanish-language dermatology journals.[24]

One of the principal strengths of the present study was that 21 dermatology journals published in Spanish were handsearched to identify RCTs. The clinical trials identified will shortly be included in the Cochrane Central Register of Controlled Trials (CENTRAL), making them available for future systematic reviews and other summary documents. As reported by the earlier article, which identified the RCTs[7] analyzed in the present study, finding 70 RCTs and retrieving the full texts of those articles would have been impossible through an electronic search because only 1 journal is indexed on MEDLINE (Actas Dermo-Sifiliográficas) and only 4 are indexed on EMBASE[7] (*Dermatología Revista Mexicana, Revista Argentina de Dermatología, Medicina Cutánea Ibero Latinoamericana* and *Piel*). Another strength of the present study was the duplicate analysis of the quality of the RCTs and the use of internationally-recognized and validated Cochrane tools. (Available from: http://handbook.cochrane.org/chapter_8/8_assessing_risk_of_bias_in_included_studies.htm).

The main limitation of this study was the impossibility of assessing all the volumes and issues of 3 journals: 2 published in Ecuador and 1 published in the Dominican Republic. However, it is unlikely that our results would have differed significantly with a complete analysis of these 3 journals since no RCTs were found in the issues we were able to review. Furthermore, none of those journals have endorsed the CONSORT statement or require its use. Another limitation was the variability of the endpoints and the way these were measured in the RCTs identified. This variability led to a high level of heterogeneity among the studies, making it difficult to quantitatively summarize the results in a meta-analysis

In conclusion, the risk of bias of the clinical trials published in Spanish-language dermatology journals between 1997 and 2012 was high, mainly because the study reports provided insufficient information on which to base any assessment of the quality and methodological rigor of the studies. Moreover, in many cases the authors failed to report on sources of funding and possible conflicts of interest. Complete reporting of all methodological aspects of trials is recommended, as this would allow readers to detect possible sources of bias and design flaws. A complete description of the study is important because it facilitates proper analysis of the evidence and because it ensures that a trial is not classified as having a high risk of bias solely because of omissions in the information provided. Complete reporting will benefit patients—the foundation of evidence-based dermatological practice—and will contribute to more effective decision-taking in this field of practice. Finally, and as a future strategy, we plan to contact the publishers of the dermatology journals analyzed with a view to standardizing prospective tools for the identification of the RCTs published in their journals. The implementation of such a system will facilitate continual updating of this work, thereby obviating the need to repeat the manual search in the future.

Ethical Disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals during the course of this study.

Data confidentiality. The authors declare that no private patient data are disclosed in this article.

Right to privacy and informed consent. The authors declare that no private patient data are disclosed in this article.

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Conflicts of Interest

The authors declare that they have no conflicts of interest.

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Publicación 3: Sanclemente G, Mancilla GA, Hernandez G. A double-blind randomized controlled trial to assess the efficacy of daylight photodynamic therapy with methyl-aminolevulinate vs. Placebo and daylight in patients with facial photodamage. Actas Dermosifiliogr. 2015 Nov 28. pii: S0001-7310(15)00436-6. doi: 10.1016/j.ad.2015.10.002.

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De los 84 pacientes seleccionados, 19 no cumplieron los criterios de elegibilidad y cinco se negaron a participar. Por consiguiente, 60 individuos fueron asignados al azar a alguno de los dos grupos. Todos los pacientes se expusieron al sol durante 120 minutos. El promedio de iluminancia en cada sesión fue de 82.478, 70.419 y 72.528 lux (sesiones 1, 2 y 3, respectivamente). El promedio de irradiancia solar (Watts/m2) fue de 480, 430 y 435 (sesiones 1, 2 y 3, respectivamente).

El riesgo de fracaso fue menor en el grupo MAL + luz del día (RR: 0,18; IC95 %: 0,08-0,41; p = 0,00). Además, en la comparación entre los dos grupos se encontraron diferencias significativas en las variables de fotodaño específico después del tratamiento. Las puntuaciones de dolor después de las sesiones 1 y 3 no fueron significativamente diferentes entre los dos grupos, mientras que sí lo fueron en la sesión 2. Los efectos secundarios como la exudación, el edema y la vesiculación no se dieron en ningún grupo una semana tras cada sesión. El eritema y la descamación fueron significativamente diferentes en todas las sesiones cuando se compararon ambos grupos. Por otro lado, la pigmentación fue estadísticamente diferente solo después de la última sesión.

En lo referente a la escala de calidad de vida solo los ítems 5 y 14 del Skindex-29 del grupo MAL + luz solar mostraron diferencias estadísticamente significativas ($p<0,05$, prueba de Wilcoxon). Cuatro pacientes del grupo MAL – luz solar presentaron eventos adversos, dos de ellos graves no relacionados con el producto (cólico renal y corrección de prolapso genital), y otros dos no serios (recurrencia de herpes simple y una reacción a la diacereína).

Asimismo, se realizó un análisis post-hoc por subgrupos y confusión de acuerdo con las variables de sexo, fototipo de piel, irradiancia y tiempo entre las sesiones para evaluar posibles interacciones. El efecto de las intervenciones también se valoró ajustando por la edad de los pacientes, la irradiancia y el tiempo entre sesiones. Dado que por el azar se encontró un desequilibrio entre los grupos en la variable sexo y fototipo 1, no fue posible evaluar la interacción en estos subgrupos. Sin embargo, al ajustar por el fototipos 2 y 3 se encontraron diferencias estadísticamente significativas entre el producto recibido y la mejoría del fotodaño facial (valor de p= 0,032), pero no en la irradiancia (valor de p= 0,396). Por otra parte, no se encontró asociación entre la edad y el tiempo entre las sesiones y la respuesta a la terapia (valor de p= 0,92). Por último, la interacción entre subgrupos (excluyendo los hombres y al fototipo 1) no fue estadísticamente significativa (valor de p= 0,776).

PUBLICACIÓN 3

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ORIGINAL ARTICLE

A double-blind randomized controlled trial to assess the efficacy of daylight photodynamic therapy with methyl-aminolevulinate vs. Placebo and daylight in patients with facial photodamage

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KEYWORDS
Daylight;
Photodynamic therapy;
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Abstract

Background: Daylight PDT (dPDT) is easy to use and does not require light equipment. Such therapy has been exhaustively proved to be successful in the treatment of actinic keratosis, but its use in skin photodamage remains unclear.
Objective: To evaluate dPDT's efficacy in skin facial photodamage.
Patients and methods: This was a parallel-group double-blind, randomized placebo-controlled trial. Sixty participants with symmetric facial photodamage were allocated to topical methyl aminolevulinate (MAL) and daylight vs. matching placebo and daylight. Primary outcome was global photodamage improvement/failure 1 month after the third session. Secondary outcomes included: pain evaluation; specific photodamage severity scores; sun irradiance quantification and Skindex-29 scores. Adverse events were also investigated.
Results: Primary analysis included all randomized patients. All patients sun-exposed for 120 min in 3 sessions. The risk of failure was lower in the MAL-dPDT group than in the placebo plus daylight group (RR: 0.18; 95% CI: 0.08–0.41). Mean solar irradiance (W/m^2) during the first, second and third sessions was 480.82, 430.07 and 435.84, respectively. Items 5 and 14 of Skindex-29 in the MAL-dPDT group showed statistical significant differences. Two patients in the MAL-dPDT group had serious and non-serious events not directly related to the product.
Conclusion: dPDT with MAL was un-painful, effective and safe for the treatment of facial photodamage. Herpes simplex prophylaxis should be considered before sessions.
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PALABRAS CLAVE
Luz del día;
Terapia fotodinámica;
Ensayo Clínico Controlado con Asignación Aleatoria;
Fotodaño

Ensayo clínico aleatorio controlado, doble ciego para valorar la eficacia de la terapia fotodinámica con luz de día con metilaminolevulinato frente a placebo y luz de día en pacientes con fotodaño facial

Resumen

Introducción: La terapia fotodinámica con luz-día (TFDd) es fácil de usar y no requiere de equipo alguno. Tal terapia ha demostrado ser útil en el tratamiento de las queratosis actínicas, pero su uso en el fotodaño no es claro.

Objetivo: Evaluar la eficacia de la TFDd en el fotodaño facial.

Pacientes y Métodos: Se realizó un ensayo clínico doble-ciego controlado con placebo y con asignación aleatoria. Sesenta participantes con fotodaño facial simétrico se asignaron a recibir bien TFD con Metil-Aminolevulinato (MAL) y luz de día o placebo y luz de día. El resultado primario fue la mejoría/fracaso en el fotodaño facial global un mes después de la tercera sesión. Los resultados secundarios incluyeron: dolor; fotodaño específico, irradiancia recibida y la puntuación en el Skindex-29.

Resultados: Todos los pacientes se expusieron a la luz de día durante 120 minutos en 3 sesiones. El riesgo de fracaso fue menor en el grupo de TFD con MAL y luz de día que en el grupo placebo (RR:0,18; 95%; IC:0,08 a 0.41). La media de la irradiancia solar ($W.m^{-2}$) durante la primera, segunda y tercera sesión fue de 480,82, 430,07 y 435,84, respectivamente. Los ítems 5 y 14 del Skindex-29 en el grupo de TFDd con MAL mostraron diferencias estadísticamente significativas. Dos pacientes en el mismo grupo presentaron eventos adversos serios y no serios pero estos no tuvieron relación directa con el producto evaluado.

Conclusión: La TFDd con MAL fue es un tratamiento indoloro, eficaz y seguro para el tratamiento del fotoenvejecimiento facial. La profilaxis del Herpes simple debe ser considerada antes de cada sesión.

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Introduction

As worldwide population's average age has risen,[1] skin care and self-perception concerns have both increased.[2] Chronic sun or ultraviolet (UV) light exposure cause physical and structural changes to the skin that result in photodamage,[3] which could also be a marker for the development of actinic keratosis or skin cancer.

Available treatments for photodamage have included multiple procedures such as topical and systemic retinoids, chemical peels, intense-pulsed light, lasers, and photodynamic therapy (PDT).[4–7] With the exception of PDT,[8] published evidence of such procedures efficacy in photodamage is lacking.[9]

Photodynamic therapy is based in the use of photosensitizers activated by light which localize in the diseased cells resulting in the formation of reactive oxygen species that leads tissue damage and cell death.[10] The most often used topical photosensitizers for the skin are 5-aminolevulinic acid (ALA) and methyl aminolevulinate (MAL) which are endogenously converted to protoporphyrin-IX (PpIX).[11]

Conventional PDT (cPDT) relies on the incubation of any of these photosensitizers with occlusion for several hours, with severe pain during illumination as a main disadvantage of the procedure.[8,12]

Daylight PDT (dPDT) is easy to use and less expensive due to the lack of need of light equipment.[11,13,14] It has also been described to be better tolerated by patients, as continuous activation of porphyrins during daylight exposure can lead to less pain.[15] Such therapy has been exhaustively proved to be successful in the treatment of actinic keratosis,[13,15,16] but its use in skin photodamage remains unclear. Therefore, the aim of this study was to evaluate the efficacy of dPDT vs. placebo in adult patients with facial photodamage in terms of failure and improvement according to Dover's et al. scale.[7] Such study contributes with trial evidence in this field, as it has been confirmed that daylight-mediated photodynamic therapy is possible throughout the year in Medellin, Colombia, according to a recent meteorological study performed in Central and South America.[17]

Patients and methods

Patients

Patients screened belonged to an ambulatory clinic (IPS Universitaria, Universidad de Antioquia). All adult patients, willing to participate, between 35 and 75 years-old with symmetric facial photodamage grade 2 or 3 according to Dover's scale, were included. Exclusion criteria were nursing or pregnancy; photosensitizing disorders; active infectious skin diseases or history of herpes simplex in the face; subjects with less than 6 months of any previous rejuvenation interfering treatments; history of systemic isotretinoin in the last year; history of hypersensitivity to the active product; and subjects requiring concurrent treatment that would have interfered with the aims or assessments of the study. All patients were enrolled by one dermatologist, and each eligible patient was sequentially assigned with a number starting from 1.

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Design and randomization

This was a phase IIb-trial designed to elucidate mainly dPDT's efficacy in another indication such as skin photodamage, as it has been previously proved to be effective in the treatment of Actinic Keratosis (AKs).[13,15,16]

This was a unicentre Phase II, 2 arms, parallel group double blind, randomized placebo-controlled trial. Sixty participants were allocated using a ratio of 1:1 to receive either topical MAL (Metvix®, Galderma Laboratories, France) plus daylight or topical matching placebo-daylight. Allocation sequence was generated by an external statistician through a simple random sampling without replacement.[18]

Allocation concealment was warranted by sending the generated sequence by the statistician to the pharmacist chemist who was entailed to label and supply the active intervention and matching placebo according to a ''A'' or ''B'' code's assignment list. This coded list was thereafter sent by the pharmacist chemist to the nurse in charge of the application of the topicals who did not know the generated sequence.

Setting

The study setting and data collection was held in one center in Medellin, Colombia at an ambulatory clinic (IPS Universitaria, Universidad de Antioquia).

Ethics

Study approval was obtained from the Ethics Committees/Institutional Review Boards at the participating centre. The study was designed to follow the International Conference on Harmonization of good clinical practice (GCP) guidelines, local regulations and laws, as well as to conform to Helsinki Declaration. All participants gave written informed consent before study start.

Interventions

Patients were randomized to receive 1 g of topical MAL or matching placebo applied to the whole face <30 min before sun exposure for 2 h (3 sessions, 2–4 weeks apart) in a double-blind fashion (investigators and patients).

To enhance product/placebo skin penetration a subtle abrasion with sandpaper 400 grit to the whole face, was performed. Immediately after skin abrasion, a sunscreen (Cetaphil Dermacontrol SPF30®) was applied to the entire sun-exposed area including the treatment area in both groups during daylight-PDT, to avoid sunburn. Thereafter, 15 min after sunscreen application, MAL was applied.

If ambient temperature and/or sunny sky were uncomfortable for the patients, they were allowed to stay under a gazebo. Also, patients receiving placebo were allowed to receive the active intervention after data analysis and prove of efficacy.

Safety assessments

Patients were assessed for safety one week after each session by a Dermatologist. Patients were monitored for adverse events using INVIMA's (Instituto Nacional de Vigilancia de Medicamentos y Alimentos) criteria and serious adverse events were reported in the first 24 h after knowledge of the event. Pain after each session was assessed by a trained nurse.

Efficacy assessments

Efficacy was evaluated after 1 month of the third (last) daylight session by another dermatologist not involved in assessing safety secondary outcomes.

Assessment of light dose

Ambient temperature, daylight illuminance and irradiance were measured during all 3 sessions with LP-471 probes connected to a Delta-Ohm 9847 data-logger (Caselle di Selvazzano (PD), Italy), which performed measurements every minute starting from the time the first patient started daylight exposure, until the last patient ended exposure. This equipment was calibrated by the manufacturer.

Primary outcomes

The primary outcome was measured with the Dover's photodamage scale,[7] 1 month after the third daylight PDT session. According to a previous publication,[8] outcome was labeled as ''success if there was a decrease in global photodamage score to a severity score of 0 or if there was a >1 grade of decrease in global photodamage score from baseline. A failure or lack of improvement was considered if, after therapy, the patient had the same severity score found at baseline''.

Secondary outcomes

Secondary outcomes included: pain evaluation with the visual analog scale (VAS) measured immediately after sessions 1, 2 and 3; specific photodamage severity score for fine lines, coarse lines, tactile roughness, mottled pigmentation, sallowness, and erythema measured one month after the third daylight PDT session, according to Dover's photodamage scale[7]; and sun irradiance quantification during daylight exposure. Another secondary objective was quality of life assessment before/after treatment measured with the validated version of the Colombian Skindex-29 Instrument. Secondary safety objectives included assessment of any adverse event at all times, and therapy tolerance measured 1 week after sessions 1, 2 and 3. No changes in trial outcomes were added after the start of the trial.

Study variables

Global and specific photodamage variables (fine lines, mottled pigmentation, sallowness, tactile roughness, coarse lines, and erythema) were measured by Dover's photodamage scale (Severity score: from 0 to 5).

Pain was measured by the quantitative visual analog scale (rated from 0 to 10).

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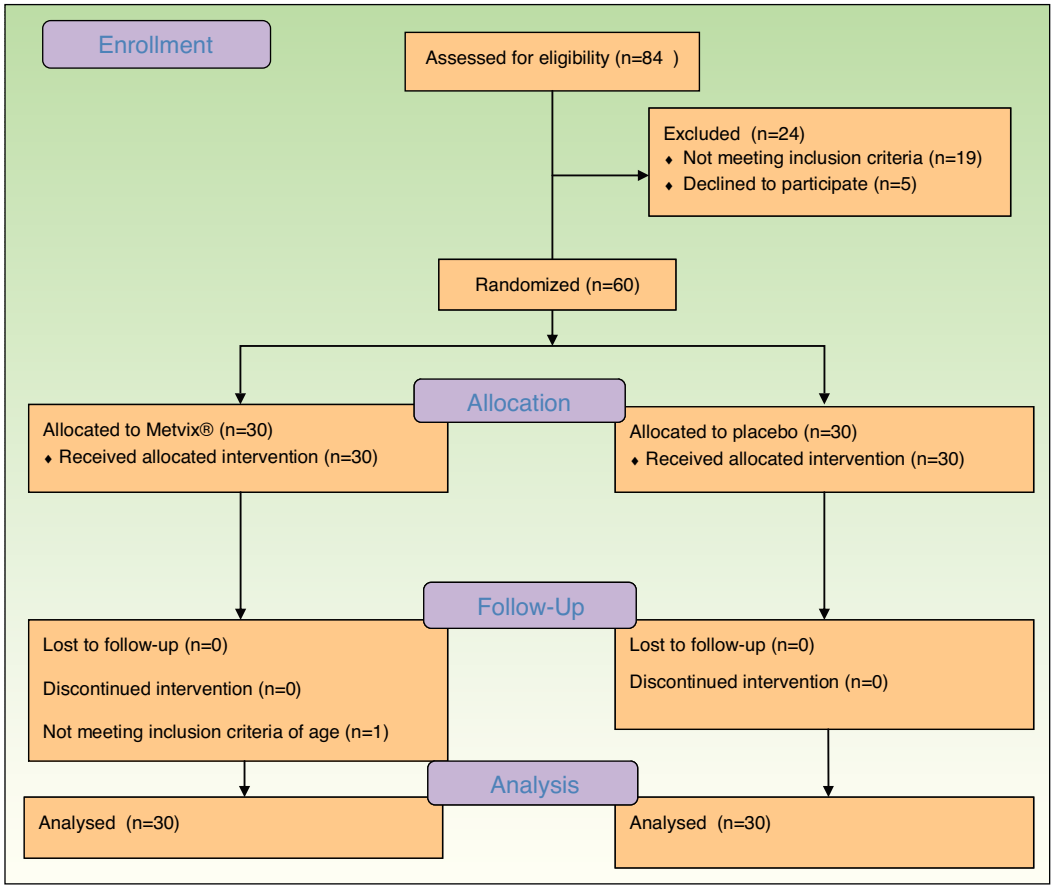

Figure 1 Flow diagram of patients.

Therapy tolerability (oozing, erythema, edema, desquamation, pigmentation and vesiculation) was measured 1 week after session 1 and session 2 (rated from 0 to 3).

In all variables, absolute and relative values were depicted, accordingly.

Statistical analysis

A minimum of 58 patients was required to give the study at least 80% power at a two-tail 5% level of significance to detect a difference in proportions of the primary outcome of 70% with MAL-dPDT vs. 30% with placebo-dPDT. These calculations were performed using Epidat®.[19]

All randomized patients (intention to treat (ITT) population) were included in the primary analysis. The population considered for efficacy and safety analysis consisted in all patients who received at least one dose of the study medication.

Efficacy was assessed with the calculation of the relative risk (RR) of failure with its respective 95% confidence interval. Differences between proportions of primary outcome and qualitative secondary endpoints were assessed using the χ^2 test or Fisher exact test, as required. When more than 50% of cells were found to have ceros a test for comparison of proportions, was performed. Wilcoxon signed rank test was used to compare global facial photodamage and secondary outcomes severity scores on each patient, at baseline and 1 month after session 3, and the *U*-Mann Whitney test was used to compare pain differences.

Post hoc logistic regression to evaluate confounding and subgroup-treatment effect interactions was performed, according to gender, skin phototype, sun irradiance and time between sessions. The effect of the interventions was also evaluated adjusting for age, sun irradiance and time between sessions.

Results

A total of 84 patients were initially screened but from these, 19 did not fulfill eligibility criteria and 5 refused to participate, obtaining 60 eligible participants. (Fig. 1) The first patient was enrolled on April 10th 2014, and the last patient completed the study on the 3rd of October 2014. The trial was registered at http://clinicaltrials.gov with the identifier: NCT02139618.

Demographic and clinical baseline characteristics of patients are depicted in Table 1.

Primary outcomes

The ITT analysis included all 60 patients (54 females/6 males) for the primary outcome, according to allocation. As there were no exclusions or patients lost to follow-up, all 60 individuals were included in all other analyses.

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Table 1 Baseline characteristics of patients.

Variables	Placebo + daylight ($n = 30$)	MAL + daylight ($n = 30$)	p value	95% CI[a]
Age	60 (sd: 7.6)	60.5 (sd: 8.1)	0.62	−3.55 to 4.55
Gender				
Males	5 (17%)	1 (3%)	0.20	−4% to 31%
Females	25 (83%)	29 (97%)	0.58	−31% to 4%
Skin phototype				
I	1 (3%)	0 (0%)	0.68	–
II	18 (60%)	15 (50%)	0.50	−18% to 38%
III	11 (37%)	15 (50%)	–	−41% to 14%
IV	0 (0%)	0 (0%)		–
V	0 (0%)	0 (0%)		–
VI	0 (0%)	0 (0%)		–
Dover's global photodamage score				
1	0 (0%)	0 (0%)	–	–
2	6 (20%)	3 (10%)	0.48	−11% to 31%
3	24 (80%)	27 (90%)	0.7	−31% to 11%
4	0 (0%)	0 (0%)	–	–

[a] 95% confidence interval for means and percentages differences.

MAL-dPDT was found to have a significantly greater treatment effect than placebo-daylight, with the majority of patients of the first group having facial improvement (15 out of 30) and 10 out of 30 having facial success vs less patients of the placebo group having facial improvement (2 out of 30) and 1 out of 30 having facial success ($p = 0.00$). Clinical effects are shown in Figs. 2 and 3.

For RR calculation, the number of whole faces that succeeded was added to the number of whole faces that improved. The risk of failure was lower in the MAL-dPDT group than in the placebo-daylight group (RR: 0.18; 95% CI: 0.08–0.41). The number needed to treat (NNT) to have a benefit from the experimental therapy was 1 (95% CI: 1.11–1.78).

After randomization, one patient was eligible according to her global facial photodamage, but he did not meet the age criteria (she was 33 years-old). However, she completed the study and was analyzed accordingly to the group in which she was allocated.

Also, time between the second and the third session was extended more than a month due to administrative reasons that caused a delay in placebo shipping.

Secondary outcomes

Significant differences were also found in specific photodamage variables (Table 2).

Figure 2 Before and after clinical photographs. After treatment with MAL + daylight, facial skin appears lighter, with improvement of frontal and external eye wrinkles.

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Figure 3 Before and after clinical photographs. After treatment with MAL + daylight, facial skin appears lighter, with improvement of frontal wrinkles and of nasolabial folds and perioral wrinkles.

Table 2 Photodamage severity scores.

Photodamage severity Scores	Placebo + daylight	MAL + daylight	*p* value	RR of failure with 95% CI[a]
Global photodamage scores				
Failure	27 (90%)	5 (17%)		
Improvement	2 (7%)	15 (50%)	0.000	0.18 (0.08–0.41)
Success	1 (3%)	10 (33%)		
Specific photodamage severity scores				
Fine lines				
Failure	27 (90%)	6 (20%)		
Improvement	2 (7%)	13 (43%)	0.000	0.22 (0.10–0.45)
Success	1 (3%)	11 (37%)		
Mottled pigmentation				
Failure	23 (77%)	7 (23%)		
Improvement	4 (13%)	18 (60%)	0.000	0.30 (0.15–0.59)
Success	3 (10%)	5 (17%)		
Sallowness				
Failure	25 (83%)	5 (17%)		
Improvement	2 (7%)	9 (30%)	0.000	0.20 (0.08–0.45)
Success	3 (10%)	16 (53%)		
Tactile roughness				
Failure	25 (83%)	5 (17%)		
Improvement	2 (7%)	6 (20%)	0.000	0.20 (0.08–0.45)
Success	3 (10%)	19 (63%)		
Coarse lines				
Failure	27 (90%)	9 (30%)		
Improvement	3 (10%)	15 (50%)	0.000	0.33 (0.19–0.58)
Success	0 (0%)	6 (20%)		
Erythema				
Failure	26 (86%)	6 (20%)		
Improvement	2 (7%)	16 (53%)	0.000	0.23 (0.11–0.47)
Success	2 (7%)	8 (27%)		

[a] Relative risks of failure with their 95% confidence intervals calculated by adding values of improvement and success vs. failure.

