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Review

# Should non-steroidal anti-inflammatory drugs be used continuously in ankylosing spondylitis?

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ABSTRACT

*Objective:* The 2010 update of ASAS/EULAR recommendations for managing ankylosing spondylitis (AS) specify that continuous non-steroidal anti-inflammatory drug (NSAID) treatment should be preferred in patients with persistently active, symptomatic disease. Here, our objective was to assess whether continuous NSAID therapy improves disease control and influences radiographic progression compared to on-demand therapy. We also assessed the safety profiles of both regimens.
*Methods:* We performed a review by searching the PubMed and Embase databases using two MeSH term combinations to compare continuous and on-demand NSAID therapy in terms of disease control, radiographic progression, and safety.
*Results:* The only study evaluating the impact of continuous NSAID therapy on disease control showed no significant difference with on-demand therapy. In four studies, continuous treatment was associated with slower radiographic progression, as assessed in three studies using the modified Stoke Ankylosing Spondylitis Spinal Score (m-SASSS). Three studies compared the safety of continuous and on-demand celecoxib, two in osteoarthritis and one in AS, and found no significant differences regarding the usual side effects of Cox-2 inhibitors.
*Conclusions:* Several studies showed slower radiographic progression with continuous NSAID therapy in AS. No studies demonstrated superiority of continuous NSAID therapy regarding symptom control. Continuous NSAID therapy (at least with Cox-2 inhibitors) does not modify safety compared to on-demand therapy.


Non-steroidal anti-inflammatory drugs (NSAIDs) have demonstrated considerable efficacy in ankylosing spondylitis (AS) and are also recommended in non-radiographic axial spondyloarthritis (SpA), providing prompt relief of inflammatory back pain and stiffness [1–4]. However, the poor long-term safety profile limits the use of NSAIDs for chronic therapy, and side effects require permanent NSAID discontinuation in a substantial proportion of patients. Non-selective NSAIDs are associated with an increased risk of gastrointestinal bleeding or perforation, with relative risks ranging across NSAIDs from 2 to 15 compared to a placebo. Gastrointestinal toxicity is lower with Cox-2 inhibitors but nevertheless non-negligible [5]. Long-term non-selective or selective NSAID therapy is also associated with increased risks of stroke and cardiovascular death [6]. NSAIDs are a major cause of renal function impairment in subjects with renal disease [7]. Given the risk of side effects, many clinicians are reluctant to prescribe continuous NSAID therapy. In practice, the decision to initiate continuous NSAID therapy for AS depends as much on disease activity as on the patient's history. Furthermore, when TNFα antagonist therapy is started, NSAID therapy is usually reduced or discontinued. Thus, there is considerable reason to challenge the use of continuous NSAID therapy in patients with AS, except when symptom control is inadequate with on-demand therapy.

The 2010 update of the ASAS/EULAR recommendations for managing AS specify that continuous NSAID therapy should be preferred in patients with persistently active, symptomatic disease and that it is unclear whether NSAIDs should be taken continuously to prevent new bone formation [8]. However, the superiority of continuous over on-demand NSAID therapy has not been incontrovertibly demonstrated, even in patients with persistently active,

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symptomatic disease. The 2010 recommendation is warranted only if the published evidence demonstrates greater effectiveness or other benefits of continuous NSAID therapy, at least in the most active forms of AS.

The objectives of the present study were to assess whether continuous NSAID therapy improves disease control and slows radiographic progression compared to on-demand NSAID therapy in AS patients. We also compared the safety profiles of continuous and on-demand therapy in patients with AS or other conditions.

## 1. Methods

We conducted a literature review by searching the PubMed and Embase databases for articles published as of June 2012. For the PubMed search, we used two different MeSH term combinations to compare continuous and on-demand NSAID therapy in terms of disease control, radiographic progression, and safety. For disease control and radiographic progression, the terms were "Spondylitis, Ankylosing" and ("Anti-inflammatory Agents, Non-Steroidal" or "Cyclo-oxygenase 2 Inhibitors") and "Drug Administration Schedule". For safety, we used "Drug Administration Schedule" and ("Anti-inflammatory Agents, Non-Steroidal" or "Cyclo-oxygenase 2 Inhibitors"); this search was extended to other populations than AS patients but was limited to comparative studies.

Reference lists of selected publications were screened manually for additional relevant studies. The abstract databases of the American College of Rheumatology (ACR) and European League Against Rheumatism (EULAR) meetings held in the last 3 years were searched.

We read the abstracts of the retrieved publications to select the articles relevant to our study. We did not use validated instruments to assess the quality of selected articles. We selected studies comparing continuous and on-demand NSAID therapy (or comparing NSAID therapy to a placebo when evaluating radiographic progression), regardless of the definitions of continuous and on-demand therapy and of the study design. For each selected publication, we recorded the following data: author names, year of publication, journal, study population, prospective or retrospective design, number of patients, mean age, sex, criteria set used for the diagnosis, study duration, NSAIDs used, method used to evaluate disease activity and/or radiographic progression, method used to assess continuous/on-demand NSAID use, and adverse events.

