
NSAIDs in ankylosing spondylitis

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ABSTRACT

Nonsteroidal Anti-Inflammatory Drugs (NSAIDs) effects in Ankylosing Spondylitis (AS) are only suspensive but because of their rapid efficacy on inflammatory symptoms they are the first-line treatment in AS. Short term efficacy of NSAIDs in AS is observed for most patients but the correlation of NSAID intake with the long term prognosis and its potential influence on the structural progression of the disease is still unknown. Therefore, and due to the gastrointestinal side effects of these drugs, daily practice is mostly in favour of discontinuous intake of NSAIDs, following the clinical relapses. However, the recent introduction of specific Cox-2 inhibitors, with a lower risk of severe gastrointestinal adverse events, may modify this attitude. Moreover, some patients are inadequately relieved of pain and inflammation by NSAIDs. The number of NSAIDs to be tested and for each NSAID, the optimal dosage that must be used before categorizing a patient as «refractory to NSAID therapy» have to be clarified. The recent determination of response and remission criteria for NSAIDs therapy is the first step towards well-defined guidelines for short-term and long-term management of NSAIDs in AS.

A diagnostic tool for spondyloarthropathy

NSAIDs are the first line treatment in ankylosing spondylitis (AS) and to a large extent in painful clinical manifestations of arthritis or enthesiopathies observed in spondyloarthropathy. The remarkable efficacy of NSAIDs with a quick-acting symptomatic effect is a diagnostic criteria according to Amor classification which includes twelve items, each of them counting for one to three points (1). A minimum of six points are necessary to classify a patient as suffering from a spondyloarthropathy. Item 12 is relative to NSAIDs efficacy: “clearcut improvement within 48 hours after NSAID intake or rapid relapse of pain after their discontinua-

tion”. Its value of two points in this classification illustrates the notable weight of NSAIDs response in a diagnostic approach. A multicenter cross-sectional study conducted in 741 patients complaining of back pain (69 AS and 672 controls) permitted calculation of the positive and the negative predictive value of NSAIDs efficacy, respectively 34% and 97% (2). Thus, in this particular population of patients suffering from back pain, in case of NSAIDs inefficacy, the probability of AS was very low (3%).

Determination of outcome variables to evaluate NSAIDs efficacy

In order to define clinical and biological outcome variables in AS, an international working group was created in 1995: the “Assessments in Ankylosing Spondylitis (ASAS) Working Group” and a preliminary core set of endpoints was suggested (3). Another study precisely defined domains and measures within each domain that should be assessed as relevant to best discriminate between placebo and fast acting drugs in AS in terms of efficacy (4). Assessment criteria from four domains were retained as response (Table I) and remission (Table II) criteria: patient global assessment, pain, functional impairment and inflammation (morning stiffness) (5). Both sets of criteria were based on data obtained in placebo controlled trials evaluating NSAIDs. Using these criteria, the expected response levels for patients naïve to treatment

Table I. ASAS response criteria (5).

Improvement of at least 20% and absolute improvement of at least 10 on a 0-100 scale in at least 3 of the following domains*:

Patient global assessment
Pain
Function
Inflammation

Absence of deterioration (of at least 20% and absolute deterioration of at least 10 on a 0-100 scale) in the potential remaining domain.

Table II. ASAS remission criteria (5).

A value below 20 on a 0-100 scale in each of the 4 domains*:

Patient global assessment
Pain
Function
Inflammation

*Definition of the domain:

Patient global: Visual Analog Scale (VAS) (0-100)

Pain: VAS global, last two days (0-100)

Function: Bath Ankylosing Spondylitis Functional Index (BASFI) (0-100)

Inflammation: First choice 2 last question of the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI); Second choice: morning stiffness duration with a maximum of 120 min or a 0-100 scale.

are 25% for placebo and 50% for NSAIDs treatment and the remission rate 3% with placebo and 11% with NSAIDs. These recommendations together with the proposition of a composite set of responder criteria have dramatically facilitated the medical language permitting a homogenous presentation of the results; moreover, the individual basis of these results (i.e. responder: yes/no) also facilitates the comparison between studies.