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Table 3 Pain scores and effects after 1 week of all sessions.

Other secondary outcomes	Placebo + daylight (mean(median))	MAL + daylight (mean(median))	*p* value	95% CI[a]
Pain VAS score after session 1 (0–10)	0.50 (0)	0.70 (0)	N.S.[b]	−0.51 to 0.91
Pain VAS score after session 2 (0–10)	0.23 (0)	1.63 (0)	0.00	0.41 to 2.39
Pain VAS score after session 3 (0–10)	0.80 (0)	1.10 (0)	N.S.[b]	−0.69 to 1.29

[a] 95% confidence interval for mean differences.
[b] Non-significant.

Oozing, edema and vesiculation were not present in any group one week after each session (Table 3). Erythema and desquamation were significantly different in all sessions when both groups were compared, whereas pigmentation was statistically different only after the last session (Table 3).

Pain VAS scores after session 1 and 3 were not significantly different between the two groups, whereas they were found to be significantly different in session 2 (Table 4).

The majority of Skindex-29 scores showed non-statistical differences when baseline/after treatment scores were compared ($p > 0.05$). However, individual scores of the MAL group in item 5 (*My skin condition affects my social life*) and item 14 (*I tend to do things by myself because of my skin condition*) showed statistical significant differences ($p < 0.05$).

Overall, mean outside temperature during sessions was 28.60 °C. All patients sun-exposed for 120 min. Mean illuminance in each session varied from 82,478.75 through 72,528.56 and 70,419.1736 lx (sessions 1, 2 and 3, respectively). Mean solar irradiance (W/m^2) during the first, second and third sessions was 480.82, 430.07 and 435.84, respectively.

Post hoc analysis

There was an imbalance between both groups in gender (more women than men) and just 1 patient in skin-phototype-I, it was not possible to evaluate effect interactions in these subgroups. However, when controlling only for skin phototype-II and III, a statistical significant association was found between the product received, and facial photodamage improvement (OR: 0.09; 95% CI: 0.01–0.81; $p = 0.03$), whereas no statistical significant association was found between the intervention and the placebo group when irradiance was tested (OR: 1.00; 95% CI: 0.99–1.00; $p = 0.39$). No association was found neither between age (OR: 1.05; 95% CI: 0.96–1.15; $p = 0.24$) and treatment response, nor between facial photodamage improvement and time lapse between sessions (OR: 1.00; 95% CI: 0.95–1.05; $p = 0.92$)

Also in the post hoc evaluation of subgroups interaction (excluding men and skin phototype-I), we did not find statistical significance of this relation (OR: 1.28; 95% CI: 0.23–7.17; $p = 0.77$).

Adverse events (AE)

Two patients in the MAL group had serious events not related to the product. Another two patients (belonging to the MAL group) had non-serious adverse events which corresponded to a recurrence of herpes simplex related to sun-exposure (not previously reported by the patient) and a stressful situation. Another patient had a reaction to diacerein which was prescribed by her physician one week after the third session. Also, none of the patients in the placebo group presented with any AE.

Discussion

This study showed that dPDT was unpainful, safe and effective in the treatment of facial photodamage. The size of the effect obtained by dPDT was so high that just one patient has to be treated to have a benefit with this intervention. Although no previous published study has evaluated the benefits of dPDT in photodamage as main outcome, this study supports what has been observed in other studies in which skin photodamage signs improve after cPDT in the treatment of AKs or facial photodamage.[8,20,21]

The median age of individuals in this trial was 60 years, which is in agreement with the age of most people with photodamage signs in any country, although such signs could present earlier or more pronounced in Equator zones or in highly sun exposed people such as farmers or outdoor workers.[22,23]

In MAL-treated patients, a higher effect was found in sallowness and tactile roughness, although other photodamage signs (i.e., fine lines, mottled pigmentation erythema, coarse lines), also improved. These findings are in agreement with reported effects obtained with cPDT, except for erythema.[8] Such results could be explained by the light source used, as conventional PDT with red-light has been reported to induce more erythema.[16,24] Regarding mottled pigmentation, Dover's photodamage scale does not differentiate pigmentation due to seborrheic keratosis, lentigos, melasma or pigmented actinic keratosis. As we did not include these specific outcomes in efficacy assessment, we hypothesize that facial pigmentation improvement could have been obtained by MAL's proved effect in pigmented AKs and perhaps in lentigos.

Pain during illumination in cPDT is the main unwanted effect of the procedure.[8,15,25] In this study, facial photodamage treatment resulted in overall low pain scores which is a very relevant finding as pain is the main drawback of all other available facial photodamage therapy modalities or rejuvenating procedures such as chemical peelings, IPL and lasers.[7,26,27]

Early secondary effects after PDT sessions have been extensively studied.[8,15,16,24] In this study only erythema and desquamation were found to be significantly different in

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Table 4 Secondary effects scores after 1 week of all sessions (*Z* test for proportions comparison).

Other secondary outcomes	Placebo (mean(median)) *n* (%)	MAL + daylight (mean(median)) *n* (%)	*p* value for individual percentage differences	*p* value (*Z* test for global proportions comparisons)	95% CI[a]
Reaction 1 week after session 1					
Oozing					
0	30 (100%)	30 (100%)			
1	0 (0%)	0 (0%)	*	*	–
2	0 (0%)	0 (0%)			
3	0 (0%)	0 (0%)			
Erythema					
0	30 (100%)	15 (50%)	<0.05		28–71%
1	0 (0%)	13 (43%)	<0.05	0.00	−64% to −22%
2	0 (0%)	2 (7%)	>0.05		−18% to 5%
3	0 (0%)	0 (0%)	–		–
Edema					
0	30 (100%)	30 (100%)			
1	0 (0%)	0 (0%)	*	*	–
2	0 (0%)	0 (0%)			
3	0 (0%)	0 (0%)			
Desquamation					
0	30 (100%)	9 (30%)	<0.05		50–89%
1	0 (0%)	14 (47%)	<0.05	0.00	−67% to −25%
2	0 (0%)	7 (23%)	<0.05		−41% to −4%
3	0 (0%)	0 (0%)	–		–
Pigmentation					
0	28 (93%)	30 (100%)	>0.05		−18% to 5%
1	2 (7%)	0 (0%)	>0.05	N.S.[b]	−5% to 18%
2	0 (0%)	0 (0%)	–		–
3	0 (0%)	0 (0%)	–		–
Vesiculation					
0	30 (100%)	30 (100%)			
1	0 (0%)	0 (0%)	*	*	–
2	0 (0%)	0 (0%)			
3	0 (0%)	0 (0%)			
Reaction 1 week after session 2					
Oozing					
0	30 (100%)	30 (100%)			
1	0 (0%)	0 (0%)	*	*	–
2	0 (0%)	0 (0%)			
3	0 (0%)	0 (0%)			
Erythema					
0	29 (97%)	12 (40%)	<0.05		34–78%
1	1 (3%)	18 (60%)	<0.05	0.00	−78% to −34%
2	0 (0%)	0 (0%)	–		–
3	0 (0%)	0 (0%)	–		–
Edema					
0	30 (100%)	30 (100%)			
1	0 (0%)	0 (0%)	*	*	–
2	0 (0%)	0 (0%)			
3	0 (0%)	0 (0%)			
Desquamation					
0	30 (100%)	8 (27%)	<0.05		54–92%
1	0 (0%)	19 (63%)	<0.05	0.00	−83% to −42%
2	0 (0%)	3 (10%)	>0.05		−24% to 4%
3	0 (0%)	0 (0%)	–		–

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Table 4 (*Continued*)

Other secondary outcomes	Placebo (mean(median)) *n* (%)	MAL + daylight (mean(median)) *n* (%)	*p* value for individual percentage differences	*p* value (*Z* test for global proportions comparisons)	95% CI[a]
Pigmentation					
0	30 (100%)	29 (97%)	>0.05		−6% to 13%
1	0 (0%)	1 (3%)	>0.05	N.S.[b]	−13% to 6%
2	0 (0%)	0 (0%)	–		–
3	0 (0%)	0 (0%)	–		–
Vesiculation					
0	30 (100%)	30 (100%)			
1	0 (0%)	0 (0%)	*	*	–
2	0 (0%)	0 (0%)			
3	0 (0%)	0 (0%)			
Reaction 1 week after session 3					
Oozing					
0	30 (100%)	30 (100%)			
1	0 (0%)	0 (0%)	*	*	–
2	0 (0%)	0 (0%)			
3	0 (0%)	0 (0%)			
Erythema					
0	30 (100%)	19 (63%)	<0.05		16–57%
1	0 (0%)	11 (37%)	<0.05	0.00	−57% to −16%
2	0 (0%)	0 (0%)	–		–
3	0 (0%)	0 (0%)	–		–
Edema					
0	30 (100%)	30 (100%)			
1	0 (0%)	0 (0%)	*	–	–
2	0 (0%)	0 (0%)			
3	0 (0%)	0 (0%)			
Desquamation					
0	27 (90%)	10 (33%)	<0.05		33–80%
1	3 (10%)	17 (57%)	<0.05	0.00	−70% to −22%
2	0 (0%)	3 (10%)	>0.05		−24–4%
3	0 (0%)	0 (0%)	–		–
Pigmentation					
0	30 (100%)	24 (80%)	<0.05		2–37%
1	0 (0%)	6 (20%)	<0.05	0.02	−37% to −2%
2	0 (0%)	0 (0%)	–		–
3	0 (0%)	0 (0%)	–		–
Vesiculation					
0	30 (100%)	30 (100%)			
1	0 (0%)	0 (0%)	*	–	–
2	0 (0%)	0 (0%)			
3	0 (0%)	0 (0%)			

* Unable to calculate statistics because variables were constant.
[a] 95% confidence interval for percentages differences.
[b] Non-significant.

all sessions. Such agreements or disagreements with published literature could be explained by the time at which such outcomes are assessed, as the majority of studies have evaluated these endpoints during the first 3 days when inflammatory signs are more frequent.[15,16,24] When early pigmentation was evaluated, we found that it increased gradually from session to session resulting in significant differences after the third session. This could be explained by transient post-inflammatory pigmentation or a cumulative pigmentation due to ethnic skin responses to sun exposure, a fact that has already been reported in a similar population treated with cPDT.[8] Importantly, mottled pigmentation improved in the MAL group when compared to placebo, one month after the third session.

When irradiance was analyzed, no statistical differences were found between both groups. This finding could be explained by a high mean solar irradiance during the daylight sessions of our study, which has exceeded the mean irradiance that has proved to induce a clinical benefit (305 Watts/m^2).[17,28,29]

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In this study we quantified QOL with the skindex-29 scale, which is the only instrument properly validated and adapted in Colombia.[30] Although the majority of item scores did not change after therapy, this could be explained by a whole scale failure and lack of sensitiveness to detect baseline or final impact in facial photodamage. However, significant findings and changes in 2 function items of the scale (pre-/post-treatment) suggest that some important QOL features are impaired in skin photodamage and they in fact could be improved by dPDT. Even though no previous published studies regarding this issue have been found.

In our study, adverse events were more frequent in MAL-dPDT group. However, although such events were not related directly with the study product, the practitioner has to be cautious regarding sun exposure and consider herpes simplex prophylaxis in patients with a history of recurrent episodes.

The strength of this study lies on the double-blind placebo-controlled randomized design chosen, and the methodological rigor of trial performance and monitoring, which followed strict good clinical practice regulations. This is important as very few well designed trials exists to evaluate the efficacy of treatments for photodamage.

Limitations of our trial include the inability of this study for generalizing findings in men and in patients with skin phototype-I and the lack of the use of a validated and reliable scale for photodamage assessment, which could have led to more objective and quantitative measures of therapy effects. Also, in this study, an imbalance in important baseline characteristics (gender, skin phototype and global photodamage score) was found, having more men and lighter skin patients in the placebo group whereas skin photodamage was increased in MAL-group individuals. Nevertheless, after performing post hoc sub-group analysis and covariate adjustment, only skin phototype was found to have a role in the main outcome and no relationship was found with age. This finding is very important as we are not aware of any published study reporting such results. However, we have to bear in mind that post hoc subgroup analyses and non a priori covariate adjustment are both merely exploratory.

In conclusion, dPDT with MAL was painless, effective and safe for the treatment of global facial photodamage when compared with placebo. This therapy was also useful for the treatment of fine lines, coarse lines, tactile roughness, mottled pigmentation, sallowness, and erythema. Also, in high risk patients, herpes simplex prophylaxis should be considered before sessions. Results obtained are encouraging as dPDT with MAL not only is effective, but also easy to apply and straightforward to be monitored by any dermatologist. Finally, larger studies such as phase III designs with a more objective quantification of photodamage signs are required in order to confirm efficacy but also to evaluate long-term safety and to determine subgroup differences for men and certain skin phototypes.

Conflict of interest

Methyl aminolevulinate (Metvix®), matching placebo and Cetaphil Dermacontrol SPF30® were provided free of charge by its manufacturer (Galderma SA Laboratories), but the pharmaceutical lab was not involved in trial design, and did not participate in analysis of the data or in the preparation of the final manuscript or in the publication of results.

Ethical disclosures

Protection of human and animal subjects. The authors declare that the procedures followed were in accordance with the regulations of the responsible Clinical Research Ethics Committee and in accordance with those of the World Medical Association and the Helsinki Declaration.

Confidentiality of data. The authors declare that they have followed the protocols of their work centre on the publication of patient data.

Right to privacy and informed consent. The authors must have obtained the informed consent of the patients and/or subjects mentioned in the article. The author for correspondence must be in possession of this document.

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Se incluyó un solo estudio con 211 participantes (promedio de edad: 13 años), con dos grupos de tratamiento: uno con etanercept y otro con placebo. El seguimiento se realizó durante un periodo de 48 semanas. Puesto que solo se logró incluir un estudio con numerosas publicaciones, no se pudo realizar un análisis cuantitativo de los resultados (metanálisis).

En la semana 12, el 57 % de los pacientes del grupo de etanercept lograron obtener un PASI-75 (RR: 4,95; IC95 %: 2,83-8,65) con evidencia de alta calidad, frente al 11 % de los del grupo de placebo. La reducción del riesgo absoluto fue del 45 % (IC95 %: 33,95-56,40), y el número que fue necesario tratar (NNT) para obtener un beneficio con etanercept fue de dos (CI95 %: 1,77-2,95).

El porcentaje de mejoría con respecto al valor basal de las puntuaciones de la escala de calidad de vida (CDLQI) fue mejor en el grupo de etanercept que en el de placebo (52,3 % frente a 17,5 %, respectivamente [p= 0,0001]) a la semana 12 de tratamiento. El análisis entre estos grupos mostró un tamaño del efecto que fue clínicamente importante (diferencia de medias de 2,30; IC95 %: 0,85-3,75) como resultado de una evidencia de alta calidad.

Durante el estudio se reportaron tres eventos adversos graves que se resolvieron sin secuelas. La muerte u otros eventos como tumores malignos, infecciones oportunistas, tuberculosis o desmielinización no se dieron durante el estudio.

Además, el 13 % de los participantes en el grupo placebo y el 53 % en el de etanercept lograron una mejoría del PGA con aclaramiento parcial o total de la enfermedad a la semana 12 de tratamiento (RR 3,96; IC95 %: 2,36-6,66), hecho sustentado por evidencia de alta calidad.

PUBLICACIÓN 4

Anti-TNF agents for paediatric psoriasis (Review)

Sanclemente G, Murphy R, Contreras J, García H, Bonfill Cosp X

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[Intervention Review]

Anti-TNF agents for paediatric psoriasis

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ABSTRACT

Background

Psoriasis is a chronic skin disease that may develop at any age. Estimates for the United States and Europe suggest that psoriasis accounts for 4% of skin diseases in children. In most cases, the condition is mild and can be treated with creams. However, a small percentage of children have moderate to severe disease that requires drugs, such as ciclosporin or methotrexate, and some will require injections with newer biological agents, such as anti-TNF (tumour necrosis factor) drugs. Anti-TNF drugs (among them etanercept, infliximab, and adalimumab) are designed to reduce inflammation in the body caused by tumour necrosis factor. Evidence for the safety and efficacy of these biological agents in paediatric psoriasis is lacking.

Objectives

To assess the efficacy and safety of anti-TNF agents for the treatment of paediatric psoriasis.

Search methods

We searched the following databases up to July 2015: the Cochrane Skin Group Specialised Register, the Cochrane Central Register of Controlled Trials (CENTRAL; 2015, Issue 6), MEDLINE (from 1946), Embase (from 1974), and LILACS (from 1982). We also searched 13 trials registers and checked the reference lists of included studies and key review articles for further references to relevant randomised controlled trials (RCTs). We handsearched conference proceedings and attempted to contact trial authors and relevant pharmaceutical manufacturers. We searched the US Food and Drug Administration's and European Medicines Agency's adverse effects databases.

Selection criteria

All relevant RCTs that evaluated the efficacy and safety of anti-TNF agents for the treatment of chronic plaque psoriasis in individuals less than 18 years of age.

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Data collection and analysis

Two review authors independently checked titles and abstracts and performed data extraction and 'Risk of bias' assessment of the included studies. One review author entered data into Review Manager (RevMan), and a second review author checked the data. We also attempted to obtain unclear data from the trial authors where possible.

Our primary outcomes were investigator-assessed number of participants achieving a 75% improvement in Psoriasis Area and Severity Index-75 (PASI 75) compared to baseline, improvement in quality of life using an instrument such as Children's Dermatology Life Quality Index (CDLQI), and adverse effects. Our secondary outcomes included the proportion of participants achieving PASI 50 and the Physician's Global Assessment (PGA).

Main results

We included one study with 211 participants (median age 13 years), in which etanercept (dosage ranged from 0.8 to 50 mg per kilogram of body weight) was compared to placebo. Follow-up was over a 48-week period.

At week 12, 57% versus 11% who received etanercept or placebo, respectively, achieved the PASI 75 (risk ratio 4.95, 95% confidence interval (CI) 2.83 to 8.65; high-quality evidence). Absolute risk reduction and the number needed to treat to obtain a benefit with etanercept was 45% (95% CI 33.95 to 56.40) and 2 (95% CI 1.77 to 2.95), respectively.

The percentage improvement from baseline of the CDLQI scores at week 12 was better in the etanercept group than the placebo group (52.3% versus 17.5%, respectively (P = 0.0001)). Analysis between the groups showed an effect size that was clinically important (mean difference 2.30, 95% CI 0.85 to 3.75; high-quality evidence). However, means, medians, and minimal important difference results and results of the Pediatric Quality of Life Inventory, Stein Impact on Family Scale, and Harter Self-Perception Profile for Children scores must be interpreted with caution, as they were not prespecified outcomes.

Three serious adverse events were reported, but they were resolved without sequelae. Deaths or other events such as malignant tumours, opportunistic infections, tuberculosis, or demyelination were not reported in the included study.

Also, 13% of participants in the placebo group and 53% in the etanercept group had a PGA of clear or almost clear (risk ratio 3.96, 95% CI 2.36 to 6.66; high-quality evidence) at week 12.

Authors' conclusions

This review found only one RCT evaluating the use of this type of biological therapy. Although the risk of publication bias was high, as we included only one industry-sponsored RCT, the risk of allocation, selection, performance, attrition, and selective reporting biases for all outcomes (except for CDLQI) was low, and no short-term serious adverse events were found.

We can conclude, based on this single included study, that etanercept seems to be efficacious and safe (at least in the short term) for the treatment of paediatric psoriasis. However, as the GRADE approach refers not to individual studies but to a body of evidence, we shall wait for the results of the ongoing studies in a future update of this review. In addition, future studies should evaluate quality-of-life endpoints established a priori and standardise primary outcome measures such as PASI 75, and should include the PGA as a secondary endpoint. Also, collating and reporting adverse events uniformly is required to better evaluate safety.

PLAIN LANGUAGE SUMMARY

Anti-TNF agents for paediatric psoriasis

Background

Psoriasis is a long-term skin disease that may develop at any age. Estimates for the United States and Europe suggest that psoriasis accounts for 4% of skin diseases in children. In most cases, the condition is mild and can be treated with creams. However, a small percentage of children have moderate to severe disease that requires drugs, such as ciclosporin or methotrexate, and some will require injections with newer biological agents, such as anti-TNF (tumour necrosis factor) drugs. Anti-TNF drugs (among them etanercept, infliximab, and adalimumab) are designed to reduce inflammation in the body caused by tumour necrosis factor.

Review question

Are anti-TNF drugs such as etanercept, infliximab, and adalimumab safe and effective for treating moderate to severe psoriasis in children under 18 years of age?

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Study characteristics

We searched for all randomised controlled trials (RCTs) that assessed the efficacy and safety of anti-TNF agents for the treatment of long-term plaque psoriasis in individuals younger than 18 years of age. We searched databases up to July 2015. Only one study (with three phases: a 12-week randomised, double-blind, placebo-controlled phase; a 24-week open-label phase, and a 12-week phase of a randomised, double-blind, withdrawal-retreatment design) investigating one anti-TNF agent (etanercept) in 211 participants met the inclusion criteria.

Key results

Evidence from this single included study suggests that by week 12 etanercept reduced the extent of the psoriasis in children when compared with placebo. Although a few adverse events were reported, they were resolved without subsequent problems. We did not find any evidence on long-term side effects of this drug from this included study.

Quality of the evidence

Although this one RCT provided high-quality evidence for the Physician's Global Assessment and all Psoriasis Area and Severity Index scores (75, 90, and 50) and moderate-quality evidence for quality-of-life outcomes, we found no further randomised studies either evaluating etanercept or comparing other anti-TNF agents, highlighting the need for further well-designed randomised studies involving the use of biological therapies in children and young people with psoriasis. Several studies are ongoing that have not yet been completed or published. We plan to include the results of these in future updates of this review.

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SUMMARY OF FINDINGS FOR THE MAIN COMPARISON *[Explanation]*

Etanercept compared to placebo for paediatric psoriasis

Patient or population: people with paediatric psoriasis
Settings: multicentre
Intervention: etanercept
Comparison: placebo

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Placebo	Etanercept				
PASI 75 Participants achieving a 75% improvement in the Psoriasis Area and Severity Index Follow-up: 12 weeks	**114 per 1000**	**566 per 1000** (323 to 989)	**RR 4.95** (2.83 to 8.65)	211 (1 study)	⊕⊕⊕⊕ **high**	As this review assessed the quality of evidence of just 1 individual trial, a greater body of evidence is needed to make a full recommendation
PASI 50 Participants achieving a 50% improvement in the Psoriasis Area and Severity Index Follow-up: 12 weeks	**229 per 1000**	**745 per 1000** (517 to 1000)	**RR 3.26** (2.26 to 4.71)	211 (1 study)	⊕⊕⊕⊕ **high**	As this review assessed the quality of evidence of just 1 individual trial, a greater body of evidence is needed to make a full recommendation
PASI 90 Participants achieving a 90% improvement in the Psoriasis Area and Severity Index Follow-up: 12 weeks	**67 per 1000**	**273 per 1000** (125 to 597)	**RR 4.10** (1.88 to 8.95)	211 (1 study)	⊕⊕⊕⊕ **high**	As this review assessed the quality of evidence of just 1 individual trial, a greater body of evidence is needed to make a full recommendation

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PGA Participants achieving a PGA of 'clear' or 'almost clear' Follow-up: 12 weeks	**133 per 1000**	**528 per 1000** (315 to 888)	**RR 3.96** (2.36 to 6.66)	211 (1 study)	⊕⊕⊕⊕ **high**	As this review assessed the quality of evidence of just 1 individual trial, a greater body of evidence is needed to make a full recommendation
CDLQI Scores range from 0 to 30. Lower scores indicate better health-related quality of life. Calculations are based on the change from baseline to week 12 in both groups Follow-up: 12 weeks	-	The mean **CDLQI** in the intervention groups was **2.30 higher** (0.85 to 3.75 higher)	-	211 (1 study)	⊕⊕⊕◯ **moderate**[1]	As this review assessed the quality of evidence of just 1 individual trial, a greater body of evidence is needed to make a full recommendation

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CDLQI: Children's Dermatology Life Quality Index; **CI:** Confidence interval; **PASI:** Psoriasis Area and Severity Index; **PGA:** Physician's Global Assessment; **RR:** Risk ratio

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] Downgraded one level due to selective reporting of means, medians, and the minimal important difference, as they were not prespecified in the methods section of the original study.

