Recommendations

Pharmacotherapy (excluding biotherapies) for ankylosing spondylitis: Development of recommendations for clinical practice based on published evidence and expert opinion

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Abstract

Objectives: To develop recommendations about pharmacotherapy (excluding biotherapeutic agents) for patients with axial forms of ankylosing spondylitis seen in everyday clinical practice.

Methods: The recommendations were based on evidence from the literature. First, a scientific committee used a Delphi procedure to select five focal points about which recommendations were needed. Then, a literature task force looked for relevant publications in the following: Cochrane, PubMed, and Ovid databases; and abstracts from the French Society for Rheumatology, European League Against Rheumatism, and American College of Rheumatology. Based on the data in these publications, recommendations were drafted then validated by a group of experts. The strength of each recommendation was determined, as well as the extent of agreement among the experts.

Results: The four focal points were the best strategy for using nonsteroidal anti-inflammatory drugs, role for systemic glucocorticoid therapy, role for glucocorticoid injections into the sacroiliac joints and enthesis, and role for slow-acting drugs (e.g., methotrexate, sulphasalazine, leflunomide, thalidomide, and pamidronate). Of the 661 promising publications identified by the literature search, 173 were found to be relevant. The evidence in these 173 papers was reported to experts during interactive workshops. At the end of the workshops, the experts drafted recommendations, which were then validated by having all panel participants vote during a final meeting. There were seven recommendations, whose strength ranged from A to D.
Conclusion: Seven recommendations about pharmacotherapy in patients with AS were developed. They can be expected to improve clinical practice uniformity and, in the longer term, to optimize the management of patients with AS in France.

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Keywords: Ankylosing spondylitis; Pharmacotherapy; Everyday clinical practice; Recommendations

1. Introduction

Ankylosing spondylitis (AS) is a major disease seen in everyday practice by both hospital- and office-based rheumatologists. Although the introduction of biotherapies for the treatment of AS in the last few years has yielded a rich harvest of publications, many unresolved issues remain regarding other pharmacological treatments, such as nonsteroidal anti-inflammatory drugs (NSAIDs), systemic glucocorticoids, glucocorticoid injections into the sacroiliac joints or entheses, and slow-acting drugs (e.g., methotrexate, sulfasalazine, leflunomide, thalidomide, and pamidronate).

The objective of this work was to develop recommendations about the use of medications other than biotherapies in patients with AS seen in everyday practice. We used a previously described method in which evidence retrieved by an extensive search of the international literature was examined by experts and, when needed, supplemented by expert opinion [1].

2. Methods

The procedure used to develop the recommendations has been described elsewhere [2]. It was carried out by a scientific committee of rheumatologists working full-time in teaching hospitals (A.C., P.C.P., R.M.F., P.G., X.L.L., J.F.M., X.M., A.S., T.S., J.T., D.W., B.C.), a literature review task force (E.D., F.L., S.P.), and 79 experts.

2.1. Selection of areas of interest by the scientific committee

The scientific committee selected three areas of interest: imaging studies for the diagnosis and follow-up of AS [2], clinical and laboratory follow-up for patients with AS [3], and pharmacotherapy (excluding biotherapies) for AS [7]. This paper deals with the third of these three areas of interest.

2.2. Selection of focal points within each area of interest

A Delphi consensus procedure [4] was used to select focal points. Five focal points were identified for recommendations about pharmacotherapy (excluding biotherapies) in AS: the optimal strategy for using NSAIDs in AS (including whether use should be continuous or limited to flare-ups, dosage, criteria for selecting a second NSAID after failure of the first, continuation rate, and reasons for discontinuation), role for systemic glucocorticoid therapy in AS, whether glucocorticoid injections into the sacroiliac joints and entheses are helpful (and in which specific situations), whether slow-acting drugs (methotrexate, sulfasalazine, leflunomide, thalidomide, and pamidronate) are effective and in which situations, and which is the best pharmacotherapy strategy within the first year after the diagnosis of AS.

No data were found in the literature about the fifth focal point, which was consequently eliminated.

2.3. Literature review

A systematic literature review was conducted as described by Pham et al. [4]. The Cochrane, PubMed, and Ovid databases were searched, as well as the abstracts presented at the 2004 and 2005 meetings held by the French Society for Rheumatology, the European League Against Rheumatism, and the American College of Rheumatology. Articles published in English or French before May 2006 were considered. The key indexing terms used for the search are listed below.

