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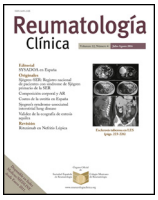

Original Article

Effectiveness of Conventional Disease-modifying Antirheumatic Drugs in Psoriatic Arthritis: A Systematic Review☆

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ABSTRACT

Background: Due to the clinical heterogeneity of psoriatic arthritis (PsA), recommendations have been developed by international groups to guide therapeutic decisions of the rheumatologist. The objective of the current systematic review (RS) was to evaluate the evidence of efficacy of disease-modifying antirheumatic drugs (DMARDs) in PsA.
Methods: Literature search in Medline, EMBASE, Cochrane Library, from 2008 to 2014. We included RS, randomized clinical trials and observational studies, in patients with PsA and an evaluation of efficiency of conventional DMARDs (methotrexate, sulfasalazine, leflunomide), according to the following outcomes: peripheral and axial symptoms; peripheral radiological damage; enthesitis according to power Doppler ultrasound or magnetic resonance imaging (enthesitis count before and after therapy); dactylitis; uveitis.
Results: Title and abstract were used to retrieve 1662 documents for this review (Medline, n = 433; EMBASE n = 1132; Cochrane, n = 97), and 48 studies were selected for detailed reading; finally, 8 studies were included.
Conclusions: Since the studies included are not robust, and there are arguments to support the effectiveness of methotrexate, the evidence observed with the treatment of DMARDs in PsA is not conclusive.

Eficacia de los fármacos antirreumáticos modificadores de la enfermedad sintéticos en artritis psoriásica: una revisión sistemática

Palabras clave:
Artritis psoriásica
Fármacos antirreumáticos modificadores de la enfermedad
Revisión sistemática

RESUMEN

Antecedentes: Dada la heterogeneidad clínica de la artritis psoriásica (APs), se han elaborado recomendaciones por grupos internacionales para orientar las decisiones terapéuticas del reumatólogo. Esta revisión sistemática (RS) tiene el objetivo de evaluar la evidencia sobre la eficacia de los FAME en APs.
Métodos: Búsqueda bibliográfica en Medline, Embase, Cochrane Library, desde 2008 hasta 2014. Se incluyeron RS, EC y estudios observacionales, en pacientes con APs con evaluación de eficacia de FAME sintéticos (metotrexato, sulfasalazina y leflunomida), los siguientes desenlaces: síntomas periféricos; daño estructural radiológico periférico; síntomas axiales; entesopatía por ecografía o resonancia magnética (número de entesis antes y después del estudio); dactilitis, y uveítis.
Resultados: Se recuperaron 1.662 documentos para revisar por título y «abstract» (Medline, n = 433; Embase n = 1.132; Cochrane, n = 97), se seleccionaron 48 estudios para su lectura detallada, y se incluyeron 8 estudios.
Conclusiones: Ya que los estudios incluidos no son consistentes, y hay argumentos para apoyar la eficacia del metotrexato, la evidencia observada con el tratamiento de FAME en APs no es concluyente.

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Introduction

Psoriatic arthritis (PsA) is a systemic inflammatory disease that affects 20%–30% of patients with psoriasis. It is characterized by inflammation involving the musculoskeletal system and the skin, including its clinical manifestations, the axial spine, peripheral joints, enthesitis, dactylitis and nail and skin lesions.[1] Certain patients have a mild course, whereas others can develop radiological joint damage, peripheral joint destruction and functional disability. Systematic reviews (SR) have been carried out, some with a meta-analysis,[2–4] on the efficacy of treatment in PsA,[2–5] and have demonstrated a low level of evidence (LE) regarding the effectiveness of synthetic disease-modifying antirheumatic drugs (DMARDs). However, in the attempt to offer guidance to specialists, given the heterogeneity of the clinical presentation and the different degrees of severity in joint involvement,[1] 2 international groups, on the basis of those SR, have formulated recommendations concerning treatment. These groups are the European League Against Rheumatism (EULAR),[6] with an algorithm focused mainly on musculoskeletal symptoms, and the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA),[7] that evaluated 5 domains (peripheral arthritis, skin and nail involvement, enthesitis, dactylitis and axial arthritis).[8] As a result, for active peripheral arthritis, both recommended treatment with DMARDs, such as methotrexate (MTX), sulfasalazine (SSZ) and leflunomide (LEF).

Methotrexate has frequently been utilized as the first DMARD to be administered in PsA because of the efficacy it shows in the treatment of joint and skin disorders.[9] Despite the low LE, MTX is still one of the most widely used drugs in PsA.[1] Thirty percent of the visits to the rheumatology department of patients referred from dermatology involves the addition of a new DMARD, with MTX being that most frequently employed.[10] The scarcity of high-quality clinical trials supporting its efficacy in PsA compelled us to ask the reason for the generalized use of MTX in PsA,[1] its effectiveness and for which clinical phenotype of PsA. Moreover, although clinical trials have not shown that the efficacy of MTX versus placebo is sufficiently significant, it is considered that the design of those studies had methodological limitations that make it unviable to draw definitive conclusions.[11] Therefore, the objective of this report was to carry out a systematic reassessment of the available evidence on the utility of DMARDs in the management of PsA. This forms part of the process of updating the clinical practice guidelines for the treatment of axial spondyloarthritis and PsA of the Spanish Society of Rheumatology (SER) (ESPOGUIA),[12] the previous version of which was issued in 2009.