BACKGROUND

Description of the condition

Psoriasis is a chronic skin disease that may develop at any age. The prevalence of condition is estimated to range from 0.5% to 3.8% worldwide (Augustin 2010; de Jager 2010a; Seyhan 2006; Tollefson 2010). A United Kingdom study of both adults and children and a paediatric population study in the United States demonstrated an incidence of 140 per 100,000 and 40.8 per 100,000, respectively (Huerta 2007; Tollefson 2010). It has been suggested that the incidence of psoriasis in children and adults may be increasing over time (Tollefson 2010). Approximately one-third of people with psoriasis developed the condition before 20 years of age (Ferrándiz 2002; Tollefson 2010). Psoriasis in childhood and adolescence differs from the onset of psoriasis in adulthood, which has led to the concept of 'paediatric onset psoriasis' (POP) in contrast to 'adult onset psoriasis' (AOP) (Raychaudhuri 2000; Sticherling 2011). As in adults, in children chronic plaque psoriasis is the most common subtype, accounting for between 30% and 60% of the reported types in children. It is common for the scalp and face to be affected when it presents. Compared with adults, guttate psoriasis is more frequent in children, as is flexural or inverse psoriasis, often affecting the genital area (Benoit 2007; Leman 2001; Sticherling 2011).

The pathogenesis of psoriasis is still not fully understood, but it is thought to develop in genetically predisposed individuals, since 23.4% to 71% of children have a family history of psoriasis (Silverberg 2009). An environmental trigger, such as a streptococcal infection (Burden 1999; Farber 1999; Marji 2010), has been also described. Psoriasis is a T-cell-mediated disease with elevated levels of pro-inflammatory cytokines, such as interleukin-17 (IL-17) (Chiricozzi 2011; Harper 2009), interferon-γ (IFN-γ) (Cai 2012; Victor 2003), tumour necrosis factor-alpha (TNF-α) (Victor 2003), IL-22, and IL-23 (Cai 2012; Chiricozzi 2014). Blocking the effects of TNF-α with biological therapies has been shown to be therapeutically effective in moderate to severe psoriasis (Blandizzi 2014; Victor 2003).

There is currently no universally agreed outcome measures to assess severity and extent of disease in a paediatric population. By default, the Psoriasis Area and Severity Index (PASI) has been adopted as a measure of disease extent in clinical trials, although its use has never been validated in children (Spuls 2010). In this index, lesion characteristics and affected area are included in a formula that results in a score from 0 to 72 (Spuls 2010), but it is less accurate in younger children due to differences in body surface area (BSA) (Langley 2011).

Other tools used for the assessment of psoriasis in children are the Patient Global Assessment, the seven-point Psoriasis Global Assessment score (Paller 2008; Paller 2010a), and BSA, which is based on the "rule of nines" (the head and neck, each arm, the front and back of each leg, as well as the four trunk quadrants each cover 9% of body surface area with the genitalia covering the final 1% of the body surface area) (Ramsay 1991; Spuls 2010).

The impact of psoriasis on children and their families is less well documented than in adults, but data are emerging in this area showing that there is significant disease impact in these people and their families, mainly due to the associated symptoms of joint pain and itch (Gånemo 2011). A quality of life (QOL) study on 379 children and adolescents aged between 5 and 16 years found QOL impairment scores in psoriasis that were higher than in children with acne or urticaria and similar to children with atopic dermatitis (Beattie 2006).

Regarding the relationship between PASI and PGA and health-related quality of life outcomes in children, only a moderate correlation between PASI and PGA severity scores and Children's Dermatology Quality of Life Index (CDLQI) in paediatric psoriasis was found (de Jager 2010b).

Also, for children with psoriasis, there are limited supporting data for associated comorbidities, such as cardiovascular disease. In recent years, hypertension has been found to be increased in childhood psoriasis (Augustin 2010).

Most psoriasis in children can be easily managed with topical therapies. However, moderate to severe disease can be more difficult to manage due to licensing limitations and the lack of efficacy data related to the use of standard systemic agents and the newer biological therapies (Sticherling 2011; Vogel 2012).

Children with more extensive lesions often require short courses of phototherapy or systemic therapies. The commonly used oral therapies in childhood (as in adults) are ciclosporin, methotrexate, and acitretin (de Jager 2010a). Clinical studies of the use of ciclosporin in childhood psoriasis are scarce; only case reports have been described (Sticherling 2011).

The use of ciclosporin is justified for those with moderate to severe disease, however adequate renal function and blood pressure monitoring must be carried out (Sticherling 2011). Methotrexate is available for longer term use in the paediatric population (Sticherling 2011). Clinical double-blind studies exist for juvenile idiopathic arthritis, and psoriatic arthritis rather than psoriasis. Studies on the treatment of psoriasis in childhood are lacking, and only individual case reports have been published. In addition, acitretin can be used to treat psoriasis in children, but its effects on epiphysial closure and on bone growth limit its use (Sticherling 2011).

The newer biological therapies may be beneficial for the treatment of psoriasis in children. Evidence is required to assess the efficacy of these agents and their side effects in a paediatric population.

Description of the intervention

A biologic or biotechnology-derived product is defined as "a protein or nucleic acid-based pharmaceutical substance used for therapeutic or *in vivo* diagnostic purposes, which is produced by means other than direct extraction from a native (nonengineered) bio-

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logical source" (Walsh 2002). Recently, it has been shown that children with moderate to severe psoriasis, which is poorly controlled with other treatments, may benefit from biologic therapies described below (Sticherling 2011). Currently, there are no US Food and Drug Administration (FDA)-approved systemic treatments for moderate to severe psoriasis in children and adolescents. However, an etanercept study in children over eight years of age resulted in the licensing of the medication in Europe for children over this age (Sticherling 2011).

The anti-TNF class of drugs includes etanercept, infliximab, and adalimumab, which act to down-regulate the biological effect of the cytokine TNF-α, which has been shown to be integral in the pathogenesis of chronic plaque psoriasis (Fallon-Friedlander 2002; Krueger 2004).

These biological therapies have FDA approval for the treatment of other inflammatory disorders affecting children four years of age or older, such as rheumatoid and psoriatic arthritis and Crohn's disease (Fallon-Friedlander 2002; Krueger 2004).

Whilst all these therapies block the biological effects of TNF-α (Krueger 2004), they are different drugs.

The first of these agents to gain FDA approval, infliximab, is a chimeric monoclonal antibody that binds to TNF-α, blocking the binding to receptors, with the consequent inactivation of the inflammatory process, which is thought to play a key role in the pathogenesis of psoriasis (Menter 2004). It is administered via intravenous infusion, and although licensed for use in psoriasis in adults, it is not currently licensed for use in children. Nevertheless, its use in children older than six years of age has been licensed for therapy-refractory Crohn's disease (Menter 2004; Sticherling 2011).

Adalimumab is a fully human monoclonal antibody that binds to TNF-α, blocking its interaction with cell surface TNF receptors (Lapadula 2014). It is licensed only for adults for the treatment of chronic plaque psoriasis. Its use in children older than four years of age has been licensed for polyarticular juvenile idiopathic arthritis (Menter 2004; Sticherling 2011). In 2015, adalimumab was licensed for the treatment of severe chronic plaque psoriasis in children older than four years of age (EMA 2015).

Etanercept is a fusion protein that binds to the extracellular domain of the human TNF-α receptor, inhibiting the binding of TNF-α to cell surface receptors. It is administered twice weekly by subcutaneous injection (Fallon-Friedlander 2002; Krueger 2004). It currently has FDA approval for juvenile idiopathic arthritis in children as young as four years of age and was approved in 2002 for psoriatic arthritis. It is the only TNF-α agent licensed for use in the United Kingdom and Europe for children from eight years of age with moderate psoriasis (Fallon-Friedlander 2002; Krueger 2004). A randomised controlled trial (RCT) of etanercept administered to children for 12 weeks and subsequent long-term data at 96 weeks suggest that the drug is beneficial for psoriasis and appears to be well tolerated (Paller 2008; Paller 2010a).

In addition to direct TNF-α blocking agents, there are other biologics that interfere indirectly with TNF-α cellular release, such as agents targeting T-cells or antigen-presenting cells (alefacept and efalizumab), IL-12/IL-23 blockers (ustekinumab, briakinumab), and phosphodiesterase-4 inhibitors (apremilast) (Elliott 2009; Gordon 2012; Schafer 2012; Weger 2010). Recent emerging biologics for psoriasis (ixekizumab, brodalumab) have also focused on the inhibition of IL-17, which acts synergistically with TNF-α (Chiricozzi 2011; Leonardi 2012; Papp 2012).

How the intervention might work

Tumour necrosis factor-α is an inflammatory cytokine that orchestrates the inflammatory response and the production of adhesion molecules (for example intercellular adhesion molecule 1, P-selectin, E-selectin) and pro-inflammatory molecules (for example IL-1, IL-6, IL-8, NF-kappaB) (Victor 2003). The anti-TNF therapies described reduce the biological activity of this cytokine by down-regulating the stimulated pathways of keratinocyte proliferation and cell adhesion, which drive psoriasis (Krueger 2002; Mittal 2010).

The immune system of some people with psoriasis does not respond to treatment with TNF-blocking agents. This is called primary treatment failure. Other individuals may respond initially, with the treatment becoming less effective, demonstrating secondary treatment failure (Puig 2013). Finally, there is also a paradoxical 'triggering' of psoriasis in a subgroup of people treated with anti-TNF agents for conditions such as rheumatoid arthritis and Crohn's disease (Iborra 2011).

Why it is important to do this review

Children with moderate to severe psoriasis require adequate treatment, and this cannot always be achieved with the conventional systemic therapies described above. Individuals with severe and recalcitrant disease may benefit from biological therapies, which are still relatively new, high-cost drugs each estimated to cost around GBP 10,000 per person per year (NICE 2012).

Evidence is required to assess the efficacy and safety of systemic therapies for children in general, but particularly for these newer biological therapies for which the long-term side effects are unknown. The short-term side effects of these drugs in adults are increasingly well understood and include reactions at the injection site, allergic reactions, and re-activation of infections, particularly tuberculosis (Marji 2010). Also, such long-term effects of these drugs as lymphoma in children have been described (McCroskery 2010). It is therefore important to evaluate the short- and long-term adverse effects of these agents when they are used to treat children with psoriasis.

In this systematic review we looked at the evidence for the efficacy and safety of a subset of biological therapies in children, namely the anti-TNF agents.

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We published the plans for this review as a protocol: Anti-TNF agents for paediatric psoriasis (Sanclemente 2012).

OBJECTIVES

To assess the efficacy and safety of anti-tumour necrosis factor (anti-TNF) agents for the treatment of paediatric psoriasis.

METHODS

Criteria for considering studies for this review

Types of studies

All RCTs that evaluated the efficacy and safety of anti-TNF agents for chronic plaque psoriasis treatment in individuals younger than 18 years of age.

Types of participants

In this review, we included any children (under 18 years old) with a clinical or histopathological diagnosis of chronic plaque psoriasis. This included types of psoriasis where there was an indication for the use of anti-TNF agents, that is children with moderate to severe plaque psoriasis who did not respond to, had a contraindication to, or who did not tolerate other systemic therapies, including ciclosporin, methotrexate, or photochemotherapy using psoralen (PUVA).

Types of interventions

Any anti-TNF agent (or any agent that acts to block the biological activity of TNF-α) at any dosage, administered either orally, subcutaneously, or intravenously, either alone or in combination with additional agents. The considered comparators were:

1. any alternative active treatment (PUVA, narrow-band ultraviolet B, acitretin, methotrexate, ciclosporin A, or any other biologic);
2. placebo; or
3. no treatment.

Types of outcome measures

Primary outcomes

1. Investigator-assessed improvement: proportion of participants achieving PASI 75. (If this scale was not available, we planned to use PASI 50 or PASI 90) (see Differences between protocol and review).
2. Improvement in quality of life: assessed using a recognised instrument (generic, dermatology-specific (such as CDLQI), Pediatric Quality of Life Inventory, or a disease-specific instrument).
3. Proportion of participants having any minor or major adverse outcomes.

Secondary outcomes

1. Proportion of participants achieving PASI 50, PASI 90, or both.
2. Investigator-assessed improvement: PGA.
3. Investigator-assessed improvement: affected BSA.
4. Participant-assessed improvement: Patient Global Assessment.
5. Psoriasis remission, recurrence, and resource use.

Timing of outcome assessment: We planned to consider main and secondary endpoint data (PASI 50, PASI 90, PGA, BSA, and adverse events) at less than three months, between three months and one year, and after one year. We grouped these into short, medium, and long term, according to how they were assessed in the trials.

Search methods for identification of studies

We aimed to identify all relevant RCTs regardless of language or publication status (published, unpublished, in press, or in progress).

Electronic searches

We searched the following databases up to 20 July 2015:

- the Cochrane Skin Group Specialised Register using the search strategy in Appendix 1;
- the Cochrane Central Register of Controlled Trials (CENTRAL) 2015, Issue 6, in the Cochrane Library using the strategy in Appendix 2;
- MEDLINE via OVID (from 1946) using the strategy in Appendix 3;
- Embase via OVID (from 1974) using the strategy in Appendix 4; and
- LILACS (Latin American and Caribbean Health Science Information database, from 1982) using the strategy in Appendix 5.

Trials registers

We searched the following trials registers on 9 July 2015, using the search terms in Appendix 6:

- The metaRegister of Controlled Trials (www.controlled-trials.com).
- The US National Institutes of Health ongoing trials register (www.clinicaltrials.gov).

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- The Australian New Zealand Clinical Trials Registry (www.anzctr.org.au).
- The World Health Organization International Clinical Trials Registry Platform (www.who.int/trialsearch).
- The ISRCTN Register (http://isrctn.org).
- Netherlands Trial Register (http://www.trialregister.nl/).
- UMIN Clinical Trials Registry (UMIN-CTR) (http://www.umin.ac.jp/ctr).
- NIH Clinical Research Studies (http://clinicalstudies.info.nih.gov).
- Chinese Clinical Trial Registry (http://www.chictr.org.cn/index.aspx).
- Clinical Trials Registry - India (http://ctri.nic.in/Clinicaltrials/advancesearchmain.php).
- Registro Público Cubano de Ensayos Clínicos (http://rpcec.sld.cu/).
- Registro Nacional de Ensayos Clínicos del Peru (http://www.ins.gob.pe).
- The Latin American Clinical Trial Registry (http://www.latinrec.org), but found it to be currently inactive.

Searching other resources

References from included studies

We scanned the bibliographies of included and other important studies and key review articles for further references to relevant trials.

Unpublished literature

We corresponded with the following pharmaceutical companies in order to obtain information about unpublished or ongoing trials: Abbott and Amgen Inc (in 2002 Immunex was acquired by Amgen Inc). In the United States, etanercept (Enbrel®) has been co-marketed by Amgen and Pfizer, and Wyeth (which is part of Pfizer) was its sole marketer outside the United States excluding Japan. We corresponded with the following pharmaceutical companies, which we believe market or distribute anti-TNF therapies, in order to obtain information about unpublished or ongoing trials: Abbott; Amgen Inc; Pfizer; Wyeth (which is part of Pfizer); UCB Inc; Janssen-Cilag Ltd, which is now a subsidiary of Johnson & Johnson; UCB S.A.; Merck Serono; and Janssen Biotech, Inc.

Conference proceedings

We scanned the abstracts of the American Academy of Dermatology from February 2011 through to March 2015, and the European Academy of Dermatology and Venereology meetings from September 2011 through to September 2014. We also scanned the abstracts from the 23rd World Congress of Dermatology held in Vancouver, Canada, in June 2015.

Adverse effects

We reviewed the US Food and Drug Administration quarterly reports from April 2008 through to June 2015 without the use of a specific search term. We consulted the European Medicines Agency reports up to June 2015 to obtain safety data (see search strategy in Appendix 7).

We also considered adverse and side effects described in our included and excluded studies.

Data collection and analysis

Selection of studies

Two review authors (GS and JC) checked the titles and abstracts identified from the searches. After reviewing the abstracts, they retrieved the full text of potentially relevant studies for assessment. Both review authors independently assessed if, from reading the full text, each study met the predefined selection criteria. A third review author (RM) was available to resolve any differences through discussion. We have listed excluded studies and reasons for their exclusion in the Characteristics of excluded studies tables.

Data extraction and management

Two review authors (GS and JC) independently performed data extraction. One review author (GS) entered final data into Review Manager (RevMan 2014), and a second review author (JC) checked the data. A third review author (RM) was available to resolve any differences through discussion. We attempted to obtain clarification regarding unclear data from the trial authors. The review authors were not blinded to the names of trial authors, journals, or institutions.

Assessment of risk of bias in included studies

We used The Cochrane Collaboration's tool for assessing risk of bias (Higgins 2011). We evaluated the following relevant domains:

1. sequence generation;
2. allocation concealment;
3. blinding of participants, personnel, and outcome assessors;
4. incomplete data for outcomes (participants lost to follow-up, intention-to-treat analysis (participants analysed in the groups to which they were randomised), and if differences between comparison groups were found);
5. selective reporting of outcomes; and
6. biases from other sources.

Specific methodological assessment included the following: aims clearly defined, information about interventions (drug doses and treatment duration) and outcome measures clearly stated; whether participants were assessed for baseline balance in terms of age, sex, duration of psoriasis, and the severity of the disease; whether the statistical analyses used were appropriate for the types of variables.

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Measures of treatment effect

We defined successful treatment as the proportion of participants obtaining a PASI 75. If this was not available, we used PASI 50, PASI 90, or a PGA of "almost clear" or better.
For dichotomous variables, we expressed the results as risk ratios and 95% confidence intervals (CI). For continuous variables, we planned to use the mean difference with its 95% CI. We also expressed the results as number needed to treat for an additional beneficial outcome, where appropriate.

Unit of analysis issues

We planned to include only parallel design trials, thus the unit of analysis was the child of each trial.

Dealing with missing data

We contacted trial authors in order to obtain missing data. If we were unable to obtain missing data, we planned to conduct sensitivity analyses, imputing missing data considering the best- and the worst-case scenario.

Assessment of heterogeneity

We planned to evaluate clinical, statistical, and methodological heterogeneity. However, we were unable to do this since we identified only one eligible study.
If future updates of this review include new studies, we will assess heterogeneity using the I^2 statistic (Higgins 2011). If substantial heterogeneity (I^2 greater than 50%) is found for the primary outcomes, we will explore reasons for heterogeneity, such as disease severity, dosage, and duration of treatment. Where it is not possible to perform a meta-analysis, we will summarise the data for each trial qualitatively.

Assessment of reporting biases

We planned to explore funnel plot asymmetry following the approach of Egger if there had been a sufficient numbers of included studies (at least 10) (Egger 1997).
If future updates of this review include new studies and at least 10 studies are added, we will assess reporting biases using the funnel plot method and perform tests to evaluate its asymmetry as required.

Data synthesis

We planned to calculate a pooled intervention effect estimate as a weighted average of the intervention effects estimated in the individual studies. We planned to use risk ratios with a random-effects model for the pooling of dichotomous outcomes, and standardised mean differences with 95% CI to pool continuous outcomes where different scales or cut-offs have been used.

Subgroup analysis and investigation of heterogeneity

If statistical heterogeneity was present and there were an adequate number of studies, we planned to investigate the potential influence of some variables by conducting subgroup analyses with respect to:

- sex;
- disease duration;
- psoriasis severity; and
- body mass index.

In the future, if there are a sufficient number of included studies we will perform subgroup analysis taking into account these variables.

Sensitivity analysis

If there were an adequate number of studies, we would have performed sensitivity analyses based on separation of studies according to the risk of bias of allocation concealment (high, low, or unclear) and blinding of outcome assessment (high, low, or unclear) (Higgins 2011). However, the number of included studies was inadequate to perform sensitivity analyses.
If future updates of this review include new studies, we will assess reporting biases, as planned.

RESULTS

Description of studies

See Characteristics of included studies and Characteristics of excluded studies.

Results of the search

We retrieved 2369 records from our database searches, and were left with 2205 following removal of duplicates. We screened the titles and abstracts of these and excluded 2185 records that did not meet our inclusion criteria. Where possible, we obtained the full text of the remaining 20 records. We excluded two studies that were not RCTs (see Characteristics of excluded studies). Five studies (reported in seven references) were ongoing (see Characteristics of ongoing studies). We included one trial reported in 11 references in this review.
See Figure 1 for a summary of our screening process. After scanning the bibliographies of included studies, we did not find any additional relevant references. We obtained replies from all the pharmaceutical companies we contacted, except from UCB S.A. and Amgen Inc.

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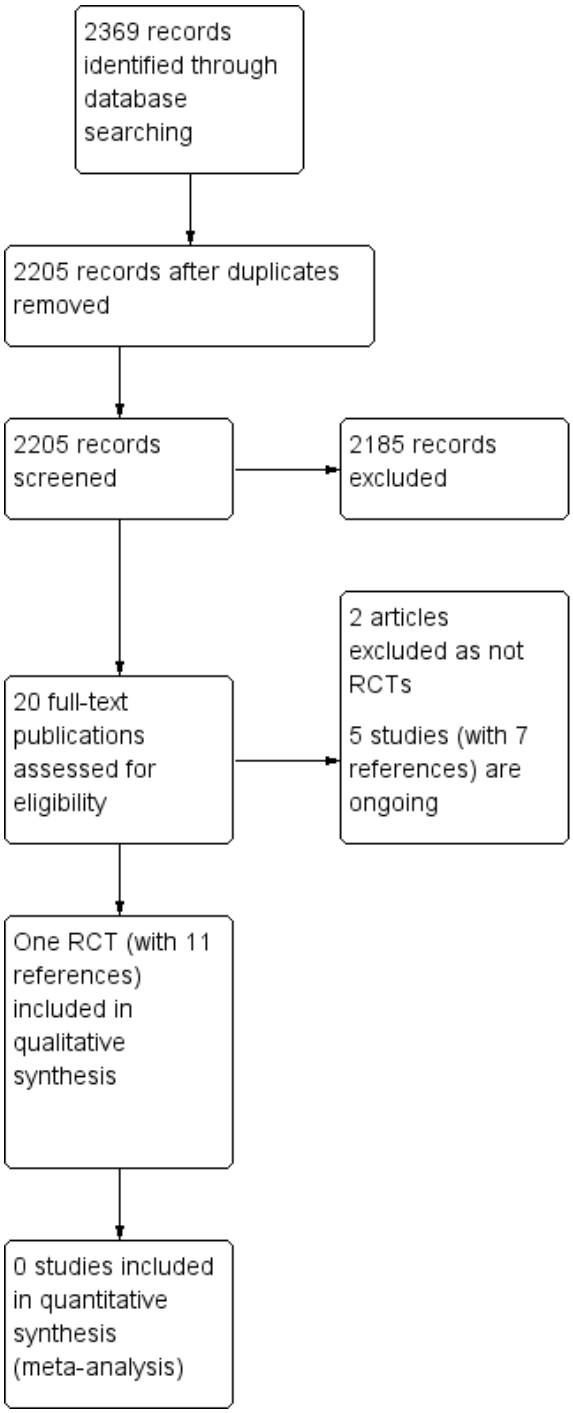
Figure 1. Study flow diagram.



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Included studies

For a full description of the included trial see Characteristics of included studies.

We found one study that fulfilled our inclusion criteria with 11 associated publications. Paller 2008 was marked as the primary reference of this group of publications, which assessed the efficacy and safety of etanercept in children and adolescents with moderate to severe plaque psoriasis.

