Current Evidence of the Management of Undifferentiated Spondyloarthritis: A Systematic Literature Review

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Objective: To examine the efficacy of available drugs in undifferentiated spondyloarthritis (u-SpA).

Methods: Systematic review of studies retrieved from Medline (1961-July 2009), Embase (1961-July 2009), and Cochrane Library (up to July 2009). A complementary hand search was also performed. The selection criteria were as follows: (population) u-SpA patients; (intervention) nonsteroidal anti-inflammatory agents, disease-modifying antirheumatic drugs, anti-tumor necrosis factor α, anakinra, abatacept, biphosphonates, or thalidomide; (outcome) pain, function, structural damage and quality of life; (study design) randomized controlled trials (RCT), cohort studies, and case reports; (level of evidence) according to The Oxford Centre for Evidence-based Medicine (update 2009). An additional narrative review was performed to analyze the effects of drug therapies in patients with spondyloarthritis according new Assessment of Spondyloarthritis International Society criteria.

Results: The following 7 studies were included: 2 RCT, 1 cohort study, and 4 case reports, which included 117 patients with u-SpA (mostly young men). No evidence related to the effect of nonsteroidal anti-inflammatory agents or disease-modifying antirheumatic drugs on u-SpA patients was found. Infliximab and etanercept showed some benefit regarding clinical outcomes, function, and quality of life. Two RCT reported important benefit of infliximab and adalimumab also in patients with predominantly axial spondyloarthritis. Rifampicin plus doxycycline improved some clinical outcomes but ciprofloxacin had no benefit. Anecdotal positive evidence was reported with pamidronate. No serious adverse events were reported in the retrieved studies.

Conclusion: Low-quality evidence suggests a benefit of tumor necrosis factor α blockers in u-SpA and good-quality evidence in predominantly axial spondyloarthritis. The use of antibiotics remains controversial. High-quality trials are needed to definitively assess the effect of available drugs in these patients.

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The spondyloarthritis (SpA) comprise a group of closely related diseases with common, genetic, clinical, radiologic, and immunologic features. Undifferentiated spondyloarthritis (u-SpA) represents one of the most frequent SpA subtypes in clinical practice after ankylosing spondylitis (1), with an estimated prevalence between 0.7% and 1.3% (2,3). Traditionally, patients with suggestive clinical features such as inflammation of axial joints, asymmetric oligoarthritis, dactylitis, inflammatory eye disease, or enthesitis were diagnosed as u-SpA patients if they did not meet classification criteria for other SpA (4). It is well known that many of these "unclassified" patients may evolve to other SpA subsets or enter into spontaneous remission (5). This may explain, at least in part, the lack of specific evidence to guide the treatment of patients with u-SpA that traditionally have been managed according to drug patterns from other SpA (6,7). This paucity of information contrasts, however, with the im-

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portant number of "unclassified" patients affected by multiple SpA-suggestive complaints in daily practice that requires an early and appropriate treatment. Recently, the Assessment of SpondyloArthritis international Society (ASAS) has developed new classification criteria, especially for application in the early disease stage, that divided SpA patients into patients with predominantly axial (paSpA) and predominantly peripheral (ppSpA) SpA (8-10). Therefore, any evidence on treatment options specifically proposed for u-SpA patients, according to the European Spondyloarthropathy Study Group (ESSG) criteria, or their equivalent according new ASAS criteria, may result of extraordinary clinical value.

The aim of the present study was to systematically review the best evidence on the management of u-SpA patients according to traditional ESSG criteria. Besides, and due to the important value of the new ASAS criteria, we also retrieved the related evidence regarding drug therapies on paSpA or ppSpA patients, as well as we tried to apply these criteria to the u-SpA-included patients of the systematic review. Systematic literature reviews and meta-analyses are considered to ensure the highest quality for making recommendations (11). To our knowledge, no evidence-based analysis has been performed to address pharmacologic treatment of u-SpA to date.

METHODS

In context of a clinical practice guideline for the management of SpA in Spain, a systematic review was performed to address the experts' question on the efficacy of current available drugs in u-SpA. In accordance with the experts, a review protocol was established for this purpose.

Search Strategy

The studies were identified by sensitive search strategies in the main bibliographic databases under the supervision of an expert librarian (Table 1, available online at [http://www.semarthritisrheumatism.com]). The following bibliographic databases were screened: Medline and Embase from 1961 to July 2009, and the Cochrane Central register of Controlled Trials (CENTRAL) up to July 2009. We searched for English, French, and Spanish articles. All the retrieved references were managed in EndNote X1 (Thomson Reuters). Finally, a hand search was completed by reviewing the references of included studies or the information provided by the experts.

Selection Criteria

The studies retrieved by the above strategies were included if they met the following pre-established criteria: patients (aged 18 or above) with u-SpA according to ESSG criteria (12). Studies on SpA populations were only included if data corresponding to u-SpA patients were shown. Subjects should be on any of the following therapies: nonsteroidal anti-inflammatory agents (NSAID), disease-modifying antirheumatic drugs (DMARD) (including cyclophosphamide and chlorambucil), anti-TNFα [infliximab (IFX), etanercept (ETN), and adalimumab (ADA)], anakinra, abatacept, diphosphonates, or thalidomide. No restrictions related to doses or routes were considered. Clinical outcomes as the Bath Ankylosing Spondylitis Disease Activity (BASDAI), pain score, swollen joint count (SJC), tender joint count (TJC), functional disability like the Bath Ankylosing Spondylitis Functional Index (BASFI), quality of life, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and radiologic assessments (13) were examined. We selected randomized controlled trials (RCT), cohort studies, or case reports ($\geq$3 patients).

Screening of Studies, Data Collection, and Analysis

First, M.P.R. and J.A.M. designed the search strategy and screened the titles and abstract of the retrieved articles for selection criteria separately. This process was done in 20-minute sessions. Then, J.M.L.L. and J.M.M. independently examined the selected studies to determine which studies met the inclusion criteria. They also performed the manual search on list of references of selected articles and independently collected the data by using ad hoc standard forms. All collection was then double by article. If J.M.L.L. found any discrepancy between his information and that from the other reviewer, then a consensus was reached by looking at the original article. Those articles that did not fulfill all the inclusion criteria, had insufficient data, or did not allow the measurement of therapeutic effects (personal communications, conferences, consensus statement, nonclinical outcome studies or animal studies) were excluded.

Quality Assessment

For grading the quality trials, we used a modification of the Oxford Centre for Evidence-based Medicine Levels of Evidence (March 2009 Update) (14), in which the following were discussed: (1a) systematic reviews of RCT with homogeneity; (1b) individual RCT with narrow confidence intervals; (1c) trials in which all patients get harm or none does; (2a) systematic reviews of cohort studies with homogeneity; (2b) individual cohort study, or low-quality randomized controlled trials; (2c) "outcomes" research and ecological studies; (3a) systematic reviews of case-control studies with homogeneity; (3b) individual case-control study; (4) case reports and poor quality cohort and case-control studies; and (5) expert opinion without explicit critical appraisal, or based on physiology, bench research, or "first principles." RCTs were additionally ranked using Jadad score (15).

Evidence tables were produced. Meta-analysis was only planned in case enough homogeneity was present between the included studies.