

The Role of Corticosteroids for Pain Relief in Persistent Pain of Inflammatory Arthritis: A Systematic Literature Review

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ABSTRACT. *Objective.* To conduct a systematic review of the available literature addressing the effectiveness, safety, and role of corticosteroids for pain relief in persistent pain of inflammatory arthritis (IA), as part of the international 3e (Evidence, Expertise, Exchange) Initiative.

Methods. A systematic literature research (SLR) was carried out in Medline, Embase, the Cochrane Library, and the American College of Rheumatology/European League Against Rheumatism meeting abstracts, searching for studies evaluating the use of steroids for the treatment of residual pain in IA despite adequate antiinflammatory therapy.

Results. Of 3887 references retrieved by SLR, 2 randomized controlled studies and 35 review articles underwent full-text review. No article was found to adequately address the research question.

Conclusion. No data on the efficacy and safety of systemic corticosteroids in residual pain in IA could be identified from the literature. (J Rheumatol Suppl. 2012 Sept;90: 17–20; doi:10.3899/jrheum.120337)

Key Indexing Terms:

INFLAMMATORY ARTHRITIS

PAIN

GLUCOCORTICOIDS

This article is part of the 3e (Evidence, Expertise, Exchange) Initiative on Pain Management by Pharmacotherapy in Inflammatory Arthritis¹. Our objective was to systematically review the available literature addressing one of 10 selected questions as an evidence base for generating recommendations; i.e., What is the effectiveness, safety, and role of corticosteroids for pain relief in persistent pain of inflammatory arthritis (i.e. interval, formulation, and route)?

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METHODS

Based on the updated guidelines for Cochrane systematic reviews², a stepwise systematic literature review was performed. The individual steps were: (1) rephrasing of the clinical question into epidemiological terms; (2) definition of possible scenarios regarding the types of studies to be found in the literature; (3) systematic search of different databases using a refined search strategy; (4) selection of articles based on predefined inclusion and exclusion criteria; (5) data extraction and quality appraisal of included studies; and (6) data analysis.

Rephrasing the clinical question. The clinical question proposed by international rheumatology experts was translated into an epidemiological research question according to the PICO (Population, Intervention, Comparator, Outcome) method³ (for an overview of the PICO approach see section 1 of the online Appendix, available from www.3epain.com). As for all questions studied in this 3e Initiative, the population was defined as adults age 18 years or older with all types of inflammatory arthritis (IA). IA comprised patients with rheumatoid arthritis (RA) and its systemic variants (adult onset Still's disease, Felty's syndrome, Caplan syndrome) as well as all types of spondyloarthritis (psoriatic arthritis, ankylosing spondylitis, reactive arthritis, enteropathic arthritis, undifferentiated oligoarthritis). Arthritis as a manifestation of connective tissue diseases and crystal-induced arthritides were excluded according to the decision by the experts. In addition, the search was limited to patients with IA with residual pain despite adequate antiinflammatory treatment. The intervention was defined as systemically administered (oral, subcutaneous, intramuscular, intravenous) glucocorticoids. Topical or intraarticular administration of glucocorticoids was not included as decided by the experts. Any analgesic or placebo was accepted as comparator.

Two types of outcomes were assessed, efficacy and safety. Accepted efficacy measures for the reduction of pain included visual analog scales, numerical rating scales, verbal rating scales, the McGill Pain Questionnaire and its short form, the Index bidimensionnel de la douleur, Rheumatoid Arthritis Pain Scale, bodily pain subscale of the Medical Outcomes Study Short-Form 36 Survey, and pain subscales and pain-related items from various composite indices including the Arthritis Impact Measurement Scale 1 (AIMS1 and AIMS2 and their short forms), the Rheumatoid Arthritis Disease Activity

Index, the disease activity index for reactive arthritis, the Activities of Daily Living Questionnaire, the Nottingham Health Profile, the Foot Function Index, the Michigan Hand Outcomes Questionnaire, the Rheumatoid Arthritis Outcome Score, and the Bath Ankylosing Spondylitis Disease Activity Index. Effect sizes, odds ratios (OR), or number needed to treat were expected efficacy parameters. Safety was assessed in terms of incidence, relative risk (RR), or OR for adverse events and withdrawals from treatment and the number needed to harm (NNH). The final search question was rephrased (for details, see section 2 of the online Appendix, available from www.3epain.com) as follows: In patients with IA and persistent pain despite adequate antiinflammatory therapy, (1) what is the effect size/OR/NNH of systemic glucocorticoids for demonstrating a clinically meaningful reduction in pain, relative to placebo or other analgesics; and (2) what is the RR/OR/NNH of systemic glucocorticoids for total adverse events and withdrawals from treatment due to toxicity or adverse events?

Scenarios. Randomized controlled trials (RCT) directly comparing the analgesic effect of systemic glucocorticoids in residual pain with other analgesics or placebo would have been the optimal scenario. The suboptimal scenario included nonrandomized trials, cohort studies, or case-control studies. Observational studies or case reports of at least 5 cases were regarded as the least optimal scenario, as these inherently introduce methodological limitations. Since the question addresses a very specific issue, a limited yield of usable studies was expected and thus the search strategy was not limited by types of studies.