- focal point on systemic glucocorticoids: “Glucocorticoids”[Pharmacological Action] and “spondylitis, ankylosing”[MeSH];
- focal point on local glucocorticoid injections: “Spondylitis, Ankylosing”[MeSH] and “Injections, Intra-Articular”[MeSH] with all adults 19+ years;
Table 1

Recommendations about pharmacotherapy (excluding biotherapeutic agents) in patients with axial ankylosing spondylitis seen in everyday practice

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Strength of the recommendation</th>
<th>Agreement among experts: Total of “agree” and “fully agree” answers</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. In patients with symptomatic ankylosing spondylitis, a nonsteroidal anti-inflammatory drug (NSAID) should be used first, provided there are no contraindications to this drug class</td>
<td>Grade A</td>
<td>98.4%</td>
</tr>
<tr>
<td>2. No criteria are available for determining whether a specific NSAID is superior over the others, even in patients who have failed a previous NSAID. Before concluding that an NSAID is not effective, the drug should be given for at least 2 to 4 weeks, in the maximal recommended dosage, and with a dosing schedule that matches the symptom fluctuations over the 24-hour cycle</td>
<td>Grade D</td>
<td>83.9%</td>
</tr>
<tr>
<td>3. When NSAID drug therapy induces a good response, the minimal effective dosage should be determined. Given the absence of conclusive evidence that NSAIDs exert structural effects, routine continuous use of NSAIDs is not advisable</td>
<td>Grade D</td>
<td>96.8%</td>
</tr>
<tr>
<td>4. Systemic glucocorticoid therapy is not recommended in patients with ankylosing spondylitis, except in specific situations</td>
<td>Grade B</td>
<td>96.8%</td>
</tr>
<tr>
<td>5. In patients with predominant sacroiliac pain that is refractory to nonsteroidal antiinflammatory drug therapy, local glucocorticoid injection is recommended</td>
<td>Grade B</td>
<td>93.6%</td>
</tr>
<tr>
<td>6. Glucocorticoid injection at enthesitis sites may be advisable in patients with ankylosing spondylitis who have inadequate responses to nonsteroidal antiinflammatory therapy</td>
<td>Grade D</td>
<td>86.2%</td>
</tr>
<tr>
<td>7. Sulfasalazine, methotrexate, and leflunomide are not recommended to treat the axial manifestations of ankylosing spondylitis. Sulfasalazine may deserve consideration in patients with concomitant peripheral joint involvement...</td>
<td>Grade A</td>
<td>86.4%</td>
</tr>
</tbody>
</table>

3. Results

3.1. Results of the literature review

The key indexing terms retrieved 651 publications, of which 173 were relevant. The 173 full-length articles were read. Among them, the 47 articles containing the highest-level evidence were reviewed in detail for evidence relevant to the four focal points.

3.2. Development of the recommendations

The experts developed seven recommendations at the 2006 Meeting of Rheumatology Experts. The recommendations with the strength and level of agreement of each are listed in Table 1.

3.2.1. In patients with symptomatic ankylosing spondylitis, a nonsteroidal antiinflammatory drug (NSAID) should be used first, provided there are no contraindications to this drug class

Of the 35 studies containing level-1b evidence that were retrieved from the literature, 9 were placebo-controlled trials [6–14]. All the NSAIDs used in these 9 studies were significantly more effective than the placebo after 2 weeks to 1 year. Effect size ranged from 0.58 to 25.6. No randomized controlled studies comparing standard analgesics to a placebo or NSAID as first-line treatment were found. Consequently, the experts decided that is was appropriate to recommend first-line NSAID therapy in patients with AS.
This is a Grade A recommendation. The extent of agreement among experts regarding this recommendation was 98.4%.

3.2.2. No criteria are available for determining whether a specific NSAID is superior over the others, even in patients who have failed a previous NSAID. Before concluding that a NSAID is not effective, the drug should be given for at least 2 to 4 weeks, in the maximal recommended dosage, and with a dosing schedule that matches the symptom fluctuations over the 24-hour cycle.

Of 35 randomized controlled trials that investigated the efficacy of NSAIDs in AS, 32 compared NSAIDs and 6 also included a placebo group [7,9,11–40]. None of these studies found any evidence indicating that a specific NSAID was superior over the others.