The other publications of this trial are by Langley, which showed the health-related quality of life (HRQoL) data from the original study (Langley 2011); a post hoc (non a priori) subgroup analysis according to the age of participants of the included study by Landells (Landells 2010); the safety and efficacy results of the final 12-week, randomised, double-blind withdrawal and retreatment phase of the included study by Siegfried (Siegfried 2010); the report of a 96-week open-label, long-term extension of the included RCT that was also by Paller (Paller 2010a); another publication by Paller describing the PASI 50 and PASI 75 results by subgroup according to age, gender, BSA, baseline PASI, baseline PGA, disease duration, and previous systemic therapy or phototherapy (Paller 2010b); and five abstracts presented at several meetings regarding different aspects of the included study (Levy 2005; Paller 2007; Paller 2010c; Paller 2010d; Siegfried 2006). According to information provided by Dr. Amy Paller and at the time this review was written, no trials in paediatric psoriasis were ongoing in the United States.

Design

The included study had an initial 12-week randomised, double-blind, placebo-controlled phase (day 1 through to week 12) to assess efficacy; a 24-week open-label phase (weeks 13 through to 36) to evaluate the efficacy of etanercept therapy in all participants; and a 12-week phase of a randomised, double-blind, withdrawal-retreatment design (weeks 37 through to 48) to evaluate withdrawal effects of the study drug and subsequent retreatment (Paller 2008).

Another associated publication described results after 48 weeks of the former trial in an open-label design fashion (Paller 2010a).

Participants

The study included 211 participants (106 in the treatment arm, 105 in the placebo arm) with paediatric psoriasis from 4 to 17 years of age, who must have had stable moderate to severe plaque psoriasis at screening, which is defined as a PASI score of at least 12; a static PGA of at least 3 (where 0 indicates clear and 5 indicates severe psoriasis); BSA-psoriasis involvement of at least 10%; and a history of psoriasis in the last 6 months. They must also have had a poor response or a contraindication to previous or current treatment with phototherapy or systemic psoriasis therapy (for example, retinoids, methotrexate, or ciclosporin) or poorly controlled psoriasis with topical therapy.

The median age of enrolled participants was 13 years, and 64% of participants were older than 11 years of age.

The exclusion criteria of this study were lactation or pregnancy; previous treatment with anti-TNF agents; guttate, erythrodermic, or pustular psoriasis; major concurrent medical conditions; other skin conditions that would interfere with study evaluations; systemic psoriasis medications; treatment with psoralen and ultraviolet A (PUVA), ultraviolet A, ultraviolet B; oral, parenteral, or topical corticosteroids, D analogue preparations or topical vitamin A, calcineurin inhibitor or anthralin within a 14-day washout period before the study; and use of any biologic agent within a 30-day washout period before the study. Participants were allowed to use low to moderate-potency topical steroids on intertriginous areas and in the scalp.

Setting

Participants were recruited at 42 sites located in the United States and Canada.

Interventions

Participants in the treatment arm received once-weekly subcutaneous injection of etanercept at a dose of 0.8 mg per kilogram of body weight (maximum dose: 50 mg), whereas participants in the placebo arm received matching placebo. Follow-up was initially over a 48-week period in the original RCT (Paller 2008), but the active intervention was provided in an open-label fashion later on (Paller 2010a).

Outcomes

The primary outcome of the sole included study was PASI 75 at week 12. Secondary efficacy endpoints were PASI 90, PASI 50, a PGA of clear or almost clear (score of 0 or 1), and CDLQI at week 12, which were evaluated at weeks 2, 4, 8, and 16 and every 4 weeks thereafter, as well as the improvement of the mean percentage in PASI score at all time points.

Participants were randomised to etanercept or placebo for 12 weeks. Thereafter at week 13 all participants received etanercept in an open-label scheme until week 36. At week 37, participants who achieved 75% improvement in PASI from baseline (PASI 75) were re-randomised for a double-blind withdrawal and retreatment period for another 12 weeks. During this phase, participants

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received either placebo or etanercept as long as they maintained a clinical response, defined as PASI 75. Participants whose response fell below PASI 75 were retreated with etanercept in an open-label fashion until study completion. PASI 75 was assessed every four weeks during the withdrawal and retreatment period.

Patient-reported outcomes in the Langley publication included the CDLQI, Pediatric Quality of Life Inventory (PedsQL), Stein Impact on Family Scale, and Harter Self-Perception Profile for Children. The CDLQI was administered at baseline and at weeks 2, 4, and 12 during the double-blind period. The other three scales were completed at baseline and at week 12 (Langley 2011).

Safety outcomes included non-serious adverse events, serious adverse events, as well as non-serious infections, serious infections, malignancies, injection-site reactions, laboratory results, etanercept concentration in serum, and disease recurrence during the withdrawal period, which was defined as "the worsening of PASI by more than 125% from baseline within 3 months after discontinuation of treatment".

In the 96-week open-label trial extension, the primary endpoint was the occurrence of adverse events and secondary efficacy endpoints included PASI 50, -75,-90, CDLQI, improvement in joint pain, and static Physician's Global Assessment (Paller 2010a).

Excluded studies

We excluded two studies: One was a report of paediatric psoriasis cases treated with etanercept that was not a RCT (Beikert 2012), and the other was a retrospective study (Alsuwaidan 2011). (See Figure 1.)

Ongoing studies

We identified five ongoing trials by searching trials registers (see Characteristics of ongoing studies for details). One ongoing study, NCT01251614, has been presented in several preliminary publications, two as meeting abstracts: one, Papp 2014, presented the design of the study and the PGA, CDLQI, and itch visual analogue scale improvements according to baseline characteristics of the participants, and the other, Papp 2015, included efficacy and safety results presented as a poster during the last World Dermatology Congress held in Vancouver, Canada in June 2015. Once this ongoing trial is published, we will consider it for inclusion in future updates of this review.

Risk of bias in included studies

Please see Figure 2, which shows our judgement of the risk of bias for the following domains.

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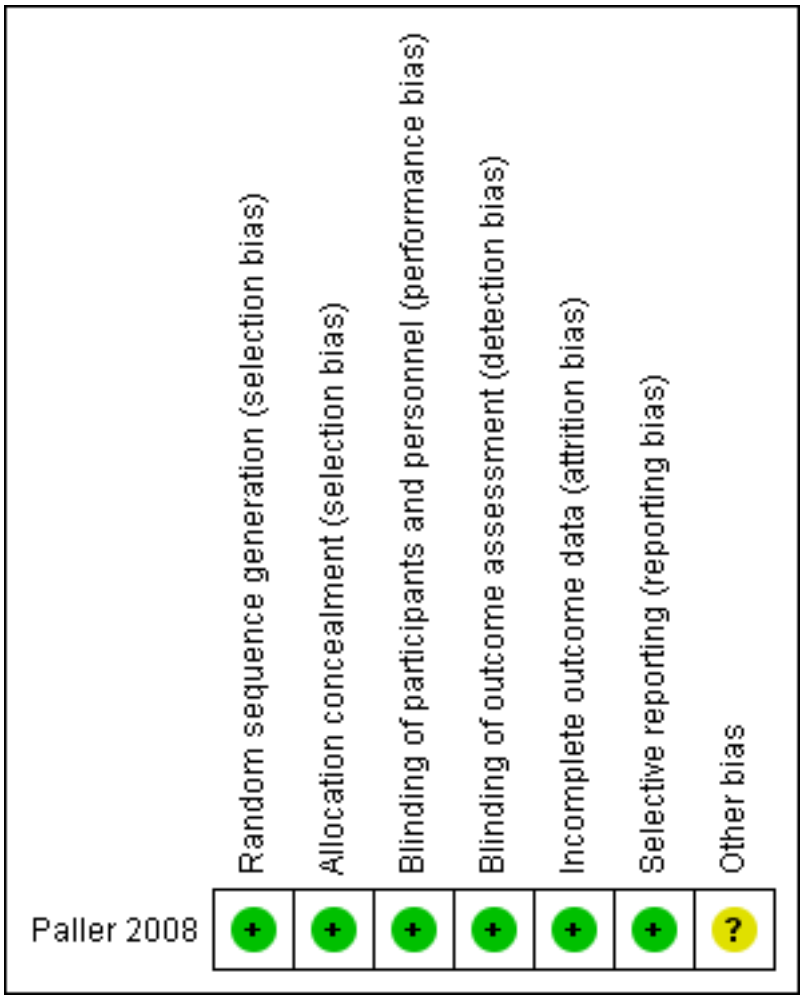
Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



Allocation

We judged the original published study to be at low risk of bias for random sequence generation, as the participants underwent randomisation in a 1:1 ratio by an interactive voice-response system (Paller 2008). According to information provided by Pfizer, Amgen generated the allocation sequence, so the identity of the investigational product assigned to participants was concealed using an interactive voice-response system.

Blinding

The study was described as "double-blind" in the abstract and methods, but it was not clear who was blinded and whether blinded outcome assessment was attempted. We therefore contacted the main author and Pfizer, who confirmed that all participants, study site personnel, and Amgen staff were blinded until the data up to week 12 was finalised. They confirmed that the outcome evaluators were dermatologists or dermatologists in training, who were certified in the use of PASI training materials and blinded as outcome assessors.

Incomplete outcome data

In the original study, analysis was performed according to the intention-to-treat principle (ITT) during the first 12 weeks, thus bias was avoided. However, analysis of the 12-week randomised, double-blind withdrawal and retreatment period (over the weeks 37 to 48) was not performed according to the ITT principle.

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We contacted one of the trial authors to try to obtain trial-level data, which was not originally reported. Although we received a reply, the trial author was not able to provide any further data and referred us to the pharmaceutical company, who was the sponsor of the only included study (Amgen-Immunex). We finally obtained a reply from Pfizer (which comarkets etanercept with Amgen in the United States), but they replied that only the data described in the primary publication was available, as follows: "A non response imputation was applied to post-baseline data that were missing and to all efficacy endpoints after patients entered the escape group; missing data of binary endpoints were imputed as non-responses, and missing data of continuous endpoints were imputed to include all baseline values".

Selective reporting

There was no evidence of selective reporting in this single included study.

Other potential sources of bias

Participants had stable moderate to severe plaque psoriasis at screening (defined as a PASI score equal to or greater than 12); stable disease; PGA of at least 3; BSA-psoriasis involvement of at least 10%; a history of psoriasis in the last 6 months; and previous or current treatment with phototherapy or systemic psoriasis therapy (for example retinoids, MTX, or ciclosporin) or poorly controlled psoriasis with the use of topical therapy.

The control arm had slightly lower disease duration at 5.8 years compared to 6.8 years in the intervention group. More participants had a history of previous systemic therapy or phototherapy in the control group at 59%, versus 55% in the intervention group, and there was more psoriatic arthritis in the control group (13% versus 5%) at baseline. Although it is unlikely that these differences between the groups were clinically relevant, it remains unclear if the higher percentage of participants with psoriatic arthritis in the placebo group had an impact on CDLQI scores at week 12. Participant demographics, PASI score, affected percentage of BSA, and PGA prior to entry into the study did not differ between the two groups.

This was the only RCT found, and it was an industry-sponsored trial. We therefore sought out missing or unclear information initially by contacting the principal investigator and thereafter by contacting the pharmaceutical laboratory (Pfizer), which provided clearer information in April and May 2013 regarding sequence allocation, allocation concealment, blinding of participants and personnel, and blinding of outcome assessment.

Effects of interventions

See: **Summary of findings for the main comparison** Etanercept compared to placebo for paediatric psoriasis

The only comparison was between etanercept and placebo. Our prespecified timings were: less than three months, between three months and one year, and after one year. We grouped these into short, medium, and long term, according to how they were assessed, so these fit well with the main and secondary endpoint data in the original included study, which were evaluated at 12 (short term), and at 24, 36, and 48 weeks (medium term). Long-term data was reported in one of the publications associated with the primary study (Paller 2010a), in which the authors describe an open-label extension phase of 96 weeks, after the former 48 weeks of the original study.

We expressed efficacy results as risk ratios (RR) with their respective 95% CI, and for such calculations, events obtained in all scales were labelled as improvement. For CDLQI, the percentage change towards improvement at week 12 was presented, as reported in the original study (Paller 2008). For this outcome, we also calculated the mean difference (MD) between groups according to data presented in another publication of the included study (Langley 2011). No meta-analyses were possible, but we have presented the results for primary endpoints using forest plots.

As several trials of anti-TNF agents in paediatric psoriasis are ongoing, in future updates of this review we plan to perform meta-analyses if there are sufficient numbers of included studies.

Primary outcomes

1) Investigator-assessed improvement: proportion of participants achieving PASI 75

PASI corresponds to the Psoriasis Area and Severity Index. PASI 50 and PASI 75 mean improvements in the PASI of 50% and 75%, respectively, when compared to baseline.

At week 12 (short term), 60 out of 106 participants (57%) who received etanercept achieved PASI 75 compared to 12 out of 105 (11%) who received placebo (RR 4.95, 95% CI 2.83 to 8.65; high-quality evidence) (Analysis 1.1, Figure 3). The reduction of the absolute risk and the number needed to treat to obtain a benefit with etanercept was 45% (95% CI 33.95 to 56.40) and 2 (95% CI 1.77 to 2.95), respectively. In subgroup analysis and at week 12, 38 out of 59 participants (64%) of the lower-dose (0.8 mg/kg) group (37 children and 22 adolescents) achieved PASI 75, as compared with 22 out of 47 participants (47%) receiving the higher dose of etanercept (maximum 50 mg) (1 child and 46 adolescents). The response rate of PASI 75 was 58% in children and 56% in adolescents in the etanercept group at week 12 (short term) (Paller 2008).

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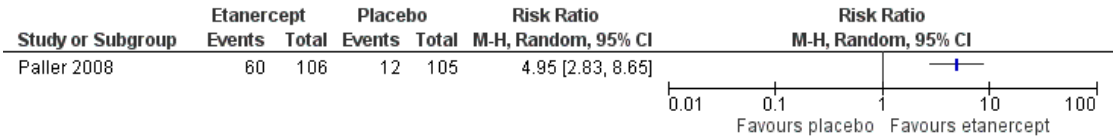
Figure 3. Forest plot of comparison: 1 Etanercept vs Placebo, outcome: 1.1 Achievement of PASI 75 at week 12.



During the open-label period (week 12 through to week 24) (medium term), all participants received etanercept without blinding. Among these, 64 out of 103 participants (62%) in the original placebo group and 72 out of 105 participants (69%) in the original etanercept group achieved PASI 75, which was maintained to week 36.

At week 36, "94% of individuals in each treatment group began this phase with a PASI 75 response" (Paller 2008). From this point, 138 out of 211 participants started a withdrawal-treatment period (week 36 through week 48), in which participants were randomly assigned either to continue etanercept or to switch to placebo. After this period and at week 48, 29 out of 69 participants (42%) assigned to placebo at week 36 lost their PASI response (and were switched to etanercept) compared with 19% assigned to etanercept (Siegfried 2010).

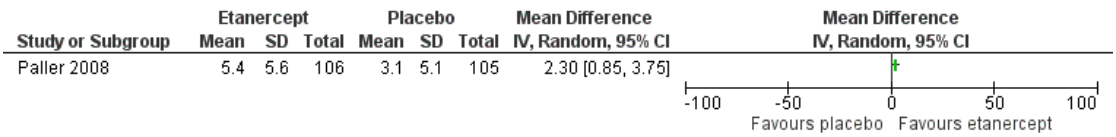
After week 48, an extension study period was added, in which only 126 out of 211 participants remained in the study at 96 weeks (Paller 2010a). Sixty-one percent of participants in this extension study achieved PASI 75 at week 96 (Paller 2010a). In this phase of the study, sensitivity analysis was performed, showing a PASI 75 in 58% of participants using the last observation carried forward (LOCF) imputation method, and 46% using imputation according to treatment failure.

2) Improvement in quality of life

According to the HRQoL published study (Langley 2011), the CDLQI was assessed at baseline and at weeks 2, 4, and 12 during the double-blind period. The cartoon version of the CDLQI was completed by children 4 to 12 years of age. Adolescents 13 to 17 years of age completed the written version. In the included study at week 12 participants in the etanercept group demonstrated greater improvement from baseline in total CDLQI scores when compared to the placebo group (52.3% (median 66.7%) versus 17.5% (median 15.5%), respectively (P = 0.0001) (Langley 2011). Indeed, participants with PASI 75 at week 12 who were treated with etanercept had CDLQI total score improvements at weeks 2, 4, and 12 compared to participants treated with etanercept who did not achieve PASI 75 (Langley 2011). At week 36, the mean improvements in CDLQI were 63% and 59% for the original etanercept group and the placebo group, respectively.(Langley 2011). The CDLQI total scores at baseline and weeks 24, 48, 72, and 96 were 59.5%, 55.0%, 59.2%, 57.5%, and 61.1%, respectively compared to an improvement of mean percentages of 59.5% at baseline, 55% at 24 weeks, 57.3% at 48 weeks, 51.7% at 72 weeks, and 54.9% at 96 weeks using the imputation method of the LOCF, whereas using treatment failure imputation mean percentages were 59.5%, 49.3%, 50.7%, 45.2%, and 44.5%, respectively (Paller 2010a).

Our assessment of the MD between groups according to the data described in the Langley 2011 publication showed an improvement in quality-of-life scores in participants treated with etanercept (Figure 4; Analysis 1.2), as the CDLQI minimally important difference (MID) was established to be 2.5 (Langley 2011; Lewis-Jones 1995). Although the MID was also reached in the placebo group, the effect size was clinically important (MD 2.30, 95% CI 0.85 to 3.75; moderate quality evidence). Also, as shown in Langley 2011, when median values were compared, only etanercept-treated participants achieved the MID. However, such analysis of the means, medians, and MID and the following participant-reported outcomes endpoints were only exploratory, as they were not specified a priori.

Figure 4. Forest plot of comparison: 1 Etanercept vs Placebo, outcome: 1.2 Children's Dermatology Life Quality Index (CDLQI) response. (Data were extracted from Langley 2011. Means calculation for each group was not a prespecified outcome.)



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The PedsQL was also assessed at baseline and at week 12 during the double-blind period. Children 4 to 7 years of age had caregiver or parent assistance for both tests. Mean total PedsQL scores were similar in both the etanercept and placebo groups at baseline (74.8 and 76.1, respectively), but at week 12 significant improvement was not found, although slightly higher mean PedsQL total scores were found for the etanercept group versus the placebo group (81.7 and 79.8, respectively).

The Stein Impact on Family Scale assessed the impact of psoriasis on the lives of participants' families. During the 12-week double-blind phase, caregivers or parents completed the questionnaire, obtaining similar scores at baseline (etanercept-group mean total score: 46.3; placebo-group mean total score: 46.1) compared to week 12 (etanercept-group mean total score: 48.2; placebo-group mean total score: 47.4).

The Harter Self-Perception Profile for Children (with two versions according to participant's age) evaluated the impact of psoriasis on participants' self esteem. No improvement was found in this scale over time (Langley 2011).

3) Proportion of participants having any minor or major adverse outcomes

In the first published study (Paller 2008), the proportion of participants having adverse events was not specified. Adverse outcomes were depicted as "exposure-adjusted rates for which there were at least 10 events per 100 patient-years in the etanercept group" (Paller 2008). Also, as described in the article, "the number of exposure-years was 18.8 for the placebo group and 164.8 for the etanercept group" (Paller 2008).

The rates of non-infectious adverse events corresponded to "430.5 per 100 patient-years for placebo and 287.6 per 100 patient-years for etanercept" (Paller 2008). Infection rates varied from 229.3 per 100 patient-years in the etanercept group to 308.3 per 100 patient-years in the placebo group. The majority were not serious, except for 10 events (placebo group: 3; etanercept group: 7). Reactions in the injection site were not serious and generally transient. During the double-blind phase of the study, the most common events were upper respiratory tract infection, nasopharyngitis, and headache. Overall, no serious adverse events occurred during the placebo-controlled phase.

During the open-label phase of treatment, the only information that was provided in the first published study included three serious adverse events that were observed: a 7-year-old girl with a history of asthma had a basilar pneumonia requiring hospitalisation, intravenous antibiotics, and etanercept discontinuation; a 9-year-old with gastroenteritis and dehydration required hospitalisation; and a 14-year-old with a haemorrhagic ovarian cyst required surgical removal and etanercept discontinuation (Paller 2008). No sequelae were reported after these adverse events were resolved. No deaths, demyelination events, malignant tumours, tuberculosis, or opportunistic infections were reported (Paller 2008). Three participants had abnormal haemoglobin concentrations (a grade 3 toxic effect) that self resolved. No grade 4 toxic effects were reported in either group (Paller 2008).

During the withdrawal-retreatment period, no serious adverse events were encountered, and no participant withdrew as a consequence of an adverse event (Siegfried 2010).

In the open-label phase of the original trial (from week 48 to week 96), adverse events occurred in at least 5% of participants, with 80.1% of participants having one or more adverse events (upper respiratory tract infections in 24.9%, nasopharyngitis in 17.1%, streptococcal pharyngitis in 12.7%, headache in 11.6%, and sinusitis in 10.5%) (Paller 2010a). Through the 96-week extension trial, two participants withdrew from the study due to an adverse event or infection not related to etanercept (sinusitis and Crohn's disease), and no deaths, opportunistic infections, or malignancies were reported (Paller 2010a).

Secondary outcomes

1) Proportion of participants achieving PASI 50, PASI 90, or both

More participants in the etanercept group versus the placebo group, 79 out of 106 (75%) versus 24 out of 105 (23%), respectively, achieved PASI 50 (RR 3.26, 95% CI 2.26 to 4.71; high-quality evidence; Analysis 1.3), and PASI 90 occurred in 29 out of 106 participants (27%) in the etanercept group versus 7 out of 105 participants (7%) in the placebo group (RR 4.10, 95% CI 1.88 to 8.95; high-quality evidence; Analysis 1.4).

In the etanercept group at week 12, the response rates of PASI 50 and PASI 90 were 76% and 32%, respectively, in children, and 74% and 25%, respectively, in adolescents.

The study authors included in the analysis the following participants who achieved PASI 75 at week 36: 2 out of 10 participants in the original placebo group and 5 out of 16 participants in the original etanercept group who did not achieve PASI 50 at week 24, and who opted to receive topical standard-care therapy. There was an increase in the number of participants who achieved PASI 90 and PASI 50 at 24 and 36 weeks (medium term) compared to such results obtained at week 12. Although the study authors did not show if the differences in these measures were statistically significant, according to the article, significant overall improvement was obtained in PASI from baseline when both groups were compared from week 2 (22% in the etanercept group versus 5% in the placebo group, $P < 0.001$) through to week 12 (68% versus 21%, $P < 0.001$) (Paller 2008). Likewise, authors reported "71% and 76% of the mean percentage of PASI improvement at weeks 24 and 36, respectively, in the original placebo group, and 77% and 77%, respectively, in the original etanercept group" (Paller 2008). Actual numbers were not reported in the article.

PASI 50 and 90 obtained at week 96 (long term) in the open-label

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phase of the primary study were 89% and 30%, respectively (Paller 2010a). In this study, sensitivity analysis was performed, showing PASI 50 and 90 scores of 85% and 29%, respectively, using the LOCF imputation method, and 68% and 23%, respectively, using imputation according to treatment failure (Paller 2010a).

2) Investigator-assessed improvement: the PGA

Physician's Global Assessment (PGA) scores ranged from 0 (clear) to 5 (severe psoriasis). A score of equal to or greater than 3 indicated moderate to severe psoriasis. At baseline, 105 out of 106 participants (99%) in the etanercept group and 104 out of 105 participants (99%) in the placebo group had moderate to severe disease, according to the PGA. Fourteen out of 105 participants (13%) in the placebo group and 56 out of 106 participants (53%) in the etanercept group had a PGA of clear or almost clear (RR 3.96, 95% CI 2.36 to 6.66; high-quality evidence; Analysis 1.5) at week 12, and improvement was seen as early as week 4.

Although the study authors did not show if the differences were statistically significant, 58 out of 103 participants (56%) in the original placebo group had a PGA of clear or almost clear, and in the original etanercept group, the PGA was clear or almost clear in 60 out of 105 participants (57%) at week 24, and in 56 out of 105 participants (53%) at week 36**.**

During the open-label phase of the primary study and at 96 weeks (long term), a PGA score of clear or almost clear was 47%, and sensitivity analysis showed a variation from 48% using LOCF imputation to 36% according to treatment failure imputation (Paller 2010a). Joint pain assessment (which was another secondary endpoint included in the 96-week extension trial) could be evaluated only in 36 participants (20%), therefore analysis of this outcome was inconclusive (Paller 2010a)

3) Investigator-assessed improvement: affected body surface area

Although the percentage of affected body-surface area was described at baseline and before the withdrawal-retreatment period (second randomised treatment), no data for statistical analysis was available in the original included study.