Systematic literature search. The databases Medline, Embase, and Cochrane Library were searched systematically for articles published between 1947 and May 2010, using a comprehensive search strategy (see section 3 of the online Appendix available from: www.3epain.com) developed in collaboration with an experienced librarian from the Cochrane Library. The scientific abstracts of the European League Against Rheumatism (EULAR) and American College of Rheumatology (ACR) annual scientific meetings 2008-2009 were also searched. The search was limited to residual pain and articles with an abstract in English. Review articles were also retrieved to identify additional references via hand search.

Selection of articles. Relevant articles were identified using a 2-step procedure. First, titles and abstracts of all identified references were screened, excluding articles that clearly did not address the topic of interest. Second, the remaining articles were reviewed in detail. Nonrelevant articles according to predefined exclusion criteria (see section 4 of the online Appendix available from: www.3epain.com) were excluded from the systematic review.

Data extraction and quality appraisal. Publication details, patient characteristics, dosage, route of administration of glucocorticoids and comparators, and data on relevant outcomes were extracted from the included articles using standard forms. Data from non-English language publications were extracted by reviewers from the international panel of the 3e Initiative (German, Portuguese, Dutch, and French). The methodological quality of each RCT was graded by a scale according to van Tulder, *et al*² with a maximum score of 11 points. The points were subsequently translated into levels of evidence according to the Oxford Centre for Evidence-based Medicine⁴.

Data analysis. For continuous variables, 3 types of effect size were calculated for the difference between baseline and end of trial data^{5,6}. Per treatment group, the effect size and the standardized response mean (SRM) were calculated as the mean change in score divided by the baseline standard deviation (SD) (effect size), or the mean change divided by the SD of the change (SRM). To compare the effect between 2 treatment groups, the pooled Cohen's effect size was calculated as the mean change in the index group minus the mean change in the comparator group divided by a pooled baseline SD. The corresponding 95% CI was constructed and indicates a statistically significant effect at the 5% level if zero is outside the interval⁷. In accordance with the literature, effect sizes were as follows: -0.2 = small, -0.5 = moderate, and > 0.8 = large, with negative effect sizes indicating worsening. For dichotomous data, OR (95% CI) were calculated for the occurrence of system-specific adverse events. Intention-to-treat data were used if available.

RESULTS AND DISCUSSION

A total of 3887 references were identified by the systematic literature search, the vast majority of which were excluded based on title and abstract screening. After detailed review of the remaining 37 articles^{8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44} none was found to answer the research question. The hand search of the ACR and EULAR abstracts retrieved no useful study. An illustration of the search process is shown in Figure 1; for a list of the 37 articles with reasons for their exclusion after detailed review, see section 5 of the online Appendix, available from: www.3epain.com.

Only 2 articles^{10,32} described randomized, placebo-controlled clinical trials (RCT), one article described an open-label study, and the other 34 were review articles. The RCT, CAPRA-1, by Buttgereit, *et al*¹¹ was excluded because it investigated the efficacy of modified-release prednisone on morning stiffness in active RA. The RCT by Li, *et al*³² on iontophoresis of dexamethasone for the treatment of knee pain in RA did not assess a systemic corticosteroid therapy. The study by Huss²⁷ was an open-label, uncontrolled, variable-dose trial on the efficacy of a composite drug containing phenylbutazone, aminophenazone, prednisolone, and dexamethasone in a population of patients with osteoarthritis, degenerative spinal disease, tendonitis, enthesitis, and periarthritis labeled as "rheumatic diseases."

The reviews were screened for references to articles not identified by the search strategy and analyzed for expert opinion regarding the research question. The majority of reviews did not address the issue of residual pain despite adequate antiinflammatory therapy^{8, 9, 10, 12, 13, 14, 15, 16, 18, 19, 22, 23, 24, 25, 26, 28, 29, 30, 31, 33, 35, 38, 40, 41, 42, 44}. Interestingly, the article by Kean, *et al*²⁹ quotes recent data indicating that neuroimmune processes are involved in the development of chronic pain of various origins, primarily nerve damage and inflammation. Both damage to the nervous system and peripheral tissue inflammation activate microglia and astrocytes which, in turn, secrete proinflammatory cytokines and various neurotransmitters that mediate permeability of the blood-brain barrier and sensitization of neuronal cells^{45,46,47}. Thus it has been postulated that glial cell activation contributes to the maintenance of pain, even after the original injury has healed. Kean, *et al*²⁹ hypothesized that corticosteroids capable of crossing the blood-brain barrier could exert an analgesic property by downregulating neuroimmune processes underlying chronic pain. However, due to the dose- and time-dependent adverse effects of corticosteroids, Kean, *et al*²⁹ do not regard them as a realistic clinical option for the treatment of chronic pain.