Some of the experts felt that phenylbutazone should be mentioned in the recommendations. Among the five studies comparing phenylbutazone to other NSAIDs, two found no difference [27,32], two showed better results with phenylbutazone [20,38], and one showed better results with the comparator drug [29]. These discrepancies preclude conclusions about whether phenylbutazone is superior over other NSAIDs in patients with AS. Given the adverse effects associated with phenylbutazone, the experts in the three workshops voted against specifically mentioning phenylbutazone in the recommendations.

Similarly, some of the experts suggested specifically mentioning indomethacin. Of the 14 controlled studies that compared indomethacin to another NSAID and/or a placebo [12,13,16,18,20,22,25,26,28,30,31,33,37,40], only two showed better results with indomethacin than with other NSAIDs [20,40]. Therefore, the experts decided not to specifically mention indomethacin in the recommendations.

No data were found in the literature about the optimal NSAID dosage or the extent to which duration of action should influence NSAID selection. Based on their experience, the overwhelming majority of experts felt that long-acting NSAIDs should be preferred in patients who report nocturnal symptoms. A 2- to 4-week period was deemed sufficient to evaluate the effectiveness of NSAID therapy in patients with AS. Among the placebo-controlled trials, four involved only 2 weeks of treatment before the final evaluation [6,8,10,11], and each of these four studies showed statistically significant improvements with the NSAID compared to the placebo.

This is a Grade D recommendation. Agreement among the participants in the final full-session vote was 83.9%.

3.2.3. When NSAID therapy induces a good response, the minimal effective dosage should be determined. Given the absence of conclusive evidence that NSAIDs exert structural effects, routine continuous use of NSAIDs is not advisable.

Of 35 studies, 5 used several dosages of the same NSAIDs [8,9,13,29,36]. None of them found statistically significant differences in the primary evaluation criterion across the dosage groups. On the other hand, several meta-analyses showed higher rates of gastrointestinal complications with higher dosages and longer durations of NSAID therapy [41]. Therefore, the experts recommended individual tailoring of the dosage based on effectiveness in relieving the symptoms, the goal being to use the minimal effective dosage at all times.

A single study compared continuous NSAID therapy with use as needed [42]. This was a 2-year study in 150 patients. Progression of radiographic spinal lesions, which was selected as the primary evaluation criterion, was significantly less marked with continuous therapy. However, the experts made several comments about this study. In particular, the clinical relevance of the difference in the pace of radiographic structural damage between continuous and as-needed therapy was challenged. The radiographic progression score difference between the two groups was only 1.1, although the maximum score was 72 points. In addition, continuous therapy was associated with a 3-fold increase in the proportion of patients with arterial hypertension and a 2-fold increase in the proportion with abdominal pain, compared to as-needed therapy. Consequently, the experts felt that the data in the literature did not warrant a recommendation to use NSAID therapy continuously.

This Grade D recommendation was agreed on by 96.8% of the experts.

3.2.4. Systemic glucocorticoid therapy is not recommended in patients with ankylosing spondylitis, except in specific situations.

A single randomized controlled trial of systemic glucocorticoid therapy in AS was identified [43]. This study compared low-dose (375 mg) to high-dose (1000 mg) methylprednisolone pulse therapy given as an intravenous infusion on 3 consecutive days, in 17 patients with active AS. The effect on back pain as assessed by the patients 6 months later using a visual analogue scale showed similarly small improvements in the two groups. Consequently, all the experts felt that systemic glucocorticoids had no place in the routine management of AS. Experts in several workshops mentioned specific situations in which systemic glucocorticoid therapy may be appropriate, such as presence of contraindications to NSAID therapy (e.g., bowel disease or pregnancy). The existence of such specific situations was incorporated into the final recommendation.

This is a Grade B recommendation. It was approved by 96.8% of the experts.

3.2.5. In patients with predominant sacroiliac pain that is refractory to nonsteroidal antiinflammatory drug therapy, local glucocorticoid injection is recommended.

A single controlled study of glucocorticoid injections into the sacroiliac joints in patients with AS was identified [44]. In this double-blind study, 10 patients (15 painful sacroiliac joints) with inflammatory buttock pain despite 1 month of NSAID therapy in an adequate dosage were injected with either a glucocorticoid (6 joints) or saline (7 joints). One month after the injection, satisfaction was reported for 5 of the 6 joints injected with a glucocorticoid compared with only 1 of the 7 joints injected with saline. Despite the small number...
of patients in this study, the experts felt that the result was convincing, as well as being corroborated by their own experience. They recommended glucocorticoid injections in patients with predominant sacroiliac pain refractory to NSAID therapy. In patients who also experience pain at other axial sites or at peripheral sites, tumour necrosis factor alpha (TNFz) antagonist therapy may be a better choice. This Grade B recommendation was approved by 93.6% of the experts.