## 2. Results

Fig. 1 shows the publication flow charts.

### 2.1. Disease activity

A single study, published in 2005, compared the effect of continuous versus on-demand NSAID therapy on disease control in patients with AS, as a secondary objective; the primary objective was an assessment of radiographic progression [9] (Table 1). In this randomized controlled trial, 215 patients meeting modified New York criteria for AS and having no peripheral arthritis or inflammatory bowel disease were randomly allocated to continuous or on-demand NSAID therapy. Patients were included only if they had a flare when stopping NSAIDs (increase in pain of at least 30%) and so, they were at least partial NSAIDS responders, and not anti-TNFα requirers. Celecoxib was used first but could be replaced by another selective or non-selective NSAID during the study in the event of inadequate efficacy or intolerance. After 2 years, no significant differences were found for the BASDAI ($P = 0.51$), patient global evaluation ($P = 0.94$), global pain ($P = 0.44$), or C-reactive protein ($P = 0.82$); The mean ± SD celecoxib dose was 243 ± 59 mg in the continuous-treatment group versus 201 ± 93 mg in the on-demand group ($P = 0.0001$).

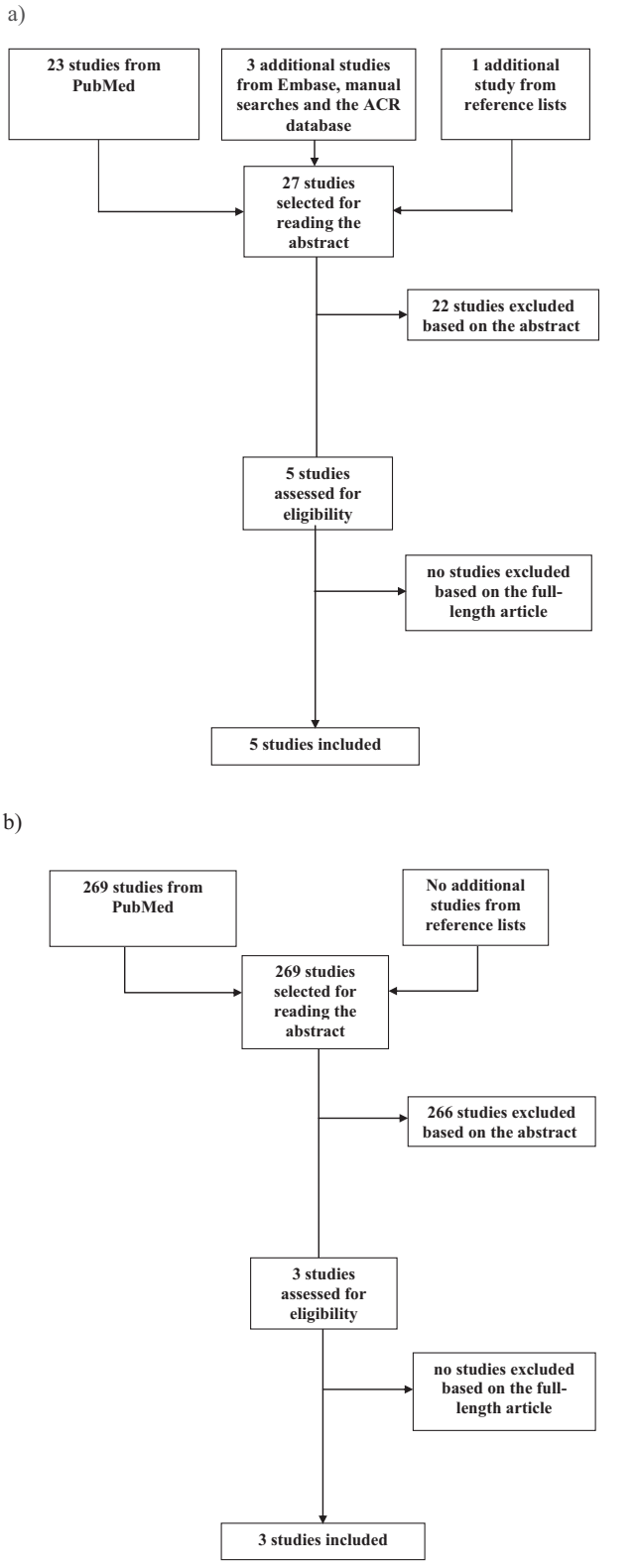


**Fig. 1.** Publication flow chart. (a) Publications on disease control and radiographic progression. (b) Publications on safety.

### 2.2. Radiographic progression

Four studies assessed the influence of continuous NSAID therapy on radiographic progression (Table 2) [9–12]. Only one prospective

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