Material and Methods

We performed a SR in 3 databases: Medline, EMBASE and the Cochrane Library. They included studies in English, Spanish and French, dating from January 2008 to November 2014, to retrieve articles on the efficacy of DMARDs in PsA. The terms employed for the search strategy involving high-sensitivity descriptors (MG) are shown in the Supplementary appendix.

Inclusion criteria: using the population, intervention, comparison and outcome (PICO) format, we selected those randomized controlled trials (RCT) that met the following requirements: (1) adults with PsA with a patient population of 50 or more individuals; (2) intervention with traditional DMARDs (MTX, SSZ, LEF) versus placebo; (3) efficacy outcome measures in terms of changes in: (a) peripheral symptoms (American College of Rheumatology [ACR] 20/50/70, EULAR response based on Disease Activity Score in 28 joints, Psoriatic Arthritis Response Criteria [PsARC]; peripheral radiological structural damage [Sharp/van der Heijde score—hands, wrists and feet—modified for PsA, which includes distal interphalangeal joints); (b) axial involvement (Bath Ankylosing Spondylitis Disease Activity Index, Bath Ankylosing Spondylitis Functional Index, Assessment of SpondyloArthritis international Society [ASAS] 20/40 5/6); (c) enthesopathy according to ultrasound or magnetic resonance imaging with number of entheses (Maastricht Ankylosing Spondylitis Enthesitis Score, Leeds Enthesitis Index) on inclusion and at the end of the study (percentage improvement); (d) dactylitis, with number of affected digits at baseline and at the end of the study (percentage improvement); and (e) uveitis, with number of episodes prior to and after treatment. *We included* SR of RCT (with preference for phase III or IV). We also selected studies that helped to partially respond to the question posed (efficacy and safety of a traditional DMARD versus a traditional DMARD or versus a combination of several traditional DMARDs). When there was no existing evidence on a question because of the design of a SR of RCT, we considered observational studies included in the SR. *We excluded* reports that did not adjust to the components of the PICO question, as well as abstracts, posters, narrative reviews, letters, editorials and any text that had not been published. The selection of the studies was performed by a reviewer (JM) in successive phases: selection of titles and abstracts from the selected titles, review of the complete text of the selected studies and their evaluation, to eliminate articles that did not meet the inclusion criteria. We also performed a hand-search in the bibliography of the studies included. Doubts that arose during the selection process were weighed by 2 methodologists from the SER (PD, DS) and a consensus was reached in every case. To manage the literature references we utilized EndNote X7. In the critical reading of the articles and the evaluation of the quality, we employed the checklists of the Scottish Intercollegiate Guidelines Network (SIGN).[13] To assign the LE, we used the Oxford system.[14]

Results

We retrieved 1662 documents to review on the basis of their title and abstract (Medline, n = 433; EMBASE, n = 1132; Cochrane, n = 97). In all, 48 articles were selected for full-text reading; of these, 40 were excluded (and can be made available on request). Ultimately, 8 studies met the inclusion criteria (Fig. 1) (Tables 1 and 2 providing evidence synthesis). In all, there were 2 SR,[2,5] 2 RCT included in 1 of these SR,[15,16] an open-label RCT not included in the SR,[17] 3 observational studies (2 prospective studies[18,19] and

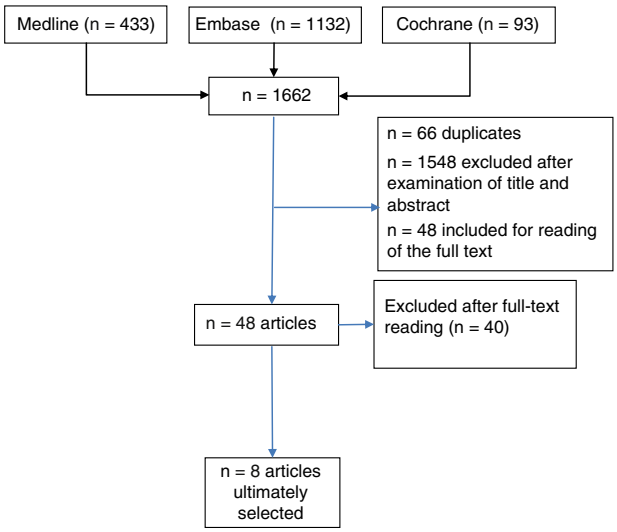

Fig. 1. Flow chart indicating the inclusion and exclusion of the studies retrieved.