4) Participant-assessed improvement: Patient Global Assessment

We did not assess this outcome.

5) Remission, recurrence, and resource use data

No economic data was available. Participant follow-up in the original included study lasted just until week 48, so recurrence and remission information after that time was not available.

DISCUSSION

Summary of main results

This systematic review examines and summarises the evidence regarding the efficacy of anti-TNF agents in paediatric psoriasis. Eleven publications described one RCT (Landells 2010; Langley 2011; Levy 2005; Paller 2007; Paller 2008; Paller 2010a; Paller 2010b; Paller 2010c; Paller 2010d; Siegfried 2006; Siegfried 2010), which compared the use of etanercept versus placebo using the achievement of PASI 75 as the primary outcome. Regarding secondary outcomes, better CDLQI, PASI 50, and PASI 90 scores were found in the etanercept group compared to the placebo group at week 12 (Langley 2011). The risk of bias of the included RCT was low across the majority of the domains assessed, and although we rated publication bias down to the lowest score because we included only one industry-sponsored study, the GRADE approach still showed high-quality evidence for all outcomes (except for the assessment of quality of life, which was downgraded to moderate-quality evidence).

Fifty-seven percent who received etanercept versus 11% who received placebo achieved the PASI 75 (RR 4.95, 95% CI 2.83 to 8.65; high-quality evidence). Absolute risk reduction and the number needed to treat to obtain a benefit with etanercept was 45% and 2 (95% CI 1.77 to 2.95), respectively. Also, 13% of participants in the placebo group and 53% in the etanercept group had a PGA of clear or almost clear (RR 3.96, 95% CI 2.36 to 6.66; high-quality evidence) at week 12. A percentage improvement of CDLQI scores was found in the etanercept group versus the placebo group at week 12 (52.3% versus 17.5%, respectively; P = 0.0001), and analysis showed an effect size that was clinically important (MD 2.30, 95% CI 0.85 to 3.75; high-quality evidence). However, results of quality-of-life scores, other than the percentage of improvement from baseline in the CDLQI through week 12, must be interpreted with caution, as they were not prespecified outcomes.

The most common adverse events during the double-blind period of the only included RCT were non-serious. During the open-label treatment, three serious adverse events were observed, but these were all resolved without sequelae or death. During the withdrawal-retreatment period, no serious adverse events were reported, and no participants withdrew as a consequence of an adverse event (Siegfried 2010).

Trial authors may depict adverse events as exposure-adjusted rates. The exposure-adjusted incidence rate is defined as "the number of subjects with a specific event divided by the total exposure-time among the subjects in the treatment group and at risk of an initial occurrence of the event" (Liu 2006). However, although such an approach is valid when the specific event-incidence rate is relatively constant over the duration of the study, it fails to provide adverse effect information of time or exposure duration for all events or for several events that occur in the same individual. In addition, some other adverse events in the included RCT, e.g. upper respiratory

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tract infection (URTI), might be correlated with nasopharyngitis, and similarly, headache could be correlated with URTI and nasopharyngitis (Siddiqui 2009). Therefore, more advanced statistical methods to evaluate safety are needed. Also, as children could be on lifelong biologic treatment, safety issues must be presented in a friendly format for clinicians.

Although malignancies were not found in the included RCT, an increased risk for the development of malignancies, including lymphoma, has been reported with the use of TNF-blocking agents (EMA 2011; EMA 2013; US FDA 2009; US FDA 2012). Therefore, there are still uncertainties in this field.

Overall completeness and applicability of evidence

We found only one eligible high-quality study evaluating anti-TNF therapy for moderate to severe paediatric psoriasis. The median age of participants in this trial was 13 years (range from 4 to 17 years). Although the applicability of evidence in younger children could be limited, psoriasis in children younger than four years old is unusual and mostly mild and limited to small areas. (Bell 1991; Bronckers 2015) The applicability of the evidence could also be limited due to the fact that only short-term safety was evaluated and just one type of anti-TNF agent (etanercept) was used. Due to these limitations, the findings of this review should not be generalised to other types of anti-TNF agents.

Quality of the evidence

We assessed the quality of evidence for each important outcome through the use of GRADE and rated it as high (Summary of findings for the main comparison), except for the CDLQI outcome, which we rated as moderate. As only one industry-sponsored RCT was eligible, risk of bias was strongly suspected, and inconsistency across studies and mid- and long-term safety could not be evaluated. However, this was a double-blind RCT with adequate blinding of outcome assessors, it had a complete accounting of participants and outcome events, and there was no selective reporting or indirectness.

Potential biases in the review process

According to our rigorous systematic search of published and unpublished literature and since we contacted leading experts, it is unlikely that we have missed studies with substantial numbers of participants. However, the fact that six studies have not yet been incorporated may be a source of potential bias.

As we included only one eligible study, it was not possible to perform a meta-analysis.

Agreements and disagreements with other studies or reviews

To our knowledge, this is the first systematic review to assess the evidence for the efficacy and safety of anti-TNF agents for paediatric psoriasis. Current guidelines on the management of psoriasis with systemic therapy have focused mainly on adults (Tan 2010), and there is a paucity of studies of therapies for children with moderate to severe psoriasis. What studies there are have been mainly based on descriptive studies or case series. Therefore, more well-performed RCTs such as this sole included study are needed as they may provide a body of evidence for the efficacy of systemic treatments for children with moderate to severe psoriasis.

AUTHORS' CONCLUSIONS

Implications for practice

Except for the quality-of-life outcomes, the quality of evidence of the sole RCT that evaluated the use of this kind of biological therapy was high. This review has concluded that the anti-TNF agent etanercept is effective in improving psoriasis in a paediatric population as assessed by PASI 75, 50, and 90 and PGA. During the open-label treatment, three serious adverse events were observed, but all these adverse events were resolved without sequelae or death. Although no serious adverse events were reported in the other phases of the study, mid- and long-term safety were not evaluated.

The GRADE approach refers not to individual studies but to a body of evidence. As this review assessed the quality of evidence of just one individual trial, so far we cannot make a full recommendation for the use of anti-TNF agents in paediatric psoriasis. We shall therefore wait for the results of the ongoing studies, as the conclusions of this review may be altered once they are available for inclusion in a future update.

Implications for research

A significant aspect of drug trials is to assess safety alongside efficacy. Well-designed RCTs assessing the safety (both short and long term) of biological therapies in paediatric psoriasis as one of the main objectives are therefore needed in order to provide high-quality evidence to ease clinical decision-making. Furthermore, efficacy and safety trials with a sufficient number of younger participants (less than 11 years old) are also required, as current evidence applies mostly to older children.

Although other RCTs are ongoing, a lack of standardisation of outcomes and time-frames between studies will impact any meta-analyses of future evidence in this field. It is therefore necessary to take these factors into account when designing trials in this population in the future. Future studies should preferably consider the following.

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- PASI 75 and PGA as main outcomes (unless a better and validated measurement tool arises), as well as quality of life and short- and long-term adverse effects.

- Given the high cost of these therapies, it would be useful to collect information on cost of treatment.

- Standardised outcome measures among RCTs would make studies easier to compare.

- More advanced statistical methods should be investigated to report adverse events, and such results need to be presented in a format that is readily understood by clinicians.

- We believe that head-to-head RCTs evaluating the effectiveness of biologics and classical systemic treatments in paediatric psoriasis would be worthwhile.

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* *Indicates the major publication for the study*

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CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Paller 2008

Methods	Study design had a 12-week randomised, double-blind, placebo-controlled period, thereafter a 24-week open-label phase, and lastly a randomised, double-blind withdrawal-retreatment period from week 37 to 48
Participants	211 participants (106 in the treatment arm, 105 in the placebo arm) with paediatric psoriasis from 4 to 17 years of age were recruited at 42 sites in the United States and Canada Inclusion criteria: Moderate to severe plaque psoriasis at screening (defined as a PASI score of at least 12); stable disease; PGA of at least 3; BSA-psoriasis involvement of at least 10%; history of psoriasis in the last 6 months; and previous or current treatment with phototherapy/systemic psoriasis therapy (e.g. retinoids, methotrexate, or ciclosporin) or poorly controlled psoriasis with the use of topical therapy
Interventions	Participants in the treatment arm received a dose of 0.8 mg per kilogram of body weight up to a maximum intended dose of 50 mg of reconstituted etanercept in syringes for once-weekly subcutaneous injections; participants in the placebo arm received matching placebo
Outcomes	The primary outcome was PASI 75 (improvement in the PASI of 75%) at week 12. Secondary efficacy endpoints were PASI 50 (improvement in the PASI of 50%), PASI 90 (improvement in the PASI of 90%), and a PGA of clear or almost clear (score of 0 or 1), which were evaluated at weeks 2, 4, 8, and 16 and every 4 weeks thereafter The following participant-reported outcomes were assessed during the double-blind period in this study: 1. The CDLQI was administered at baseline and at weeks 2, 4, and 12. Children aged 4 to 12 completed a cartoon version (children aged 4 to 7 years had caregiver or parental assistance), and adolescents aged 13 to 17 years completed the written version 2. The PedsQL was administered at baseline and week 12; 4 age-specific versions of the PedsQL were administered: 4; 5 to 7; 8 to 12; and 13 to 17 years of age. Participants aged 8 to 17 years completed the questionnaire without assistance, whereas participants < 7 years of age were assisted by a caregiver or parent 3. The Stein Impact on Family Scale, which assessed the impact of psoriasis on the lives of participants' families, was completed by parents or caregivers at baseline and at week 12 during the double-blind period 4. The 2 age-dependent versions of the Harter Self-Perception Profile for Children, which assessed the impact of psoriasis on participants' self esteem, was completed during the double-blind period Safety outcomes included non-serious adverse events, serious adverse events, non-serious infections, serious infections, malignancies, reactions in the injection site, laboratory findings, etanercept concentration in serum, and disease recurrence during the withdrawal period, which was defined as "the worsening of PASI by more than 125% from baseline within 3 months after discontinuation of treatment" (Paller 2008)

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Notes	The analysis of the study was designed by Amgen Inc and funded by Immunex Corp, a wholly owned subsidiary of Amgen Inc, and by Wyeth, which was acquired by Pfizer Inc in October 2009. Financial support for the preparation of the manuscript was provided by Amgen Inc

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	In the included study participants underwent randomisation at a 1:1 ratio by an interactive voice-response system
Allocation concealment (selection bias)	Low risk	Not specifically stated in paper, therefore we contacted the trial authors for further details about allocation concealment; since the main investigator was not able to provide further data, we contacted Pfizer. According to information provided by Pfizer, the allocation sequence was generated by Amgen and provided by the interactive voice-response system by an unblinded randomisation group within Amgen According to the pharmaceutical lab response, the identity of the investigational product assigned to participants was concealed using an "interactive voice response system"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Stated as "double-blind" in abstract and methods of the original study. We therefore contacted the main author and Pfizer, who confirmed that all participants, study site personnel, and Amgen staff were blinded until the data through week 12 were finalised
Blinding of outcome assessment (detection bias) All outcomes	Low risk	It was not clear whether blinded outcome assessment was attempted in the original study. We therefore contacted the main author and Pfizer, who confirmed that outcome evaluators were dermatologists or dermatologists in training who were certified on PASI training materials and were also blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	In the included study, analysis was performed according to the intention-to-treat principle during first 12 weeks, thus, avoid-

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Paller 2008 (*Continued*)

		ing bias, at least in this phase of the study
Selective reporting (reporting bias)	Low risk	There was no evidence of selective reporting in the included study
Other bias	Unclear risk	Paediatric participants (aged 4 to 17 years) had stable moderate to severe plaque psoriasis at screening (defined as a PASI score >= 12); stable disease; PGA of at least 3; BSA-psoriasis involvement of at least 10%; a history of psoriasis in the last 6 months; and previous or current treatment with phototherapy/systemic psoriasis therapy (e.g. retinoids, methotrexate, or ciclosporin) or poorly controlled psoriasis with the use of topical therapy When compared to the intervention arm, the control group had slightly lower disease duration at 5.8 years versus 6.8 years, slightly more participants with history of previous systemic therapy or phototherapy (59% vs 55% in the intervention group) and more psoriatic arthritis (13% vs 5%) at baseline. In addition, even though participants were required to have a PASI $\geq$ 12 at baseline, a PGA $\geq$ 3, and a BSA $\geq$ 10%, the median baseline PASI was 16. Also, an important percentage of participants in both arms (45% in the etanercept group and 41% in the placebo group) had no previous systemic or phototherapy history This was a industry-sponsored trial with positive results. We therefore sought out missing or unclear information by contacting the pharmaceutical laboratory (Pfizer). They provided clearer information in April and May 2013 regarding sequence allocation, allocation concealment, blinding of participants and personnel, and blinding of outcome assessment

BSA: body surface area.
CDLQI: Children's Dermatology Life Quality Index.
PASI: Psoriasis Area and Severity Index.
PedsQL: Pediatric Quality of Life Inventory.
PGA: Physician's Global Assessment.

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Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Alsuwaidan 2011	This study is not a randomised controlled trial
Beikert 2012	This study was a German language report of paediatric psoriasis cases treated with etanercept, not a randomised controlled trial

Characteristics of ongoing studies *[ordered by study ID]*

NCT01090427

Trial name or title	A study of the safety and efficacy of ustekinumab in adolescent patients with psoriasis (CADMUS)
Methods	This is a phase 3 multicentre, randomised, double-blind, placebo-controlled study evaluating the of efficacy and safety of ustekinumab in the treatment of adolescent participants with moderate to severe plaque-type psoriasis (CADMUS)
Participants	People from 12 to 18 years of age with a diagnosis of plaque-type psoriasis with or without psoriatic arthritis for at least 6 months and who are candidates for phototherapy or systemic treatment of psoriasis and who have screening laboratory test results within the study parameters. Exclusion criteria are: people with non-plaque forms of psoriasis or who have used any therapeutic agent targeted at reducing interleukin-12 or interleukin-23, including but not limited to ustekinumab and briakinumab; who received conventional systemic therapies or phototherapy within the last 4 weeks or who received biologic therapies within the last 3 months
Interventions	Ustekinumab half-standard dosage (ustekinumab 0.375 mg/kg, 22.5 mg, or 45 mg based on body weight, administered subcutaneously (under the skin) at weeks 0, 4, 16, 28, and 40). In addition, all participants will receive a single subcutaneous dose of placebo at week 12 Ustekinumab standard dosage (ustekinumab 0.75 mg/kg, 45 mg, or 90 mg based on body weight administered subcutaneously at weeks 0, 4, 16, 28, and 40). In addition, all participants will receive a single subcutaneous dose of placebo at week 12 Placebo administered subcutaneously at weeks 0 and 4 or at week 12
Outcomes	Primary outcome: proportion of participants who achieve a PGA score of cleared or minimal disease at week 12 Secondary outcome measures: proportion of participants who achieve a PASI 90 response, proportion of participants who achieve PASI 75 response, and the change from baseline in CDLQI at week 12
Starting date	May 2010
Contact information	Study director: Janssen Research & Development, LLC Clinical Trial. Janssen Research & Development, LLC
Notes	This study is sponsored by Janssen Research & Development, LLC. The results are posted at www.clinicaltrials.gov (www.clinicaltrials.gov/ct2/show/results/NCT01090427). Last access date: 9 July 2015

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NCT01100034

Trial name or title	Long-term, prospective, observational cohort study of safety and effectiveness of pediatric psoriasis patients treated with etanercept in a naturalistic setting: A Post-Authorization Safety Study (PASS)
Methods	Phase 4 cohort, prospective, observational cohort study to assess safety and effectiveness of etanercept for the treatment of paediatric psoriasis
Participants	People from 4 to 17 years of age diagnosed with plaque psoriasis by a dermatologist. Prior to enrolment, there must be a clinical decision to initiate etanercept for the treatment of plaque psoriasis, and etanercept must then be initiated. Included participants must be being actively treated with etanercept, regardless of length of treatment prior to enrolment. Exclusion criteria: Prior therapy with etanercept or other biologic agent and a history of malignancy
Interventions	Etanercept
Outcomes	Primary outcome measures: number of serious adverse events including serious infections and malignancy during a 5-year follow-up, with follow-up every 3 months for the first 2 years and 6-monthly for the next 3 years Secondary outcome measures: effectiveness or lack of effectiveness after a 24-week treatment course
Starting date	November 2010
Contact information	Contact: Pfizer's phonecall centre: 1-800-718-1021
Notes	This study is sponsored by Pfizer. Most of the centres are in the recruiting phase. Estimated completion date: June 2018. Last access date: 9 July 2015

NCT01251614

Trial name or title	A double blind study in pediatric subjects with chronic plaque psoriasis, studying adalimumab vs. methotrexate
Methods	This is a phase III multicentre, randomised, double-dummy, double-blind clinical trial, in which 2 doses of adalimumab vs methotrexate will be evaluated in paediatric participants with chronic plaque psoriasis Primary outcomes: PASI 75 at week 16, period A (standard dose vs methotrexate) and the proportion of participants achieving a Physician's Global Assessment of Disease Activity of 0 or 1 at week 16, period A (standard dose vs methotrexate) and adverse events at every visit from baseline (week 0) to final visit (week 156) Secondary outcomes include: The proportion of participants achieving PASI 90, PASI 100; change from baseline in the CDLQI scores; change from baseline in the PedsQL at week 16, period A (standard dose vs methotrexate); the proportion of participants achieving PGA 0, 1 upon completion of retreatment (period C) according to the original randomised group assignment in period A (standard-dose adalimumab vs low-dose adalimumab) and time to loss of disease control (period B) according to the original randomised group assignment in period A (standard-dose adalimumab vs low-dose adalimumab and methotrexate)
Participants	People 4 to 17 years of age with body weight equal to or > 13 kilograms who failed to respond to topical therapy with a PGA equal to or > 4; BSA involved > 20%; people with very thick lesions with BSA > 10%; PASI > 20; PASI > 10 and at least 1 of the following: active psoriatic arthritis unresponsive to nonsteroidal anti-inflammatory drugs; clinically relevant facial involvement; clinically relevant genital involvement; clinically

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NCT01251614 (*Continued*)

	relevant hand or foot, or both involvement; and CDLQI > 10 If person is < 12 years of age and resides in a geographic region where heliotherapy is practical, person must have failed to respond, be intolerant, or have a contraindication to heliotherapy, or is not a suitable candidate for heliotherapy. If person is equal to or > 12 years of age, person must have failed to respond, be intolerant, or have a contraindication to phototherapy, or is not a suitable candidate for phototherapy. Study participants must have a clinical diagnosis of psoriasis for at least 6 months as determined by the person's medical history and confirmation of diagnosis through physical examination by the investigator and a stable plaque psoriasis for at least 2 months prior to baseline Exclusion criteria: Prior biologic use other than prior treatment with etanercept; treatment with etanercept therapy within 4 weeks prior to the baseline visit; methotrexate use within the past year or prior methotrexate use at any time where the person did not respond or did not tolerate methotrexate; contraindication for treatment with methotrexate during the study; erythrodermic, generalised, or localised pustular psoriasis; medication-induced or medication-exacerbated or new-onset guttate psoriasis. People with infection(s) requiring treatment with intravenous anti-infectives within 30 days prior to the baseline visit or with oral anti-infectives within 14 days prior to the baseline visit were excluded as well as people with treatment of psoriasis with topical therapies such as corticosteroids, vitamin D analogues, or retinoids within 7 days prior to the baseline visit Other exclusion criteria are people with treatment of psoriasis with ultraviolet B phototherapy, excessive sun exposure, or the use of tanning beds within 7 days prior to the baseline visit and with treatment of psoriasis with PUVA phototherapy, non-biologic systemic therapies for the treatment of psoriasis, or systemic therapies known to improve it within 14 days prior to the baseline visit
Interventions	1. adalimumab: low dose at 0.4 mg/kg up to a maximum of 20 mg every other week (other name: ABT-D2E7 Humira®) 2. adalimumab: standard dose at 0.8 mg/kg up to a maximum of 40 mg every other week (other name: ABT-D2E7 Humira®) 3. active comparator: methotrexate at 0.4 mg/kg/week up to a maximum of 25 mg per week 4. adalimumab: open label at 0.4 mg/kg up to a maximum of 20 mg every other week or 0.8 mg/kg up to a maximum of 40 mg every other week starting at week 0 in open-label period (other name: ABT-D2E7 Humira®)
Outcomes	Primary outcomes: PASI 75 week 16, period A: the proportion of participants achieving a PASI 75 response, standard dose vs methotrexate; PGA 0, 1 week 16, period A: the proportion of participants achieving a PGA 0, 1 standard dose vs methotrexate; adverse events at every visit from baseline (week 0) to final visit (week 156); and any untoward medical occurrence Secondary outcomes: PASI 90 week 16, period A: the proportion of participants achieving a PASI 90, standard dose vs methotrexate; PASI 100 week 16, period A: the proportion of participants achieving a PASI 90, standard dose vs methotrexate; CDLQI at week 16, period A: change from baseline in the CDLQI scores, standard dose vs methotrexate; change from baseline in the PedsQL at week 16, period A: change from baseline in the PedsQL, standard dose vs methotrexate; PGA 0,1 at week 16, period A; the proportion of subjects achieving PGA 0, 1 upon completion of retreatment (period C) according to the original randomised group assignment in period A (standard-dose adalimumab vs low-dose adalimumab); time to loss of disease control during time from entry into period B until loss of disease control; time to loss of disease control (period B) according to the original randomised group assignment in period A (standard-dose adalimumab vs low-dose adalimumab and methotrexate)
Starting date	December 2010
Contact information	Susan Williamson, RN, MSN, MBA, PMP tel: 847-938-7491; email: susan.williamson@abbott.com

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NCT01251614 (*Continued*)

Notes	This study is sponsored by AbbVie (prior sponsor, Abbott). Baseline characteristics of participants enrolled in this ongoing study were presented at the last 4th Congress of the Psoriasis International Network in Paris, France (July 2013). Efficacy and safety results were presented in a poster during the last World Dermatology Congress held in Vancouver, Canada (June 2015)

NCT01432249

Trial name or title	Post marketing surveillance to observe safety and efficacy of Enbrel in pediatric patients with psoriasis
Methods	This is a phase IV prospective cohort study to observe safety and efficacy of etanercept (Enbrel®) in paediatric patients with psoriasis
Participants	Paediatric patients (ages of 8 ~ 17) with psoriasis Inclusion criteria are children and adolescents aged 8 to 17 years at time of consent with chronic severe psoriasis that is inadequately controlled by, or who are intolerant to other systemic therapies or phototherapies. Exclusion criteria are people with known hypersensitivity to Enbrel® or any component of the product and people with active infections including chronic or localised infections such as tuberculosis
Interventions	Enbrel®, which will be decided by treating physicians
Outcomes	Primary outcome: Safety measured by discontinuation due to adverse events Secondary outcomes: Proportion of participants achieving a status on the PGA of psoriasis of clear (0), clear/almost clear (0/1), or clear/almost clear/mild (0/1/2) at 12 and 24 weeks; proportion of participants achieving a 50% and 75% improvement from baseline in PASI over 12 and 24 weeks
Starting date	July 2012
Contact information	Contact: Pfizer's phonecall centre: 1-800-718-1021
Notes	This study is sponsored by Pfizer. The setting of this study is Korea because it is required in order for Enbrel® to be approved by the Korea Food and Drug Administration. According to ClinicalTrials.gov, the study was withdrawn prior to enrolment. Last access date: 9 July 2015

BSA: body surface area.
CDLQI: Children's Dermatology Life Quality Index.
PASI: Psoriasis Area and Severity Index.
PedsQL: Pediatric Quality of Life Inventory.
PGA: Physician's Global Assessment.
PUVA: psoralen and ultraviolet A radiation.

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DATA AND ANALYSES

Comparison 1. Etanercept vs Placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Achievement of PASI 75 at week 12	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2 Children's Dermatology Life Quality Index (CDLQI) response	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
3 Achievement of PASI 50 at week 12	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
4 Achievement of PASI 90 at week 12	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
5 PGA of 'clear or almost clear'	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

Analysis 1.1. Comparison 1 Etanercept vs Placebo, Outcome 1 Achievement of PASI 75 at week 12.