3.2.6. Glucocorticoid injection at enthesis sites may be advisable in patients with ankylosing spondylitis who have inadequate responses to NSAID therapy

No studies on local glucocorticoid injections at sites of enthesis in patients with AS were found. However, agreement among the panellists was sufficiently strong that a recommendation was made to inject glucocorticoids into enthesis sites that remained painful despite NSAID therapy. Several experts suggested that the injections be made under ultrasound guidance, most notably at the Achilles tendon enthesis. Nevertheless, they represented a minority of panellists, and ultrasound guidance was therefore not included in the recommendation.

This is a Grade D recommendation. Agreement among the participants in the final full-session vote was 86.2%.

3.2.7. Sulfasalazine, methotrexate, and leflunomide are not recommended to treat the axial manifestations of ankylosing spondylitis. Sulfasalazine may deserve consideration in patients with concomitant peripheral joint involvement

Several controlled studies investigated the efficacy of sulfasalazine in patients with axial manifestations of AS. A meta-analysis was published recently [45]. Since then, a randomized placebo-controlled trial was published online [46]. Neither publication found any evidence that sulfasalazine improved the axial manifestations of AS, regardless of the evaluation criterion used. The meta-analysis showed a trend toward a therapeutic effect of sulfasalazine on peripheral joint involvement, which can co-exist with axial involvement. These data were consonant with the experience of the experts, who decided to recommend sulfasalazine in this specific situation.

The efficacy of methotrexate in improving the axial manifestations of AS was evaluated in a meta-analysis [47] and in a subsequently published randomized placebo-controlled trial [48]. The meta-analysis, which included 81 patients in all, found no evidence that methotrexate was effective in this situation. However, the experts challenged the relevance of the primary evaluation criterion chosen for this study, which had neither been used previously nor validated. This criterion was a composite index based on seven variables: morning stiffness severity assessed by the patient on a 100-mm visual analogue scale (VAS), physical well-being assessed by the patient on a 100-mm VAS, BASDAI, BASFI, Health Assessment Questionnaire for Spondyloarthopathy, disease activity assessed by the physician on a 100-mm VAS, and disease activity assessed by the patient on a 100-mm VAS. A 20% or greater improvement in five of these seven variables defined a response to treatment. The experts concluded that there was no conclusive evidence that long-term methotrexate therapy improved the axial manifestations of AS.

A single randomized placebo-controlled trial of leflunomide in axial AS was identified [49]. The effect of treatment in the two groups was assessed after 6 months of therapy based on the ASAS 20. No significant difference was found.

The potential roles for thalidomide and pamidronate in axial AS were considered. Two randomized controlled trials investigated pamidronate in axial AS [50,51]. In one of the reports, the data were inadequate to allow verification of the statistical test results [50]. The other study compared 60 mg to 10 mg of pamidronate as monthly intravenous infusions for 6 months in 84 patients with AS. The low pamidronate dosage was selected as likely to be ineffective (pseudo-placebo) but to induce infusion reactions. The proportion of patients with a greater than 25% BASDAI improvement was significantly larger in the 60-mg group. No studies confirming this result was available, and none of the experts had personal experience with pamidronate therapy in AS. In addition, intravenous pamidronate therapy is a costly intervention that requires hospitalization and induces adverse effects. Consequently, the experts decided not to mention pamidronate in the recommendation. The only available data on thalidomide in AS came from three open-label studies in a total of 55 patients with a mean follow-up of 6 months [52–54]. No conclusive evidence of clinical efficacy was found. Furthermore, thalidomide is associated with a risk of serious adverse effects. Therefore, the overwhelming majority of experts were in favour of excluding thalidomide from the recommendation.

This is a Grade A recommendation. Agreement among the participants in the final full-session vote was 86.4%.