Three reviews contained expert opinion about the use of corticosteroids in arthritis-related pain. Docken¹⁷ suggested that low-dose systemic steroids should be considered for the treatment of RA pain "of prohibitive severity" after an insufficient response to nonsteroidal antiinflammatory drugs, intraarticular steroid injections, splints, and other physical

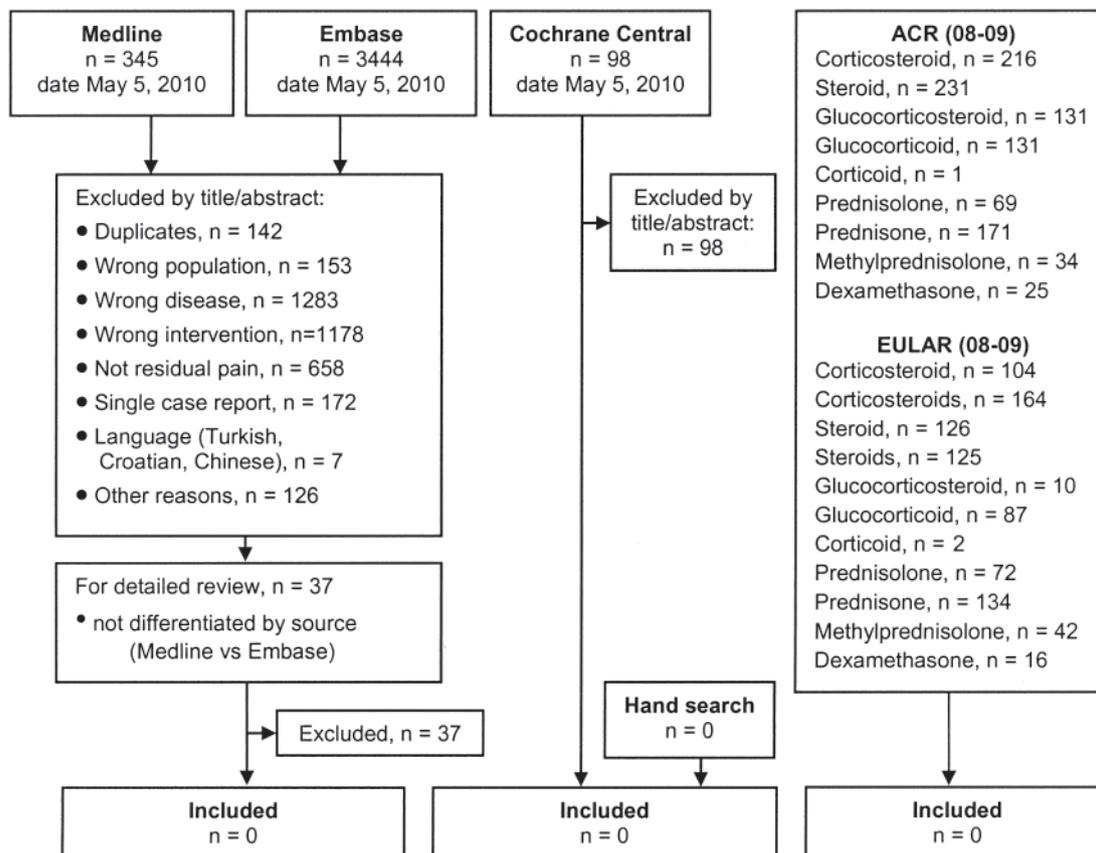


Figure 1. Literature search from which 37 articles were selected for detailed review. No article met inclusion criteria.

measures. However, this recommendation does not include disease-modifying antirheumatic drugs (DMARD) and thus today cannot be regarded as adequate antiinflammatory treatment in the sense of the research question. Fitzcharles and Shir²⁰ pointed out that in long-standing inflammatory disease it may be difficult to differentiate between inflammatory pain and nociceptive pain, which is caused by chronic structural changes. In their opinion, administration of systemic corticosteroids can help to distinguish between these 2 types of pain. A positive response would indicate inflammatory pain whereas a lack of improvement after a 7–10 day course of corticosteroids would suggest neuropathic pain. This view, however, implies that corticosteroids are indicated only for the treatment of inflammatory pain. Gerster²¹ warned against the treatment of arthralgia with corticosteroids because excessive doses would be required for complete analgesia. Corroborative data from clinical trials are not provided for any of these statements.

The remaining reviews could not be used because they studied only local steroid injections^{36,37}, assessed other treatments not including steroids^{12,24,33,41}, assessed musculoskeletal diseases other than IA^{39,43}, or evaluated the use of corticosteroids for sex hormone replacement only³⁴.

In summary, our systematic literature review was intended to retrieve and evaluate available evidence on the effectiveness and safety of systemic glucocorticoids in the treatment of residual pain in IA despite adequate antiinflammatory therapy. However, no data could be identified in the literature that would adequately address this research question. Since the experts who proposed the question feel there may be a role for glucocorticoids in this setting, the initiation of respective clinical studies may be warranted. Here, preclinical data on a neuroimmune response as one of the mechanisms underlying chronic pain^{29,45,46,47} could provide the scientific rationale for such a study using a corticosteroid that can cross the blood-brain barrier.

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