Review: Anti-TNF agents for paediatric psoriasis

Comparison: 1 Etanercept vs Placebo

Outcome: 1 Achievement of PASI 75 at week 12

Study or subgroup	Etanercept n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
Paller 2008	60/106	12/105		4.95 [2.83, 8.65]

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Analysis 1.2. Comparison 1 Etanercept vs Placebo, Outcome 2 Children's Dermatology Life Quality Index (CDLQI) response.

Review: Anti-TNF agents for paediatric psoriasis

Comparison: 1 Etanercept vs Placebo

Outcome: 2 Children's Dermatology Life Quality Index (CDLQI) response

Study or subgroup	Etanercept N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Random,95% CI	Mean Difference IV,Random,95% CI
Paller 2008	106	5.4 (5.6)	105	3.1 (5.1)		2.30 [0.85, 3.75]

Analysis 1.3. Comparison 1 Etanercept vs Placebo, Outcome 3 Achievement of PASI 50 at week 12.

Review: Anti-TNF agents for paediatric psoriasis

Comparison: 1 Etanercept vs Placebo

Outcome: 3 Achievement of PASI 50 at week 12

Study or subgroup	Etanercept n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
Paller 2008	79/106	24/105		3.26 [2.26, 4.71]

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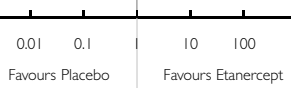
Analysis 1.4. Comparison 1 Etanercept vs Placebo, Outcome 4 Achievement of PASI 90 at week 12.

Review: Anti-TNF agents for paediatric psoriasis

Comparison: 1 Etanercept vs Placebo

Outcome: 4 Achievement of PASI 90 at week 12

Study or subgroup	Etanercept n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
Paller 2008	29/106	7/105		4.10 [1.88, 8.95]



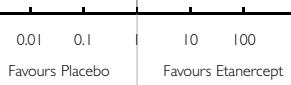
Analysis 1.5. Comparison 1 Etanercept vs Placebo, Outcome 5 PGA of 'clear or almost clear'.

Review: Anti-TNF agents for paediatric psoriasis

Comparison: 1 Etanercept vs Placebo

Outcome: 5 PGA of 'clear or almost clear'

Study or subgroup	Etanercept n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
Paller 2008	56/106	14/105		3.96 [2.36, 6.66]



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APPENDICES

Appendix 1. Skin Group Specialised Register search strategy

(Psoria* or "palmoplantar* pustulosis" or "pustulosis palmaris et plantaris" or (pustulosis and palms and soles)) and ("Tumor Necrosis Factor*" or "TNF" or "tumour necrosis factor" or "antitumor necrosis factor" or "antitumour necrosis factor" or "monoclonal antibod*" or "Immunoglobulin Fab Fragments" or infliximab* or "cA2" or remicade or "cdp571" or etanercept* or enbrel or adalimumab* or "d2e7" or humira or golimumab or simponi or Briakinumab or "ABT-874")

Appendix 2. CENTRAL (Cochrane Library) search strategy

#1 MeSH descriptor Psoriasis explode all trees
#2 (psoria*) or (palmoplantar* pustulosis) or (pustulosis palmaris et plantaris) or (pustulosis and palms and soles)
#3 (#1 OR #2)
#4 MeSH descriptor Tumor Necrosis Factor-alpha, this term only
#5 MeSH descriptor Receptors, Tumor Necrosis Factor, this term only
#6 MeSH descriptor Receptors, TNF-Related Apoptosis-Inducing Ligand, this term only
#7 (tumour necrosis factor*) or (tumor necrosis factor*) or (antitumour necrosis factor) or (antitumor necrosis factor) or "tnf"
#8 (tnf antibod*) or (tnf alpha antibod*) or (monoclonal antibod*)
#9 MeSH descriptor Antibodies, Monoclonal, this term only
#10 MeSH descriptor Immunoglobulin Fab Fragments, this term only
#11 MeSH descriptor Tumor Necrosis Factors, this term only
#12 MeSH descriptor Receptors, Tumor Necrosis Factor, Type II, this term only
#13 MeSH descriptor Receptors, Tumor Necrosis Factor, Type I, this term only
#14 (infliximab) or (monoclonal antibody cA2) or (remicade) or "cdp571"
#15 (etanercept* or enbrel) or (adalimumab* or "d2e7" or humira) or (golimumab or simponi) or (briakinumab or "abt-874")
#16 (#4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15)
#17 (#3 AND #16)

Appendix 3. MEDLINE (OVID) search strategy

1. exp Psoriasis/ or psoria$.mp.
2. palmoplantar$ pustulosis.mp.
3. pustulosis palmaris et plantaris.mp.
4. (pustulosis and palms and soles).mp.
5. or/1-4
6. exp Tumor Necrosis Factors/ or exp Tumor Necrosis Factor-alpha/ or exp Receptors, Tumor Necrosis Factor, Type II/ or exp Receptors, Tumor Necrosis Factor/ or exp Receptors, Tumor Necrosis Factor, Type I/ or exp TNF-Related Apoptosis-Inducing Ligand/
7. (anti tumour necrosis factor or anti tumor necrosis factor).mp.
8. (tumor necrosis factor-alpha or tumour necrosis factor-alpha).mp.
9. anti tnf.mp.
10. (tnf antibod$ or tnf alpha antibod$).mp.
11. (tumour necrosis factor antibod$ or tumor necrosis factor antibod$).mp.
12. (antitumor necrosis factor or antitumour necrosis factor).mp.
13. exp Antibodies, Monoclonal/ or monoclonal antibod$.mp.
14. exp Immunoglobulin Fab Fragments/
15. (infliximab$ or monoclonal antibody cA2 or remicade).mp.
16. cdp571.mp.
17. (etanercept$ or enbrel).mp.
18. (adalimumab$ or d2e7 or humira).mp.
19. (golimumab or simponi).mp.
20. (Briakinumab or ABT-874).mp.

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21. or/6-20
22. adolescent.tw.
23. children.tw.
24. Child, Preschool/
25. 22 or 23 or 24
26. randomised controlled trial.pt.
27. controlled clinical trial.pt.
28. randomized.ab.
29. placebo.ab.
30. clinical trials as topic.sh.
31. randomly.ab.
32. trial.ti.
33. 26 or 27 or 28 or 29 or 30 or 31 or 32
34. (animals not (humans and animals)).sh.
35. 33 not 34
36. 5 and 21 and 25 and 35

Lines 22-25 are an age filter from the HEDGES team - see Kastner M, Wilczynski NL, Walker-Dilks C, McKibbon KA, Haynes B. Age-specific search strategies for Medline. Journal of Medical Internet Research 2006;8(4):e25.

Lines 26-35: Cochrane Highly Sensitive Search Strategy for identifying randomized trials in MEDLINE: sensitivity- and precision-maximizing version (2008 revision).

Appendix 4. Embase (OVID) search strategy

1. exp *PSORIASIS/
2. psoria$.ti,ab.
3. palmoplantar$ pustulosis.ti,ab.
4. pustulosis palmaris et plantaris.ti,ab.
5. (pustulosis and palms and soles).ti,ab.
6. 1 or 2 or 3 or 4 or 5
7. exp *tumor necrosis factor/ or exp *tumor necrosis factor alpha/
8. exp *tumor necrosis factor receptor 1/
9. exp *tumor necrosis factor receptor 2/ or exp *tumor necrosis factor receptor/
10. exp *tumor necrosis factor related apoptosis inducing ligand/
11. anti tumour necrosis factor.ti,ab.
12. anti tumor necrosis factor.ti,ab.
13. tumour necrosis factor alpha.ti,ab.
14. tumor necrosis factor alpha.ti,ab.
15. anti tnf.ti,ab.
16. tnf inhibitor$.ti,ab.
17. tnf antibod$.ti,ab.
18. tnf alpha antibod$.ti,ab.
19. tumour necrosis factor antibod$.ti,ab.
20. tumor necrosis factor antibod$.ti,ab.
21. antitumor necrosis factor.ti,ab.
22. antitumour necrosis factor.ti,ab.
23. exp *monoclonal antibody/
24. monoclonal antibod$.ti,ab.
25. exp *"immunoglobulin F(ab) fragment"/
26. exp *infliximab/
27. infliximab$.ti,ab.
28. monoclonal antibody cA2.ti,ab.
29. remicade.ti,ab.

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30. cdp571.ti,ab.
31. exp *etanercept/
32. (etanercept$ or enbrel).ti,ab.
33. exp *adalimumab/
34. (adalimumab$ or humira or "d2e7").ti,ab.
35. exp *golimumab/
36. (golimumab$ or simponi).ti,ab.
37. exp *briakinumab/
38. (briakinumab$ or "abt-874").ti,ab.
39. or/7-38
40. random$.mp.
41. factorial$.mp.
42. (crossover$ or cross-over$).mp.
43. placebo$.mp. or PLACEBO/
44. (doubl$ adj blind$).mp.
45. (singl$ adj blind$).mp.
46. (assign$ or allocat$).mp.
47. volunteer$.mp. or VOLUNTEER/
48. Crossover Procedure/
49. Double Blind Procedure/
50. Randomized Controlled Trial/
51. Single Blind Procedure/
52. 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51
53. 6 and 39 and 52

Appendix 5. LILACS search strategy

We applied two strategies for searching in LILACS. The first one included the terms:
("pustulosis palmoplantar" or psoria$ or "palmoplantar pustulosis" or "pustulosis palmaris et plantaris" or (pustulosis and palms and soles)) and ("tumor Necrosis Factor" or "TNF" or "antitumor necrosis factor" or "antitumour necrosis factor" or "monoclonal antibodies" or "Immunoglobulin Fab Fragments" or infliximab$ or "cA2" or remicade or "cdp571" or etanercept$ or enbrel or adalimumab$ or "d2e7" or humira or golimumab or simponi or Briakinumab or "ABT-874"). This strategy combined with the Controlled clinical trials topic-specific query filter.
The second strategy included the terms:
Tw estud$ OR Tw Clin$ OR AB grupo$ OR CT COMPARATIVE STUDY OR Tw placebo$ OR Tw randomS Ti compara$ OR Ti tratamiento OR Tw control$ OR MH / dt

Appendix 6. Clinical trials registers' search strategy

This search included the following individual terms in each database: "psoriasis", "children" "pediatric" "paediatric".

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Appendix 7. EMA search strategy

This search included the following individual terms: “Etanercept”, “Infliximab”, and “Adalimumab”.

CONTRIBUTIONS OF AUTHORS

GS was the contact person with the editorial base.

GS co-ordinated contributions from the coauthors and wrote the final draft of the review.

GS and JC screened papers against eligibility criteria.

GS obtained data on ongoing and unpublished studies.

GS and JC appraised the quality of papers.

GS, JC, and RM extracted data for the review and sought additional information about papers.

GS and JC entered data into RevMan.

GS, JC, RM, and XB analysed and interpreted data.

GS, JC, RM, and XB worked on the methods sections.

GS, JC, and RM drafted the clinical sections of the background and responded to the clinical comments of the referees.

GS, JC, and XB responded to the methodology and statistics comments of the referees.

HG was the consumer coauthor and checked the review for readability and clarity, as well as ensuring outcomes were relevant to consumers.

GS is the guarantor of the update.

Disclaimer

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DECLARATIONS OF INTEREST

Dr. Gloria Sanclemente has been sponsored by Pfizer and Janssen-Cilag Ltd for attending dermatology meetings. She has received an honorarium by Pfizer for presenting or speaking about biosimilars in adults.

Dr. Ruth Murphy has not been involved in any educational work, travel grants, or lectures with respect to work with children and biological therapies for the treatment of psoriasis. She has been involved with the following work with adults: she has sat on advisory boards for Janssen-Cilag Ltd, Abbott, Serono, and Wyeth (Pfizer); she has given educational and non-promotional lectures, which were paid, about the use of biological therapies in psoriasis for Janssen-Cilag Ltd and Abbott; she has accepted expenses sponsorship in 2010 only to attend meetings at the American Academy of Dermatology, the British Association of Dermatology, and the European Academy of Dermatology and Venereology from Wyeth (Pfizer), Janssen-Cilag, and Abbott. In addition, Dr. Murphy has taken part in an industry-sponsored study (TRANSIT). She also received departmental funds in 2007-8 to train a nurse to take part in the British Association of Dermatologists Biologic Interventions Register from Pfizer.

A clinical referee on this review, Dr Esther Burden-Teh said: “I have received an educational supplement from Leo Pharma and AbbVie to attend the British Association of Dermatologists Annual Meeting and the American Academy of Dermatology Annual Meeting. Leo Pharma do not produce anti-TNF agents. AbbVie produce the anti-TNF agent Humira (adalimumab), which is now licensed to treat paediatric psoriasis in Europe.” (EMA 2015).

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

There were minor updates to the Background section.

We planned to use PASI 50 or PASI 90 if PASI 75 was not available. However, we included both outcomes in addition to PASI 75,as they added more efficacy data. The protocol planned to assess psoriasis-affected body surface area, Patient Global Assessment, remissions, recurrences, and resource use data, but such information was not assessed in the included RCT. In addition, we planned to have a short-, medium-, and long-term assessment of outcomes, but the included RCT evaluated outcomes at a maximum of 48 weeks. However, long-term data and results were evaluated in a further associated publication of the primary study. Lastly, since we included only one eligible study, it was not possible to perform a meta-analysis.

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La estrategia de búsqueda identificó 103 referencias de guías, de las cuales se seleccionaron finalmente 19 documentos, aunque solo seis publicaciones cumplieron los criterios de inclusión. Los motivos de exclusión de los demás registros son los siguientes: 12 correspondieron a opiniones de expertos; dos referencias incluían solo una opción de tratamiento; una se excluyó por ser un ensayo clínico; dos eran protocolos para el manejo del acné, de los cuales uno era una publicación duplicada de una GPC. Se excluyó también una GPC por no proporcionar el texto completo, sino simplemente su resumen. De las seis GPC seleccionadas, una se elaboró en los Estados Unidos, otra en Europa, otra en Francia, dos en Sudamérica y una en Malasia.

Evaluación de las guías

El valor global del coeficiente de correlación intraclase fue muy bueno: 0,981 (IC95 %: 0,918-0,997), y el acuerdo entre los evaluadores fue muy alto.

Alcance y finalidad

La puntuación media para este dominio de las GPC seleccionadas fue de 72,18 % (rango de 0 a 100 %); una sola guía obtuvo una puntuación inferior al 60 %.

Participación de los implicados

La puntuación media para este dominio fue de 46,23 % (rango de 14,80 a 81,40 %); cuatro GPC obtuvieron una puntuación inferior al 60 %.

El rigor del desarrollo

La puntuación media para este dominio fue de solo 58,05 % (rango de 25,60 a 94,40 %); cuatro guías obtuvieron una puntuación inferior al 60 %.

Claridad y presentación

La puntuación media para este dominio fue de 93,46 % (rango de 70,30 a 100 %); ninguna obtuvo una puntuación inferior al 60 %.

Aplicabilidad

La puntuación media para este dominio fue de 22,93 % (rango de 0 a 66,6 %); una sola guía obtuvo una puntuación superior al 60 %.

La independencia editorial

La puntuación media para este dominio fue de 63,7 % (rango de 5 a 100 %); cuatro GPC obtuvieron una puntuación superior al 60 %.

Recomendación general

Solo dos guías, la europea y la de Malasia, se recomendaron sin modificaciones adicionales. La europea presentó puntuaciones más bajas en aplicabilidad, mientras que la de Malasia obtuvo una baja puntuación en este mismo dominio y en la participación de los implicados. Las guías mexicanas, colombianas y de Estados Unidos se recomendaron con anotaciones principalmente por la falta de rigor metodológico en su elaboración, por la participación de los implicados y por su aplicabilidad.

De todas las GPC analizadas, cuatro no evaluaron la calidad individual de los estudios, y solo la europea y la de Malasia mostraron una revisión crítica de la evidencia.

Por último, la guía francesa no se recomendó, puesto que obtuvo una puntuación baja en la mayoría de los dominios evaluados.

PUBLICACIÓN 5

Clinical practice guidelines for treatment of acne vulgaris: a critical appraisal using the AGREE II instrument

Gloria Sanclemente, Jorge-Luis Acosta, Maria-Eulalia Tamayo, Xavier Bonfill & Pablo Alonso-Coello

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ORIGINAL PAPER

Clinical practice guidelines for treatment of acne vulgaris: a critical appraisal using the AGREE II instrument

Gloria Sanclemente · Jorge-Luis Acosta · Maria-Eulalia Tamayo · Xavier Bonfill · Pablo Alonso-Coello

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Abstract A significant number of clinical practice guidelines (CPGs) about the treatment of acne vulgaris in adolescents and adults have been published worldwide. However, little is known about the quality of CPGs in this field. The aim of this study was to appraise the methodological quality of published acne vulgaris CPGs. We performed a systematic review of published CPGs on acne vulgaris therapy from July 2002 to July 2012. Three reviewers independently assessed each CPG using the AGREE II instrument. A standardized score was calculated for each of the six domains. Our search strategy identified 103 citations but just six met our inclusion criteria. Agreement among reviewers was very good: 0.981. The domains that scored better were: "scope and purpose" and "clarity and presentation". Those that scored worse were "stakeholder involvement", "rigor of development", and "applicability". The European and the Malaysian CPGs were the only recommended with no further modifications. In addition, the Mexican, Colombian and the United States guidelines were recommended with provisos, with lower scores regarding stakeholder involvement, rigor of development and applicability. Only two guidelines clearly reported outcome measures for evaluating efficacy or included quality of life outcomes. CPGs varied regarding the consideration of light/laser therapy or consideration of complementary/alternative medicines. None of them included cost considerations of drugs such as systemic isotretinoin. In conclusion, published acne vulgaris CPGs for acne therapy vary in quality with a clear need to improve their methodological rigor. This could be achieved with the adherence to current CPGs development standards.

Keywords Acne vulgaris · Critical appraisal · Clinical practice guidelines · AGREE II

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Introduction

Acne vulgaris is the most common skin disorder affecting adolescents that can have a major quality of life and emotional impact, comparable to the one experienced by patients with chronic conditions, such as diabetes and epilepsy [28]. In conjunction with the considerable personal burden experienced by these patients, acne vulgaris also accounts for substantial societal and health care burden.

In the past, the decisions to provide or withhold a treatment option in any disease, including acne vulgaris, were

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primarily based on doctor's experience rather than on sound research findings [44]. The resultant variability in clinical practice was recognized by medical organizations and, subsequently, consensus meetings were conducted to develop recommendations [44]. Such evolution of practice leads to the development of clinical practice guidelines (CPGs) which have been defined as statements that include recommendations, intended to optimize patient care, that are informed by a systematic review of evidence and an assessment of the benefits and harms of alternative care options [24].

However, with the increase in published CPGs, concerns about their quality have risen [3, 17, 31, 49]. On the other hand, growth in the numbers of guidelines without application of rigorous criteria for their development and production can undermine their credibility and be more harmful than beneficial. The Appraisal of Guidelines for Research and Evaluation (AGREE) Instrument evaluates the process of practice guideline development and the quality of reporting [6, 7]. The original AGREE Instrument has been updated and methodologically refined. The AGREE II which has been proven to be valid and reliable is now the new international tool for the assessment of practice guidelines [8, 9].

To our knowledge, there is no published assessment of acne vulgaris guidelines quality. We have, therefore, appraised their methodological quality with the AGREE II instrument.

Methods

Study design

We conducted a systematic review of clinical practice guidelines and their quality assessment using the AGREE II instrument.

Eligibility criteria

Inclusion criteria: We considered published documents with systematically developed statements to assist practitioners and patients decisions about appropriate health care for acne [25]. The criteria for inclusion of articles were as follows: (1) explicit statement identifying itself as a "guideline" (2) produced at national or international levels by medical associations or governmental bodies, (3) included recommendations concerning acne vulgaris therapy, and (4) guidelines that included a systematic review of the evidence.

Exclusion criteria: Consensus statements, which are defined as a document representing the collective opinion of an expert panel not based on a systematic review of the evidence, were excluded. Hormonal acne guidelines, as well as therapy guidelines focused only on a single agent or a group of medications (i.e.: just topical/oral antibiotics/isotretinoin), were also excluded.

Selection of clinical practice guidelines

Firstly, two reviewers (G.S and J-L.A) examined titles and abstracts retrieved to verify for eligibility of these according to the selection criteria. If needed, disagreements were resolved by discussion with a third reviewer (M-E.T). Three reviewers (G.S, J-L.A and M-E.T) independently examined the full-text to further verify their eligibility. We searched databases for CPGs on the treatment of acne vulgaris published from July 2002 to July 2012. The keywords initially used in TRIP database (Turning Research into Practice) and guidelines compiler entities or clearinghouses were "acne" and "vulgaris". The clearinghouses and guidelines developers websites searched are depicted in "Appendix".

Separately, we completed our search checking MEDLINE (through PubMed) combining the above Mesh terms with Practice Guideline[pt] OR Guideline[pt] OR Practice Guidelines as Topic[mh] OR guideline*[ti] OR consensus[ti] OR recommendation*[ti] OR practice guideline*[tiab]. Finally, we scanned reference lists of included articles.

We restricted the search to documents that were published in the last ten years. The search was restricted to English, French, German and Spanish languages.

Appraisal of methodological quality of the selected clinical practice guidelines

We used the AGREE II instrument to assess CPGs quality [6]. This refined instrument provides criteria to appraise the quality of clinical guidelines and consists of 23 items grouped in six domains: (1) scope and purpose, (2) stakeholder involvement, (3) rigor of development, (4) clarity and presentation, (5) applicability, and (6) editorial independence (Available at: http://www.agreetrust.org/wp-content/uploads/2013/03/1397_AGREE+II+Users+Manual+and+23-item+Instrument-+ENGLISH1.pdf). Each item is rated on a seven-point Likert scale from strongly disagree to strongly agree (1–7, respectively) [10].

In order to improve the quality of the data collection, we pilot tested the CPGs evaluation with the reviewers (a Dermatologist, a pediatrician and a general medicine physician) and who are also clinical epidemiologists. They independently rated each one of the items of the AGREE II instrument in every CPG identified.

We determined whether guidelines were evidence-based if they reported a search strategy (including at least two databases) that classified evidence quality and graded the strength of recommendations.

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We obtained the results for each domain by summing up all scores for the individual items in a domain by scaling the total as a percentage of the maximum possible score for that domain. Then standardizing was performed as follows: (obtained score–minimum possible score)/(maximum possible score–minimum possible score).

The maximum score for each domain was the number of questions multiplied by the number of reviewers multiplied by the number of scores of 7 (strongly agree). The minimum score was the number of questions multiplied by the number of reviewers multiplied by the number of scores of 1 (strongly disagree). The minimum standardized score for each domain was, therefore, 0 % and the maximum was 100 %. We validated the scores obtained by each assessor through the online AGREE tool for appraising practice guidelines (Available at: http://www.agreetrust.org/resource-centre/).

A score of 60 % average was chosen (standardization of total points as a percentage over maximum points) to establish the proportion of guidelines which scored points above this level in each domain.

We also added the final component of the AGREE II instrument which involves other two assessments: (1) The overall assessment requires the user to make a judgment according to the quality of the guideline; (2) The user is also asked whether he/she would recommend the use of the guideline.

Statistical analysis

We performed a descriptive statistical analysis for each domain. Descriptive values were mean, standard deviation, and minimum and maximum with 95 % confidence intervals (CI). Categorical variables were calculated using number of cases and the corresponding percentages. Agreement between the three reviewers was determined by the Intraclass Correlation Coefficient (ICC) with a 95 % CI. A standardized score was calculated separately for each of the six domains. The degree of agreement was classified according to the scale proposed by Landis and Koch, as follows: poor (<0.00), slight (between 0.00 and 0.20), fair (from 0.21 to 0.40), moderate (from 0.41 to 0.60), substantial (from 0.61 to 0.80) and very good or almost perfect (from 0.81 to 1.00) [29]. This provided supplementary evidence of agreement based on continuous score calculations. All analyses were performed using the statistical package SPSS (Statistical Package for the Social Sciences, Chicago, IL, USA), version 19.

Results

Our search strategy identified 103 citations. 25 out of 103 references were identified for possible inclusion, and thereafter, 19 documents were excluded (Fig. 1).