4. Discussion

Based on data from a systematic literature review, seven recommendations about pharmacotherapy for axial AS were developed. Incontrovertible evidence exists that NSAIDs are effective in improving the axial manifestations of AS. As a result, nearly 100% of the experts agreed that NSAIDs should be used for the first-line treatment of axial AS. This is a grade A recommendation. Because there is no evidence that a specific NSAID is superior over the others, the choice of the NSAID is at the discretion of the rheumatologist. Most of the experts agreed that patients who fail to respond to one NSAID should be switched to another NSAID. The available data were considered insufficient to support continuous NSAID therapy. Continuous use of NSAIDs carries a high risk of gastrointestinal adverse events and induces only marginal structural benefits according to the single available randomized controlled study. Most experts excluded a role for systemic glucocorticoids but felt that glucocorticoid injections into the sacroiliac joints may be appropriate in some patients. Over 80% of the experts agreed that glucocorticoid injections into enthesitis sites may be used despite the absence of proof of efficacy in the literature. Finally, the experts concluded that evidence in the literature fails to support a role for conventional disease-modifying antirheumatic drugs in axial AS.
The use of TNF antagonists in AS has been the focus of several recommendations issued by learned societies (including the French Society for Rheumatology, SFR) [55]. However, no recommendations are available regarding the use of other medications to treat axial AS. Practices vary widely, probably in large part because published studies vary widely regarding several aspects including methodological quality.

The recommendations issued here stem from evidence from a systematic literature review and from the opinions of hospital- and office-based rheumatologists. They can be expected to improve clinical practice uniformity and, in the longer term, to optimize the management of patients with AS.

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References

[33] Lomen PL, Turner LF, Lamborn KR, Brinn EL. Flurbiprofen in the treat-
ment of ankylosing spondylitis. A comparison with indomethacin. Am J

[34] Nahir AM, Scharf Y. A comparative study of diclofenac and sulindac in

anti-inflammatoires non stéroïdiens dans la spondylarthrite ankylosante:

[36] Schwarzer AC, Cohen M, Arnold MH, Kelly D, McNaught P,
Brooks PM. Tenoxicam compared with diclofenac in patients with anky-

[37] Siemens P. Fenbufen in the treatment of ankylosing spondylitis. Phar-
macology 1982;25(Suppl. 1):51

[38] Villa Alcazar LF, de Buergo M, Rico Lenza H, Montull Fruitos E. Ace-
clofenac is as safe and effective as tenoxicam in the treatment of anky-
losing spondylitis: a 3 month multicenter comparative trial. Spanish
Study Group on Aceclofenac in Ankylosing Spondylitis. J Rheumatol

cross-over trial of fenoprofen and phenylbutazone in ankylosing spondy-

[40] Wasner C, Britton MC, Kraines RG, Kaye RL, Bobrove AM, Fries JF.
Nonsteroidal anti-inflammatory agents in rheumatoid arthritis and anky-

[41] Tramer MR, Moore RA, Reynolds DJ, McQuay HJ. Quantitative estima-
tion of rare adverse events which follow a biological progression: a new

Nonsteroidal antiinflammatory drugs reduce radiographic progression in
patients with ankylosing spondylitis: a randomized clinical trial. Arthritis

[43] Peters ND, Eijstrup L. Intravenous methylprednisolone pulse therapy in

[44] Maugars Y, Mathis C, Berthelot JM, Charlier C, Prost A. Assessment of the
efficacy of sacroiliac corticosteroid injections in spondylarthropa-

[45] Chen J, Liu C. Is sulfasalazine effective in ankylosing spondylitis? A sys-
tematic review of randomized controlled trials. J Rheumatol 2006;

et al. Efficacy of sulfasalazine in patients with inflammatory back pain
due to undifferentiated spondyloarthritis and early ankylosing spondyli-
itis: a multicentre randomized controlled trial. Ann Rheum Dis
2006;65:1147–53.

[47] Chen J, Liu C. Methotrexate for ankylosing spondylitis. Cochrane Data-
base Syst Rev. 2004;(3):CD004524. Review. Update in: Cochrane Data-

[48] Gonzalez-Lopez L, Garcia-Gonzalez A, Vazquez-Del-Mercado M, Mu-
noz-Valle JF, Gamez-Nava JJ. Efficacy of methotrexate in ankylosing
spondylitis: a randomized, double blind, placebo controlled trial. J Rheu-
matol 2004;31:1568–74.

[49] van Denderen JC, van der Paardt M, Nurmohamed MT, de Ryck YM,
Dijkmans BA, van der Horst-Bruinsma IE. Double blind, randomised,
placebo controlled study of leflunomide in the treatment of active anky-


[54] Wei JC, Chan TW, Lin HS, Huang F, Chou CT. Thalidomide for severe refractory ankylosing spondylitis: a 6-month open-label trial. J Rheuma-