Short term symptomatic efficacy

The short-term efficacy of NSAIDs in AS is usually easy to detect in placebo-controlled trial because of the minor placebo effect on function in AS. A recent double-blind placebo-controlled study compared celecoxib (COX2 specific inhibitor), ketoprofen and placebo. A significant functional improvement was observed with both NSAID treatments ($P = 0.05$ and $P = 0.0006$, respectively) but no placebo effect was observed (6). If the efficacy of a NSAID treatment seems relatively easy to demonstrate when tested against placebo, a dose-effect or a difference in efficacy between two or more NSAIDs seems much more difficult to establish. In effect, the short duration of a trial, i.e. a few weeks, appears insufficient to identify the optimal dosage of the tested drugs. A two-week double-blind placebo-controlled study published in 1989 compared ximoprofen at 4 regimens of dosage (5, 10, 20 and 30 mg/day) (7). The percentage of responders was defined as an improvement in pain higher than 50% on a visual analog

scale (VAS). At the end of the study, ximoprofen efficacy was demonstrated for all regimen of dosage but the optimal dosage was not identified. A further 6-weeks duration placebo-controlled study, with a 12 month double-blind extension was conducted in order to define the optimum study duration to identify efficacy (and tolerance) of an active NSAID in AS (8). The study drugs were placebo ($n = 121$) or active NSAID: piroxicam 20 mg ($n = 108$), meloxicam 15 mg ($n = 120$) and meloxicam 22.5 mg per day ($n = 124$). The life table analysis in which the event was defined by the discontinuation of the study drug because of any reason showed a highly significant difference between placebo and each of the three active groups. This approach also permit the demonstration of a statistically significant difference ($P < 0.05$) in favour of meloxicam 22.5 mg when compared to either piroxicam 20 mg or meloxicam 15 mg. Such a difference could not have been observed in a 6-weeks duration study, suggesting that a 52-weeks study was more appropriate to detect a difference between two active NSAIDs or between two different dosages of a given NSAID. Moreover a life table analysis with the percentage of patients still taking the studied drug over time should be more sensitive than the conventional mean changes or percentage of responders.

Long term management of NSAIDs in ankylosing spondylitis

A quick effect on pain and functional disability is usually observed after NSAID initiation. The question still remaining in a patient well-controlled by NSAIDs is whether such treatment has to be systematically and continuously taken on a daily basis or only "at request". A continuous administration of these drugs may facilitate the concomitant required physical therapy and may have a beneficial structural effect. On the other hand, a continuous daily intake may increase the risk of NSAIDs toxicity. Further studies in this field, in particular evaluating the coxibs are required.

In case of failure of NSAID therapy, other treatment modalities (including

anti-TNF therapy) can be considered. The definition of "refractory to NSAID therapy" must be defined; rationally, the number of previously used NSAIDs and for each of them, the use of an optimal dosage and the intake duration must be taken into account.

Conclusion

NSAIDs are a cornerstone treatment in AS. Short term efficacy of NSAIDs in AS is observed for most patients but the correlation of NSAID intake with the long term prognosis and its potential influence on the structural progression of the disease is not yet known. Well-defined guidelines for continuous versus at request intake of NSAIDs in AS also have to be determined. Undoubtedly, forthcoming studies will focus on these crucial questions.

References

1. AMOR B, DOUGADOS M, MIJYAWA M: Critères de classification des spondylarthropathies. *Rev Rhum* 1990; 57: 85-9.
2. AMOR B, DOUGADOS M, LISTRAT V *et al.*: Evaluation des critères de spondylarthropathies d'Amor et de l'European Spondylarthropathy Study Group (ESSG). Une étude transversale de 2228 patients. *Ann Med Interne* 1991; 142: 85-9.
3. VAN DER HEIJDE D, BELLAMY N, CALIN A, DOUGADOS M, KHAN MA, VAN DER LINDEN S: Preliminary core sets for endpoints in ankylosing spondylitis. Assessments in Ankylosing Spondylitis Working Group. *J Rheumatol* 1997; 24: 2225-9.
4. VAN DER HEIJDE D, CALIN A, DOUGADOS M, KHAN MA, VAN DER LINDEN S, BELLAMY N: Selection of instruments in the core set for CD-ART, SMARD, physical therapy and clinical record-keeping in ankylosing spondylitis. Progress report of the ASAS working group. *J Rheumatol* 1999; 26: 951-4.
5. ANDERSON J, BARON G, VAN DER HEIJDE D, FELSON DT, DOUGADOS M: Ankylosing Spondylitis assessment group preliminary definition of short-term improvement. *Arthritis Rheum* 2001; 44: 1876-86.
6. DOUGADOS M, BEHIER JM, JOLCHINE I *et al.*: Efficacy of celecoxib, a cyclooxygenase 2-specific inhibitor, in the treatment of ankylosing spondylitis: A six-week controlled study with comparison against placebo and against a conventional non-steroidal anti-inflammatory drug. *Arthritis Rheum* 2001; 44: 180-5.
7. DOUGADOS M, NGUYEN M, CAPORAL R *et al.*: Ximoprofen in ankylosing spondylitis: A double blind placebo controlled dose ranging study. *Scand J Rheumatol* 1994; 23: 243-8.
8. DOUGADOS M, GUEGUEN A, NAKACHE JP *et al.*: Ankylosing spondylitis: what is the optimum duration of a clinical study? A one year versus a 6 week non-steroidal anti-inflammatory drug trial. *Rheumatology* 1999; 38: 235-44.