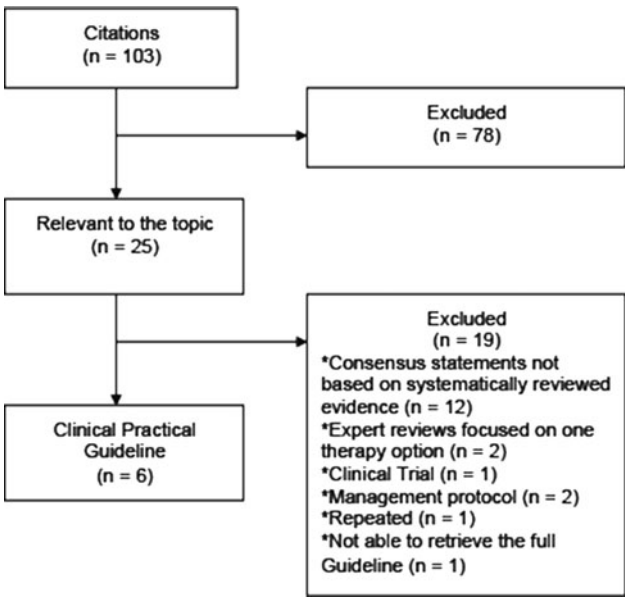

Fig. 1 Clinical practice guideline's selection process

Accordingly, six publications met our inclusion criteria [1, 33, 36, 37, 40, 48, 52].

As it is depicted in Fig. 1, reasons for document exclusion were as follows: Twelve references were not included as they were only acne expert reviews with not systematically developed statements [5, 11, 13, 16, 27, 30, 34, 35, 42, 45, 47, 50, 54, 57]; two references were excluded as they were acne expert reviews and included just one therapy option [12, 16]; one was excluded as it was a clinical trial [41]; two were not included as they were acne management protocols [23, 51]; and one guideline was repeated as it was a summary based on a CPG [52]. We excluded one CPG because we could not retrieve the whole guideline, just its summary [2].

Of the six selected CPGs, one was from the United States [52], one from Europe [37], one from France [1], two from South America [40, 48] and one from Malaysia [33].

Appraisal of guidelines

The overall ICC value among reviewers was very good: 0.981 (95 % CI 0.918–0.997). As shown, agreement among reviewers was very high. The results of the scores for each domain and their inter-rater reliability are depicted in Tables 1 and 2, respectively.

Scope and purpose

This domain covers "the overall aim of the guideline", "the specific health questions, and the target population" [10]. The mean score for the selected CPGs was 72.18 % (range 0–100 %) with just one guideline scoring below 60 %.

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Table 1 Domain scores and overall assessments according to the appraisal of guidelines for research and evaluation (AGREE II) instrument [9]

Study, year and reference	Scope and purpose	Stakeholder involvement	Rigor of development	Clarity and presentation	Applicability	Editorial independence	Overall assessment (guideline recommendation)
Strauss et al [15]	83.3	27.7	54.1	98.1	1.4	94.4	Yes, with modifications
Nast et al. [16, 17]	85.1	81.4	94.4	100	59.7	100	Yes
AFSSAPS [18]	0	31.4	43	70.3	3.0	5	No
Orozco- et al. [19]	66.6	14.8	25.6	98.1	0	22.2	Yes, with modifications
Cenetec [20]	100	55 5	47.9	98.1	6.9	66.6	Yes, with modifications
MOH and Mataela [21]	98.1	66.6	83.3	96.2	66.6	94.4	Yes
Mean (SD) Scores for each domain	72.18 (37.35)	46.23 (25.64)	58.05 (25.91)	93.46 (11.41)	22.93 (31.31)	63.76 (43.93)	

SD standard deviation

Table 2 Inter-rater reliability for each quality domain

Domain	Intraclass correlation coefficient[a] (95 % CI)
Scope and purpose	0.911 (0.835–0.994)
Stakeholder involvement	0.954 (0.804–0.993)
Rigor of development	0.974 (0.890–0.996)
Applicability	0.944 (0.762–0.991)
Editorial independence	0.916 (0.664–0.987)

Calculated for only five domains, because all guidelines received maximum possible scores from one rater for domain 4, clarity and presentation

[a] Intraclass correlation coefficient calculated using absolute agreement and two-way random effects model

Stakeholder involvement

According to the AGREE II instrument [7, 8, 10], this domain evaluates "the extent to which the guideline represents the views of its intended users", and evaluates "to what extent the guideline was developed by the appropriate stakeholders" [10]. It includes the description of the development group according to the representation of all relevant professional groups. The mean score was 46.23 % (range 14.80–81.40 %), with four of the CPGs scoring below 60 %.

Rigor of development

This domain assures the performance of a systematic search of the evidence and describes the criteria for selecting the evidence and the methods used to formulate the recommendations [10]. It also asks about an explicit link between the recommendations and the supporting evidence [10]. It also concerns with the description of health benefits, side effects and risks when formulating the recommendations, the external review of the guideline by experts prior to publication and the procedure for updating the guideline [7, 8, 10]. The mean score for this domain was just 58.05 % (range 25.60–94.40 %), and four guidelines scored under 60 %.

Clarity and presentation

According to the AGREE II instrument, "It deals with the language, structure, and format of the guideline" [10]. This domain emphasizes on the clarity, specificity and unambiguity of the recommendations [10]. The mean score obtained by the guidelines was 93.46 % (range 70.30–100 %) and none scored under 60 %.

Applicability

This domain covers "the likely barriers and facilitators to implementation, strategies to improve uptake, guideline monitoring, and resource implications of applying the guideline" [10]. The mean score in this domain was 22.93 % (range 0–66.6 %) with just one guideline scoring over 60 %.

Editorial independence

This domain "is concerned with the formulation of recommendations not being biased with competing interests" [10]. It evaluates the presence of conflicts of interest of the authors and whether the guideline was editorially independent from the funding body. The mean score was 63.7 % (range 5–100 %) with four CPGs scoring over 60 %.

Overall recommendation

It concerns with "the rating of the overall quality of the guideline and whether the guideline would be

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recommended for use in practice" [10]. According to the already described individual domains and overall scores, the European and the Malaysian CPGs were recommended with no further modifications (Table 1). From these two, the former only had applicability issues whereas the Malaysian had lower scores for the applicability and stakeholder involvement domains. In addition, the Mexican, Colombian and the United States guidelines were recommended with provisos, with lower scores regarding stakeholder involvement, rigor of development and applicability. In this respect, the latter guidelines included a very poor description of the methodology used for guideline development and they differed in the rigor of how research evidence was gathered as well as in its interpretation and application. In addition, some guidelines linked similar recommendations to a widely different body of evidence. Similarly, although all guidelines used grading systems for evaluating the quality of the evidence, four out of the six guidelines did not assess the individual quality of the studies and only the European and the Malaysian guidelines showed a critical review of the evidence.

Finally, the French CPG was not recommended due to issues in all domains, except for clarity and presentation.

In general, the best performance of CPGs was obtained in the clarity and presentation domain, followed by the scope and purpose domain. On the contrary, the harder domain to achieve was applicability (Table 1).

Other results

Although not initially considered as a priori objectives in the evaluation of CPGs, we evaluated other issues that deserve attention. Only two guidelines clearly reported outcome measures for evaluating efficacy [1, 36]. All guidelines included topical treatment and systemic treatment with antibiotics or isotretinoin but just 3 guidelines included light or laser therapy [1, 33, 40]. Importantly, just two guidelines included quality of life outcomes [33, 36]. Only one guideline included complementary and alternative medicines [52].

In addition, although all guidelines included comments on the effectiveness of systemic isotretinoin in clinical practice, none of them included the evaluation of economic analysis of such therapy. Clearly, available data for this important issue was scarce as the European CPG was the only one that added a brief discussion of this relevant issue [36].

In some guidelines the United States National Clearinghouse summary differed from the full guideline itself as some of the issues reported in the summary were not found in the whole body of the guideline [16, 52].

Discussion

Since 2002, a significant number of guidelines on the treatment of acne vulgaris in adolescents and adults have been published worldwide. Our results show that acne vulgaris therapy CPGs is moderate, varying widely between guidelines and across domains. Overall, the domains 'scope and purpose' and 'clarity and presentation' scored the highest. However, stakeholder involvement,' 'rigor of development' and 'applicability', had lower scores.

In general, the highest scores were found in the European as well as the Malaysian CPGs given that they were recommended with no further modifications. These two guidelines, however, had applicability problems and among these two, the Malaysian scored less in the 'rigor of development' and 'stakeholder involvement' domains. In this respect it is noteworthy that overall, half of the guidelines performed poorly on these two domains that focus mostly on the methodology of guideline development. Such finding requires attention since evidence gathering and interpretation must be rigorous meaning that the quality of each included study has to be assessed individually. This is important because it is suboptimal to account only the study design (i.e.: RCT or meta-analyses) as high rated evidence, as such studies could have themselves methodological or risk of bias issues.

In terms of stakeholder involvement, although some CPGs included individuals from other relevant professional groups as guideline′s developers, patient′s views were not included in the majority of CGPs, except for the European in which patients at least participated as external reviewers. This speaks poorly of guideline developers in this field as considering patients' views is crucial and may aid to the successful guideline′s implementation [21, 43].

Although high scores in the 'editorial independence' domain were obtained in 4 out of 6 CPGs, in general, such finding not necessarily reflects a real lack of influence of funders in the guideline development process, as this could reflect an insufficient or a not very explicit reporting of potential conflicts of interest. The development of sound guidelines requires methodologists, specialist and subspecialists clinicians and significant resources. Therefore, many guidelines are developed with external funding (e.g., government, professional associations, charity organizations, pharmaceutical companies). In low and middle income countries, or with limitations on the access for full-text articles, or in which the government agencies pay less importance to some medical issues (such as dermatological diseases), it is not surprising to find direct pharmaceutical industry funding. Furthermore, some professional associations in some countries need to be sponsored by the pharmaceutical industry as one of the main means to subsist. However, in terms of CPG development according to

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international standards, such associations have to be cautious in the involvement of pharmaceutical laboratories as nominators of guideline′s developers and as the only financial contributors to the whole development of the CPGs. In this respect, guidelines should include an explicit statement that the views or interests of the funding body have not influenced the final recommendations and they must also include an explicit description of any industry way of contribution in CPG′s development. Nevertheless, if complete independence for recommendations from commercial interests cannot be overcome, adapting existing guidelines to reflect the local context and circumstances is a less expensive and a potential solution [18, 26, 32, 38].

In this appraisal low and moderate scores were observed in almost all guidelines in the "applicability domain", as methods necessary to successfully implement the guidelines were not clearly reported. This finding highlights the need to improve this aspect in all CPGs in general, including a more detailed report of the facilitators and barriers to apply the guidelines [14]. Overall we found a lack of an economic perspective in the evaluated guidelines and a paucity of available data. This is relevant because clinical decisions have implications on costs and benefits to patients, and to other agents such as health suppliers, payers and society in general. Therefore, the introduction of the implications on costs and benefits in CPGs recommendations aim to provide clarity on treatment and medical technology selection in a specific clinical situation [22, 39, 55]. Such evaluations should be incorporated in guidelines of acne vulgaris treatment as most therapies are expensive. Economic analysis is also important because of the use of high cost treatment options not only by dermatologists but also by general practitioners in countries where the use of oral isotretinoin has not been regulated for its use just by specialists.

The strengths of our review lie on the broad search of documents as guidelines are not usually published in biomedical journals. It also included publications in English, in French, in Spanish, and in German, providing a more representative sample. Furthermore, since there was a very high level of agreement between appraisers, such findings strengthen our confidence in the results. However, good methodological quality and explicit reporting do not ensure optimal recommendations, and similarly, well-reported guidelines can contain inaccurate recommendations. It is also important to point out that we appraised these guidelines according to the information contained within the guidelines and did not explicitly ask for supporting documentation or background information on guideline development. It is possible that this information was simply missing from the published version of the guidelines resulting in lower domain scores.

One potential limitation is that, although we made an attempt to contact their developers, we could not locate the full-text of the Finnish guideline [2]. Since the final number of included guidelines was low, this missing evaluation might have had an effect in the analysis of inter-rater reliability particularly in the "clarity and presentation" domain.

Our review highlights the need to develop CPGs for acne therapy that uses rigorous methods that include the participation of all the relevant stakeholders. Such CPGs should also have a structured and explicit approach to evaluate the quality of the evidence and grading the strength of recommendations. It also should have a clear link of the strength of evidence with the final recommendations, be explicit in their guidance, and have a full disclosure of potential conflicts of interest.

Our results presented here are consistent with previous evaluations of CPGs about other health care topics, including the field of dermatology [3, 53, 56]. In previous appraisals regarding psoriasis, pressure ulcers and a wide range of healthcare topics guidelines, both, the "Scope and purpose" and "Clarity of presentation" domains had the highest scores whereas the scores for "Rigor of development", "Stakeholder involvement", and "Applicability" were the lowest [3, 53, 56].

In summary, the best acne vulgaris published CPGs are the European and the Malaysian which scored high, except for the applicability domain. The other CPGs vary in quality, but overall, our findings were worrying in terms of the low score obtained for the "rigor and development" domain, which accounts for methodological quality. Our review highlights the need for support to improve the quality of the majority of guidelines in Dermatology by the use and implementation of current CPGs reporting standards. Initiatives like GRADE [19, 20], AGREE II [7–9], and the Guidelines International Network (G-I–N) [46] could prove beneficial for the improvement of guidelines' quality in the near future.

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Conflict of interest Dr. Gloria Sanclemente has received speaker fees and support for attending meetings from pharmaceutical companies that sell acne vulgaris products such as Galderma and Roche laboratories, and from other companies not involved with acne products such as Pfizer and Jannsen-Cilag.

Appendix [4, 15]

Databases searched for CPGs in Acne Vulgaris.

1. National Guideline Clearinghouse (NGC) http://www.guideline.gov/.

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2. Canadian Medical Association (CMA) http://www.cma.ca/.
3. Scottish Intercollegiate Guidelines Network (SIGN) http://www.sign.ac.uk.
4. New Zealand Guidelines Group (NZGG) http://www.nzgg.org.nz/.
5. TRIP database http://www.tripdatabase.com/.
6. MEDLINE http://www.pubmed.gov/.
7. NeLH National Electronic Library for Health https://www.evidence.nhs.uk/.
8. Handbook of United Kingdom and European clinical guidelines for primary and shared care http://www.eguidelines.co.uk/about_guidelines.php.
9. AEZQ/AQuMed German Agency for Quality in Medicine http://www.aezq.de/.
10. CISMeF Catalog and Index of French-language health resources http://www.chu-rouen.fr/cismef/cismefeng.html.
11. Francophones/Catalog and Index of French -language health resources http://www.chu-rouen.fr/cismef/cismefeng.html.
12. NICE National Institute for Clinical Excellence http://www.nice.org.uk/.
13. GPC de la American Academy of Pediatrics http://www.aap.org/en-us/professional-resources/practice-support/quality-improvement/Pages/Clinical-Practice-Guidelines.aspx.
14. GPC Universidad California http://compliance.uclahealth.org/body.cfm?id=23.
15. Guidelines International Network http://www.g-i-n.net.
16. Grading of Recommendations Assessment, Development and Evaluation http://www.gradeworkinggroup.org/.
17. ICSI Institute for Clinical Systems Improvement http://www.icsi.org.
18. South African Departament of Health http://www.doh.gov.za/.
19. AHRQ Agency for Healthcare Research and Quality http://www.ahrq.gov.
20. ACP American College of Physicians http://www.acponline.org.
21. Singapore Ministery of health Guidelines http://www.moh.gov.sg/content/moh_web/home/Publications/guidelines/cpg.html.
22. CINAHL Cumulative Index to Nursing & Allied Health Literature.
23. Cochrane Library Plus http://www.update-software.com/clibplus/clibpluslogon.htm.
24. WHOLIS Sistema de información de la Biblioteca de la OMS http://www.who.int/library/databases/wholis_tutorial/es/.
25. MEDCARIB Literatura del Caribe en Ciencias de la Salud http://liscuba.sld.cu/index.php?P=FullRecord&ID=1647.
26. ADOLEC Salud en adolescencia http://www.adolec.org.ni/php/index.php.
27. PAHO Catálogo de la Biblioteca Sede de la OPS http://www.paho.org/.
28. LILACS http://lilacs.bvsalud.org/.
29. European Academy of Dermatology and Venereology http://www.eadv.org/.
30. American Aacademy of Dermatology http://www.aad.org/.
31. British Association of Dermatology (BAD) http://www.bad.org.uk.
32. American Academy of Pediatrics http://www.aap.org.
33. Associazione Italiana Dermatologi Ambulatoriali http://www.aida.it/.
34. Australasian College of Dermatologists http://www.dermcoll.asn.au/.
35. Danish Society of Dermatology http://www.danderm-pdv.is.kkh.dk/.
36. Dermatology Foundation http://dermatologyfoundation.org/.
37. Internet Dermatology Society http://telemedicine.org/.
38. Pacific Dermatologic Association http://www.pacificderm.org/.
39. Société Française de Dermatologie http://www.sfdermato.org/.
40. Society for Investigative Dermatology http://www.sidnet.org/.

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Topical tacrolimus for atopic dermatitis
Efficacy and Safety of 308-nm Monochromatic Excimer Lamp Versus Other Phototherapy Devices for Vitiligo: A Systematic Review with Meta-Analysis

DISCUSION

DISCUSIÓN

Al contrario de lo que muchos piensan, la medicina basada en la evidencia (MBE) no es un constructo nuevo o reciente(144), sino que es, en esencia, una reafirmación de los fundamentos del método científico. El método científico requiere diversos elementos: el planteamiento de una hipótesis previa, la revisión de la literatura existente sobre el tema en cuestión, una metodología bien definida, la implementación de una intervención (medicamento, procedimiento, etc.) y un análisis estadístico de los datos no sesgado.
De forma similar, la MBE implica la formulación de preguntas clínicas bien construidas, la búsqueda de la mejor evidencia para responder dichas preguntas, la evaluación crítica de dicha evidencia y su aplicación tanto en el manejo de los pacientes como en la toma de decisiones relativas al cuidado de los mismos(145).

Este trabajo de tesis doctoral integra cinco estudios con objetivos distintos pero articulados en la Dermatología Basada en la Evidencia (DME) como eje central.

Entre las enfermedades dermatológicas que más repercuten sobre la autoimagen y la calidad de vida se incluyen las que afectan a zonas expuestas de la piel (cara) como el acné vulgar y el fotodaño, además de aquellas que pueden dañar un gran porcentaje de la superficie cutánea y que van acompañadas de síntomas adicionales como el prurito, el escozor o el ardor, como ocurre con la psoriasis.

En el caso del tratamiento del daño actínico, existe limitada evidencia científica que apoye el uso preferencial de alguna de las terapias. Por otra parte, las formas moderadas a severas de la psoriasis pediátrica suelen ser más difíciles de manejar debido a las limitaciones en la aprobación de terapias sistémicas en niños, y a la incertidumbre reinante acerca del uso de la terapia biológica. Si tenemos en cuenta que los dos diseños epidemiológicos que permitirían determinar, por una parte, el efecto real de la TFD en el fotodaño y, por otra, la eficacia y seguridad de los anti-TNF en la psoriasis pediátrica

corresponderían a un ECA y a una revisión sistemática, respectivamente, entonces es relevante plantear y desarrollar estudios de este tipo en estos temas concretamente.

Con respecto a la terapia del acné vulgar (AV), su selección está determinada por la edad y las preferencias del paciente, así como por su severidad. Existen algunas terapias para las cuales hay evidencia científica que apoya su uso en el AV (como la isotretinoina por vía oral, por ejemplo). No obstante, la mayoría de tratamientos de acné han sido incluidos en guías de práctica clínica alrededor del mundo, sin que se haya realizado una evaluación crítica de las mismas hasta la fecha.

Los temas de investigación dermatológica ya mencionados cobran importancia por diversas razones: la enorme variabilidad que existe en el manejo de algunas enfermedades crónicas de la piel; la necesidad de establecer prioridades de investigación basadas en los valores y las preferencias de los pacientes, así como en criterios explícitos y verificables; la cronicidad y síntomas de la mayoría de enfermedades cutáneas; el auge en los medios de comunicación de mensajes engañosos y sin fundamento científico; y, por último, el gran influjo de la industria farmacéutica en el patrocinio de la investigación en esta especialidad.

En los apartados siguientes se profundizará en la interpretación de los hallazgos de cada estudio, en su implicación y relación en el contexto de la investigación dermatológica actual, y en las fortalezas y limitaciones encontradas para, así, construir una base para futuras investigaciones en este campo.

En esta Tesis Doctoral se ha dado respuesta a las preguntas de investigación « ¿Cuántos ensayos clínicos controlados con asignación aleatoria, y con qué características, se han publicado en revistas de Dermatología en Iberoamérica?» y « ¿Cuál es la calidad metodológica de los ensayos clínicos controlados con asignación aleatoria publicados en revistas de Dermatología en idioma español?». Además, se lograron identificar y describir de manera meticulosa y rigurosa los ensayos clínicos controlados con asignación aleatoria

(ECA) publicados en revistas de Dermatología en español, y evaluar su calidad metodológica. Para conseguirlo, se realizó una revisión exhaustiva de la literatura que consideró los elementos críticos del diseño de una revisión sistemática, y se emplearon dos importantes herramientas de la Colaboración Cochrane, a saber, la búsqueda manual de ECA y el instrumento de evaluación de los riesgos de sesgo de dichos estudios.

En estos dos trabajos se consiguieron identificar tanto todas las revistas de Dermatología en español como los ECA publicados en ellas, y se efectuó la respectiva evaluación de la calidad metodológica.

Entre los resultados destacables se incluye el reconocimiento de 21 revistas de Dermatología con un total de 144 ECA publicados entre 1969 y 2012. Se logró identificar un 80 % más de ECA en comparación con la búsqueda electrónica, lo cual coincide con lo encontrado en revistas de Dermatología como *Archives of Dermatology* (82) y *Actas Dermo-Sifiliográficas* (76, 107), y de otras áreas de la salud(108). En los 44 años evaluados se han detectado entre 1-2 ECA/año, cifra que contrasta ostensiblemente con la de revistas de Dermatología publicadas en inglés, pues, según lo reportado, una revista como *Archives of Dermatology* puede llegar a publicar hasta 11 ECA por año (82). Por otra parte, y teniendo en cuenta la implementación del CONSORT en el año 1997, se detectaron un total de 70 ECA hasta el año 2012, si bien la gran mayoría se consideraron como de "alto riesgo de sesgo" debido a la falta de información necesaria para evaluar la calidad y el rigor metodológico. Además, 15 estudios describieron las fuentes de financiación y solo cinco declararon conflictos de interés. Los hallazgos mencionados refrendan la importancia de la búsqueda manual de artículos en revistas de Dermatología, pues muchos ECA no hubiesen podido identificarse por varias razones: la poca sensibilidad de MEDLINE y EMBASE para detectar descriptores o términos en español (81, 109-111); porque solo la revista española *Actas Dermo-Sifiliográficas* está indexada en MEDLINE; o porque solo algunas de las demás revistas de Dermatología lo están en EMBASE. A lo anterior se suma la dificultad inherente a la búsqueda en otros idiomas distintos al inglés,

pues se sabe que el porcentaje de recuperación de registros entre una búsqueda en inglés y una en otro idioma puede disminuir hasta en un 37 % (112).

A pesar de lo mencionado anteriormente, el número de ECA publicados en revistas de Dermatología en español ha incrementado en las últimas décadas (118), hecho atribuible a un creciente auge de la "Medicina Basada en la Evidencia" en los últimos años que probablemente ha animado a los investigadores a centrarse en el diseño de este tipo de estudios como fuente de más evidencias y de mejor calidad.

El CONSORT, además de estandarizar la manera en que se publican los ensayos clínicos en las diferentes revistas (113), exige indirectamente una mayor calidad metodológica del estudio al obligar al investigador a describir explícitamente y en profundidad los aspectos metodológicos (113). En el primer y segundo estudio observamos que solo una de las revistas de Dermatología incluidas, *Actas Dermo-Sifilográficas*, se ceñía a esta normativa (113)(113)(113)(113)(113)(113)(113)(113)(113)(113)(113). Así, es necesario no solo promover el desarrollo de ECA, sino también la aplicación de la normativa CONSORT, tal y como lo han hecho importantes revistas de Dermatología en inglés (114). Adicionalmente, en estos 2 estudios se lograron identificar todas las revistas de Dermatología en español, aunque de algunas no se consiguió obtener información a pesar de intentar recuperar los textos completos a través de diferentes medios. Así, estos resultados dan cuenta de la necesidad imperiosa de disponer de los textos en internet, lo cual contribuiría no solo a facilitar la identificación de ECA para las revisiones sistemáticas, sino también a la globalización del conocimiento y a proporcionar una mayor visibilidad a las publicaciones en lengua hispana.

Con respecto a los temas dermatológicos más investigados en Ibero-Latinoamérica, destaca la coincidencia entre las revistas españolas y latinoamericanas en cuanto a patologías como la psoriasis, las micosis y el acné. Este hecho puede ser el reflejo o bien

de un mayor impacto de estas enfermedades en los pacientes dermatológicos—lo cual conduciría a buscar una terapia eficaz—, o de un aumento del interés por parte de la industria farmacéutica para patrocinar este tipo de estudios (115, 116).

En el tercer trabajo se logró determinar la eficacia y seguridad de una terapia en el fotodaño, trastorno para el cual no existe aún un tratamiento de oro.

El aspecto metodológico de este trabajo, como insumo de evidencia científica de alto nivel, se basó en la utilización del diseño de un ensayo clínico controlado con placebo, doble ciego y aleatorizado. Este tipo de estudio, de realizarse de manera rigurosa y de acuerdo con la reglamentación de buenas prácticas clínicas, es la metodología más apropiada y con menor riesgo de sesgos para responder a la pregunta « ¿Cuál es la eficacia y seguridad de la terapia fotodinámica con MAL y luz solar para el tratamiento de pacientes adultos con daño actínico facial?». Dicha pregunta se respondió en este trabajo de la siguiente manera: 1- determinando la eficacia clínica del metil aminolevulinato (MAL) + dos horas de luz solar comparado con placebo + dos horas de luz solar en adultos con daño actínico facial; 2- identificando los patrones clínicos basales de daño actínico de la piel y postratamiento con MAL + luz solar comparado con placebo + luz solar; 3- cuantificando el dolor que experimentaron los pacientes con cada una de las terapias inmediatamente después de cada sesión de terapia fotodinámica (TFD); 4- determinando los cambios en la escala de fotodaño facial global y específico presentados en ambos grupos de tratamiento un mes después de la tercera sesión; y 5- cuantificando la irradiancia y la luminancia durante las dos horas de cada sesión.

En respuesta a la incertidumbre reinante respecto al tratamiento del fotodaño facial, este tercer trabajo demostró que la TFD con luz solar fue segura y eficaz, lo cual concuerda con los resultados obtenidos con la TFD convencional (117). Así, el riesgo de fracaso terapéutico fue menor en el grupo de la intervención activa que el de placebo (RR: 0,18; CI95 %: 0,08-0,41). Asimismo, el número necesario a tratar para obtener un beneficio con dicha intervención fue de uno (CI95 %: 1,11-1,78).

Por otra parte, el bajo dolor experimentado por los pacientes del estudio fue un hallazgo muy relevante, pues este es el principal inconveniente de todos los procedimientos disponibles para el fotodaño como la quimioexfoliación, la luz intensa pulsada y los láseres (33, 118-120). Además, los efectos secundarios y los eventos adversos fueron mínimos; encontrándose que los eventos adversos no estaban relacionados directamente con la terapia.

En el cuarto trabajo se realizó una revisión sistemática (RS) de la evidencia disponible proveniente de ensayos clínicos aleatorizados que evaluaran el efecto de los agentes anti-TNF en los pacientes con psoriasis pediátrica. Este tipo de diseño de estudio sería el más apropiado para responder a la siguiente pregunta propuesta: « ¿Cuál es la eficacia y seguridad de los agentes Anti-TNF en el tratamiento de la psoriasis pediátrica?».
Con el desarrollo de este estudio se identifica la presencia de un ensayo clínico de alta calidad, pero simultáneamente se confirma la gran escasez de estudios realizados en niños sobre una enfermedad con un alto impacto en la calidad de vida de los pacientes (121).

En esta RS se encontraron 11 publicaciones que describían un solo ECA de este tema, lo cual prueba la duplicidad en el reporte de la información. Con respecto a lo encontrado en el artículo original, el etanercept resultó ser seguro y eficaz para el tratamiento de la psoriasis moderada a severa en niños (RR [de mejorar]: 4,95; IC95 %: 2,83 a 8,65 y RR [de no mejorar]: 0.49; CI95 %: 0,39-0,62). Los resultados de calcular la reducción del riesgo absoluto y el número necesario a tratar (NNT) para obtener un beneficio con etanercept fueron de 45 % y dos (IC95 % 1,77-2,95), respectivamente. Estos datos son una prueba adicional de la eficacia del producto a las 12 semanas. Este ECA se caracterizó por su bajo riesgo de sesgo gracias al diseño doble ciego con enmascaramiento de los evaluadores de los desenlaces, a un adecuado seguimiento de los pacientes y a no tener el reporte selectivo de los desenlaces. Sin embargo, cabe mencionar que los autores del único ECA incluido describen los eventos adversos (EA) como tasas ajustadas por exposición, lo cual podría ser válido si la tasa de incidencia de los eventos fuera constante en el tiempo, pero

en la vida real no es así. Además, algunos EA pueden correlacionarse entre sí, de manera que, para describir dichos eventos, se necesitan otros métodos estadísticos más avanzados y comprensibles por parte del personal sanitario y de los tomadores de decisiones.

A pesar de los resultados obtenidos en el único ECA publicado de agentes anti-TNF en la psoriasis pediátrica, existe aún cierto grado de incertidumbre en cuanto a la mejoría de la calidad de vida con el etanercept, así como respecto a su seguridad a medio y largo plazo en este tipo de psoriasis. Además, dado que un solo ensayo clínico no aporta un cuerpo de evidencia suficiente para recomendar una terapia, se espera que la inclusión futura de otros ensayos clínicos que se encuentran actualmente en curso permita rellenar los vacíos de conocimiento sobre este tema. Estos hallazgos cobran relevancia en la práctica médica, pues, en general, los ensayos clínicos realizados en niños son escasos en diversas áreas de la Medicina. Asimismo, se precisa evidencia de buena calidad para la toma de decisiones respecto a una enfermedad que puede manifestarse de forma severa en niños, y para la cual no existen ensayos clínicos que apoyen el uso de otras terapias ampliamente usadas en la práctica clínica, como el metotrexate y la ciclosporina.

Ante la incertidumbre reinante en el tema y el planteamiento de la pregunta « ¿Cuál es la calidad de las Guías de Práctica Clínica (GPC) publicadas sobre el tratamiento del acné vulgar?», el quinto trabajo identificó las GPC sobre el tratamiento de esta patología cutánea y valoró de manera sistemática la calidad de las guías disponibles y de sus recomendaciones, con el respectivo soporte de la evidencia.

La evaluación mostró que tan solo dos GPC de las seis incluidas fueron recomendadas sin modificaciones. En general, los dominios que presentaron menor puntuación fueron: rigor en la elaboración, participación de los interesados y aplicabilidad.

Tal hallazgo no solo esta refrendado por publicaciones previas sobre la evaluación de GPC en diferentes áreas de la salud (122-124), sino que requiere atención, ya que tanto la recopilación como la interpretación de la evidencia deben incluir un análisis meticuloso de cada estudio que soporte dicha evidencia. La necesidad de realizar dicho análisis tiene su

origen en la preocupación respecto a que muchas de las guías evaluadas dan por seguro que todos los ensayos clínicos proporcionan evidencia de alta calidad —gracias a su diseño doble-ciego y asignación aleatoria— sin haber realizado un análisis minucioso de la calidad de cada uno de los estudios. Estas lagunas en la evaluación se ven reflejadas en el caso de un medicamento como el ácido azelaico en el tratamiento del AV, puesto que, a pesar de contar con ensayos clínicos que demuestran su eficacia, los resultados en la práctica clínica son contradictorios. Por otra parte, preocupa que sean pocas las guías que tienen en cuenta varias disciplinas en su elaboración y que en la gran mayoría de GPC no se haya reparado en la perspectiva de los pacientes, pues ambos aspectos son cruciales a la hora de implementar una GPC (125, 126).

Asimismo, aunque las puntuaciones hayan sido altas en el dominio de la «independencia editorial», no indica ausencia de influencia de los patrocinadores, pues es muy probable que la información proporcionada acerca de los conflictos de interés de los desarrolladores de las guías haya sido insuficiente o que no se haya escrito explícitamente.

Es importante resaltar que el desarrollo de una GPC no solo implica altos costos, sino que requiere metodólogos, expertos temáticos, especialistas y sub-especialistas. Así, la mayoría de GPC en países desarrollados es auspiciada por el gobierno de cada país y por asociaciones científicas. No obstante, en países en vías de desarrollo en los que el Estado asigna pocos recursos a la salud, o en los que existe un acceso limitado al texto completo de las publicaciones científicas, no es inusual que la industria farmacéutica financie directamente la elaboración de GPC; de hecho, en estos países, numerosas asociaciones científicas dependen de los laboratorios farmacéuticos para poder subsistir. Por lo tanto, y en aras de contribuir a una mayor transparencia, debe declararse explícita y completamente el tipo y grado de apoyo proporcionado por la industria farmacéutica en el proceso de elaboración o adaptación de una GPC.

En este análisis de las GPC del tratamiento del *acne vulgaris* preocupan las bajas puntuaciones en el dominio de «aplicabilidad de las guías», lo cual es el reflejo de la falta

de articulación en la elaboración de las guías y en su implementación. En este sentido, es necesario mejorar el reporte de este dominio nombrando a los facilitadores de forma explícita y explicando los obstáculos que puedan interferir en el proceso de implementación. De acuerdo con la literatura, esta problemática no es infrecuente y precisa la corrección de factores importantes que influyen de manera negativa en este proceso (127, 128).

Otro aspecto que debe analizarse en este trabajo es la ausencia de estudios económicos del tratamiento del AV, un hecho relevante si tenemos en cuenta que las decisiones clínicas repercuten en los costes que asumen los pacientes, pagadores y la sociedad en general (129-131). Estos análisis económicos son todavía más imperativos en países que no regulan que solamente los dermatólogos puedan prescribir terapias de alto costo para el AV, como la isotretinoina oral, los láseres o la luz intensa pulsada. De todo lo revisado se destaca la necesidad de desarrollar GPC del tratamiento del AV que utilicen una metodología rigurosa con la participación de todos los interesados, que garanticen su aplicabilidad y expliquen el proceso de implementación. Por último, un aspecto importante que hay que contemplar en la elaboración de GPC de AV en el futuro es la aplicación del sistema GRADE (*Grading of Recommendations Assessment, Development and Evaluation*) para evaluar tanto la calidad de la evidencia como la fuerza de las recomendaciones.

Fortalezas:

Entre las fortalezas de los cinco trabajos realizados, se destacan las siguientes: La integración de cinco estudios con objetivos distintos pero articulados en un eje central denominado Dermatología Basada en la Evidencia (DME). Por lo tanto, cada diseño de investigación, ha aportado en sí mismo conocimiento útil para la práctica dermatológica partiendo de lo meramente descriptivo hasta lo analítico. Específicamente en el primer y segundo estudios se evaluaron una gran cantidad de revistas, volúmenes y números evaluados de manera sistemática y exhaustiva. De esta forma se identificaron un total de

28 revistas de Dermatología, 21 de las cuales se incluirán próximamente en el Registro Central de Ensayos Clínicos Controlados de la Colaboración Cochrane (CENTRAL), y, por lo tanto, estarán disponibles para futuras revisiones sistemáticas (RS) y otros documentos de síntesis. Por otra parte, en la búsqueda electrónica se lograron hallar casi todos los ECA de la búsqueda manual, a excepción de dos referencias que se hubiesen podido identificar manualmente de haber contado con el texto completo en su momento. Asimismo, cabe resaltar que la detección y recuperación del texto completo de los 70 ECA identificados en el segundo estudio no hubiese sido posible mediante una búsqueda electrónica, pues únicamente la revista *Actas Dermo-sifiliograficas* se encuentra indexada en MEDLINE, y solo *Dermatología Revista Mexicana*, *Revista Argentina de Dermatología*, *Medicina Cutánea Ibero Latinoamericana* y *Piel* lo están en EMBASE (132, 133). Otras fortalezas de estos estudios fue el análisis por duplicado de la calidad de los ECA, y el uso de las herramientas Cochrane, las cuales han sido debidamente validadas y cuentan con reconocimiento mundial. (Disponible en: http://handbook.cochrane.org/chapter_8/8_assessing_risk_of_bias_in_included_studies.htm).

La fortaleza del tercer trabajo radicó en su diseño aleatorizado, doble ciego y controlado con placebo, así como en el rigor metodológico de su ejecución y monitorización bajo la estricta regulación de las buenas prácticas clínicas. La importancia de este tipo de diseño metodológico radica en su validez interna cuando se asegura que la única diferencia entre los 2 grupos asignados al azar es la exposición a la intervención. En este tercer trabajo a pesar de encontrar un desequilibrio en algunas de las características basales de ambos grupos (en variables que pudieran haber incidido en el desenlace principal, e.g: sexo, fototipo de piel y escala global de fotodaño), estudios recientes apuntan hacia una escasa o nula relación entre el sexo y el fototipo cutáneo, y el efecto final de la terapia fotodinámica con MAL (134, 135). Por otra parte, y en lo referente a la escala global de fotodaño, su desequilibrio explicado por el azar muestra un porcentaje mayor de pacientes con un fotodaño facial mayor en el grupo de la intervención activa, por lo que su

eficacia se encuentra aún más favorecida teniendo en cuenta que esta diferencia "castigaría" más el efecto de dicha intervención.

Por otra parte, entre las fortalezas del cuarto trabajo se incluye el desarrollo de una RS en el marco de la Colaboración Cochrane, una red mundial que busca contribuir con la preparación, actualización y divulgación de información científica de alta calidad para tomar decisiones clínicas y sanitarias bien fundamentadas (136-138). Así, la RS cumplió los altos estándares metodológicos de este tipo de diseño de estudio y, también, incluyó la búsqueda sistemática de la información, efectuada por el *Cochrane Skin Group* (CSG). Este grupo precisamente, junto con sus numerosos revisores, auditó y corrigió el protocolo inicial y el manuscrito final de la revisión. En consecuencia, se ganó más experiencia en cuanto al diseño y la ejecución de este tipo de estudios, y al desarrollo de esta clase de trabajos, con vistas a realizar muchos más en un futuro en alianza con el CSG y a formar parte de su comité editorial.

Por último, entre las fortalezas de la evaluación de GPC cabe mencionar el uso de una herramienta validada y estandarizada como el AGREE II, la búsqueda exhaustiva de la información, la inclusión de guías en cuatro idiomas y el alto grado de acuerdo entre los evaluadores; todo ello influye en la validez interna del estudio. Por otra parte, este análisis contribuyó en la identificación de las GPC de mejor calidad para su posible posterior adaptación en Colombia.

Limitaciones:

Las limitaciones de este compendio de publicaciones están dadas por las inherentes a cada diseño específico. Por lo tanto, por su carácter descriptivo y retrospectivo, entre las limitaciones del primer y segundo estudio se incluye la imposibilidad de tener acceso al 100 % de los artículos desde su publicación. Otra limitación es que se pudieron haber excluido ECA en español publicados en revistas que no trataran de Dermatología, o estudios publicados en revistas de Dermatología en otro idioma. Sin embargo, es probable

que no se hayan encontrado ECA dado que la producción científica antes de los 70 era muy baja, además de que dichas publicaciones no incorporaron los criterios CONSORT que se requieren a los autores. Otra limitación del segundo estudio es la variabilidad entre los ECA identificados en cuanto a los desenlaces y la forma de medirlos, lo cual deriva en una alta heterogeneidad entre los estudios que impide resumir los resultados cuantitativamente en un metanálisis.

Entre las limitaciones inherentes al ensayo clínico como tal, se encuentran las dos desviaciones del protocolo de tipo administrativo, si bien no afectaron a la seguridad o integridad de los participantes. Además, la imposibilidad de generalización de los hallazgos en los hombres y en pacientes con piel de fototipo I, y la falta de uso de una escala validada y confiable para la evaluación del daño solar (que podría haber dado lugar a una medición más objetiva de los efectos de la terapia), constituyen otra limitación. Adicionalmente, el análisis post-hoc de subgrupos y el ajuste de co-variables mostró que solo el fototipo de piel pudiera desempeñar un papel en el desenlace principal, y no se observó relación con la edad. No obstante, se debe tener en cuenta que el análisis post-hoc de subgrupos y el ajuste de co-variables son meramente exploratorios, pues en estudios recientes prospectivos no se ha encontrado relación entre el fototipo cutáneo y el efecto de la TFD (134, 135), mientras que la edad sí parece incidir en la formación de protoporfirina IX, pues se ha encontrado que a mayor edad se disminuye su formación(139), lo que conduciría a un menor efecto de la TFD.

Las limitaciones de la revisión sistemática (RS) incidirán necesariamente en la toma de decisiones en pacientes con psoriasis pediátrica entre moderada a severa, pues un solo ECA de un agente Anti-TNF (etanercept) resultó siendo elegible, además de la falta de evidencia científica que soporte su uso en niños menores de 4 años, y su seguridad a largo plazo en esta población. No obstante, se debe tener en cuenta que según lo reportado, la psoriasis en niños menores de cuatro años de edad es inusual y en la mayoría de los casos se limita a pequeñas áreas(140, 141). Adicionalmente, la actualización futura de esta RS

con la inclusión de estudios en curso de otros biológicos; de otros agentes anti-TNF y el seguimiento a largo plazo de los pacientes del único ECA incluido, definirá en su momento cual sería la mejor terapia y la más segura en la práctica clínica dermatológica y las correspondientes políticas de salud en este tema específico.

Por último, entre las limitaciones de la evaluación de guías de práctica clínica (GPC) se incluye que las guías se valoraron tal y como estaban publicadas, es decir, no se solicitó información adicional que argumentara o detallara el proceso de elaboración de las guías, lo cual pudo haber incidido en los resultados de la puntuación. Asimismo, no se ha podido encontrar el texto completo de la guía de Finlandia —si bien las GPC de este país se caracterizan por ser accesibles a través de bases de datos electrónicas incluidas en una página web del gobierno—, lo cual ha podido repercutir en la puntuación obtenida (142, 143).

Como reflexión final, el presente trabajo de tesis doctoral, por una parte, contesta a preguntas aún sin respuesta en cuanto a la terapia de enfermedades dermatológicas específicas como el fotodaño y la psoriasis pediátrica; y por otra, identifica vacíos en el conocimiento en lo que respecta a la evidencia científica que apoya la práctica dermatológica.

Esta contribución a la especialidad es relevante hoy más que nunca dada la avalancha de medicamentos de alto costo y el auge de la Dermatología Cosmética. Además, y al igual que sucede en otras ramas de la medicina, los dermatólogos debemos ser capaces de formular preguntas para determinar el tipo de evidencia que las responde, o para plantear los tipos de diseño de estudios que lograrían eliminar la incertidumbre reinante. Así, en el escalafón más alto en la jerarquía de la evidencia figuran los ensayos clínicos, las revisiones sistemáticas (RS) y los metanálisis, puesto que sus diseños son menos

propensos al sesgo, y deberían ser la base de la práctica dermatológica actual. Sin embargo, y de acuerdo a lo mencionado, la realidad es otra.

Aunque la Dermatología Basada en la Evidencia se promueve cada vez más, preocupa que en muchos casos las pautas de tratamiento se basen exclusivamente en las opiniones de un experto. Si bien esta problemática no se resuelve del todo con la utilización de terapias basadas en al menos un ensayo clínico, y ante la carencia de mejores fuentes de conocimiento, el deber de cualquier dermatólogo es el de adquirir las destrezas suficientes para lograr identificar la mejor evidencia disponible. Por lo tanto, este trabajo de tesis doctoral, además de generar conclusiones específicas de cada uno de los distintos tipos de estudios que lo conforman, ha contribuido a identificar discrepancias entre la práctica clínica dermatológica y la evidencia disponible. Además, se ha generado a la vez conocimiento útil directamente aplicable para un mejor control y tratamiento del fotodaño y la psoriasis pediátrica. Así, en este trabajo de tesis se han presentado evidencias en Dermatología partiendo desde lo meramente descriptivo hasta lo analítico y, además, se ha determinado la calidad de algunas de las evidencias encontradas con el fin de contribuir a la práctica dermatológica y, de forma más general, a la Dermatología Basada en la Evidencia. Es así como en la medida en que cada vez se promueva más altos estándares en la investigación clínica Dermatológica más cerca se estará de generar una evidencia ética, válida, fiable y útil tanto en la práctica clínica como en la toma de decisiones, y en el establecimiento de políticas de salud coherentes con las necesidades de la especialidad en sí misma y de los pacientes con enfermedades dermatológicas.

CONCLUSIONES

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- Se identificaron 21 revistas de Dermatología iberoamericana con un total de 144 ensayos clínicos controlados con asignación aleatoria (ECA) publicados entre 1969 y 2012, un 80 % más de los detectados en la búsqueda electrónica.

- La gran mayoría de los ECA evaluados se clasificaron como de «riesgo de sesgo alto» por la falta de reporte de la información necesaria para valorar la calidad y el rigor metodológico, así como por la escasa descripción de las fuentes de financiación y los conflictos de Interés.

- La baja calidad metodológica encontrada en la gran mayoría de los ECA evaluados en la literatura dermatológica iberoamericana no permitió generar nuevo conocimiento de calidad para poder establecer o confirmar pautas de tratamiento eficaces para las enfermedades dermatológicas estudiadas.

- La investigación clínica experimental en Dermatología que se publica en España y Latinoamérica debe mejorar ostensiblemente tanto en su diseño como en el reporte de los resultados, con el fin de ser válida, ética, coherente y útil y, además, para que se considere como evidencia de alta calidad en las revisiones sistemáticas de Cochrane.

- El metil aminolevulinato (MAL) + dos horas de luz solar en adultos con daño actínico facial fue eficaz y seguro, comparado con placebo + dos horas de luz solar, con un gran tamaño del efecto y con un número necesario a tratar (NNT) muy cercano a uno.

- Si se tiene en cuenta que no existe un "tratamiento de oro" para el daño actínico facial, el uso en la práctica dermatológica del metil aminolevulinato con luz solar para el tratamiento de esta patología cutánea es favorable según los resultados obtenidos en el ensayo con evidencia de alta calidad.

- El rigor científico del ensayo clínico controlado con placebo, doble ciego y aleatorizado contribuye a la investigación clínica dermatológica mundial. A su vez, posibilita su potencial inclusión en una revisión Cochrane sobre el tratamiento del fotodaño. No obstante, se necesita llevar a cabo en el futuro un ensayo clínico de fase III en el que se incluya la evaluación *a priori* del efecto de la intervención en subgrupos específicos (tanto en más hombres como en pacientes con fototipo I).

- Los resultados de eficacia y seguridad a corto plazo del etanercept en el tratamiento de la psoriasis pediátrica, respaldados por evidencia de alta calidad, permiten considerar el uso de etanercept en la práctica dermatológica en niños con psoriasis de moderada a severa.

- La inclusión de un solo ensayo clínico en la Revisión Cochrane tiene implicaciones para la investigación, ya que un único ensayo clínico no aporta un cuerpo de evidencia suficiente para recomendar una terapia. En consecuencia, se requiere la inclusión futura de otros ensayos clínicos de terapias anti-TNF para confirmar o no la eficacia y seguridad de estos tratamientos, máxime si tenemos en cuenta que no existen ensayos clínicos que favorezcan el uso de otras terapias ampliamente usadas en la práctica clínica como el metotrexate y la ciclosporina.

- Se identificaron dos guías de práctica clínica (GPC) de alta calidad sobre el tratamiento del acné, pero la mayoría de guías presentaron deficiencias en el rigor de la elaboración, en la participación de los interesados y en su aplicabilidad. Asimismo, es relevante emplear el sistema GRADE (*Grading of Recommendations*

Assessment, Development and Evaluation) en dichas guías, el cual permite evaluar tanto la calidad de la evidencia como la fuerza de las recomendaciones.

- La calidad de las guías de práctica clínica en el tratamiento del acné dan cuenta de la necesidad de incorporar grupos multidisciplinarios desarrolladores con expertos temáticos y metodólogos que mejoren el rigor en la elaboración, la aplicabilidad e implementación de las guías. De esta forma se estaría generando conocimiento útil y válido para la práctica dermatológica.

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