

Evidence-based recommendations for the management of ankylosing spondylitis: systematic literature search of the 3E Initiative in Rheumatology involving a broad panel of experts and practising rheumatologists

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Objective. Recommendations and/or guidelines represent a popular way of integrating evidence-based medicine into clinical practice. The 3E Initiatives is a multi-national effort to develop recommendations for the management of rheumatic diseases, which involves a large number of experts combined with practising rheumatologists addressing specific questions relevant to clinical practice.

Methods. Ten countries participated in three rounds of discussions and votes concerning the management of AS. A set of nine questions was formulated in the domains of diagnosis, monitoring and treatment, after a Delphi procedure. A literature search in MedLine was conducted. Predefined outcome parameters for the domains of diagnosis, monitoring and treatment were assessed. The evidence to support each proposition was evaluated and scored. After discussion and votes, the final recommendations were presented using brief statements by each national group, following which the final international recommendations were formulated.

Results. A total of 2699 papers were found and 467 were selected for analysis. Twelve key recommendations were developed: three in the domain of diagnosis addressing general diagnostic considerations, early AS diagnosis and general practitioners' referral recommendations; three concerning monitoring of AS disease activity, severity and prognosis; six concerning pharmacological treatment (except biologics): non-steroidal anti-inflammatory drugs/COX-II inhibitors, bisphosphonates and treatment of enthesitis. The compiled agreement among experts ranged from 72% to 93%.

Conclusion. Recommendations for the management of AS were developed using an evidence-based approach followed by expert/physician consensus with high level of agreement. Involvement of a larger and more representative group of rheumatologists may improve their dissemination and implementation in daily clinical practice.

KEY WORDS: Ankylosing spondylitis, Systemic literature search, Recommendations, Non-steroidal anti-inflammatory drugs, COX-II inhibitors, Monitoring, Diagnosis, Treatment.

Introduction

Ankylosing spondylitis (AS) is a chronic rheumatic disease with reported prevalence ranging from 0.2% to 1.1% [1–3]. Chronic inflammation, bone destruction and aberrant bone repair result in significant disability comparable with that of RA [4].

AS is a rather heterogeneous disease; patients may have only axial involvement, but they may also have peripheral joint

inflammation, extra-spinal manifestations or extra-skeletal inflammation (e.g. uveitis). This heterogeneity poses problems in everyday clinical practice to define disease activity and severity. Although diagnosis in established disease is rather easy, in the majority of the cases diagnosis is delayed by 5–10 yrs, mainly because of delayed referral by general practitioners [5]. Restriction of spinal mobility and sacroiliitis by imaging studies, the two main characteristics of AS, may be absent in early stages of the disease and thus contribute to diagnostic delay. Pharmacological treatment modalities for AS are limited. NSAIDs are the cornerstone of pharmaceutical treatment, while anti-TNF agents have been proven extremely effective for patients who are refractory to NSAIDs [6–8].

Evidence-based recommendations have been increasingly applied in everyday clinical life, to aid practising physicians in clinical decision making. They aim to improve clinical practice and reduce unjustified health-related costs. The extent of the improvement of clinical practice depends not only on the quality of the recommendations, but also on the effective dissemination and implementation in clinical practice. The 3E (Evidence, Experts, Exchange) Initiative in Rheumatology is a multinational effort of rheumatologists with a special interest in clinical research. The aim of the initiative is to improve everyday clinical practice for patients with rheumatic diseases by formulating evidence-based recommendations for practical problems. In contrast to guidelines developed by a limited panel of experts in the field like the Assessment of Ankylosing Spondylitis/ European League Against Rheumatism (ASAS/EULAR) recommendations [9], the 3E initiative involves a large number of experts combined with practising rheumatologists

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addressing specific questions relevant to clinical practice. In this first effort, we addressed issues relevant to AS in the domains of diagnosis, monitoring and treatment.

Methods

The 3E Initiative and selection of questions

In the 3E Initiative, 10 countries were represented by scientific committees. The members of the committees consisted of both AS specialists and practising rheumatologists. In each country, one principal investigator (PI) was helped by a scientific committee consisting of four to eight members and in each country 23–65 experts attended the national meetings, result in 509 rheumatologists who participated in three rounds of discussions and votes concerning the management of AS. First, a set of nine questions, three in each domain—diagnosis, monitoring and treatment—were formulated by the scientific committees (Supplementary Table S1, available as supplementary data at *Rheumatology* Online). Four international research fellows (J.A., G.H., I.-H.S., P.I.S.) were selected to perform the literature search, guided by the scientific organizer (M.D.). A literature search of MedLine and PubMed was conducted for papers published up to August 2006. The search strategy included all relevant terms for AS combined with different set of keywords specific for each question. The relevant outcome parameters to be assessed in the literature for each domain were predefined by the scientific committee. These were sensitivity, specificity and Likelihood ratio (LR) for the domain of diagnosis, while effect size (ES), number needed to treat (NNT) and number needed to harm (NNH) were assessed for the domain of treatment. Finally, concerning monitoring studies, the Outcome Measures in Rheumatoid Arthritis Clinical Trials (OMERACT) filter characteristics—namely truth, discrimination and feasibility components—were assessed. Evidence was categorized according to study design using a hierarchy of evidence in descending order according to study quality [10], and the highest level of available evidence for each question was reviewed in detail. Literature search revealed 2699 papers, 467 of which were selected for detailed analysis. We generally searched Medline for studies with humans, published between 1966 and 28 August 2006. For the domains of diagnosis and treatment studies in the English, French and German literature were searched, while for monitoring English and French literature were searched. The references of selected articles were also hand searched. The main reasons for excluding papers for detailed analysis were inappropriate study population, irrelevant outcome examined or no data on selected outcome measures and inappropriate statistics applied; case reports, studies with TNF- α antagonists, animal studies, narrative review articles, commentaries and duplications were excluded.

The evidence from the literature search was then presented in each country during national meetings (national scientific committee and invited experts). Each country formulated a set of propositions.

Finally, in a common meeting, brief statements by each individual national group were extensively discussed and a final set of propositions was presented. In a final Delphi round of votes, the final international recommendations were formulated (Table 1). Information about the members of the national scientific committees and detailed description of the procedure for selecting the final questions that were addressed are given in supplementary data available at *Rheumatology* Online.

Results

Diagnosis

Statement 1: *In chronic back pain of at least 3 months duration, the presence of several of the following features makes the diagnosis*

of AS likely: inflammatory back pain, alternating buttock pain, response to NSAIDs, onset of symptoms before age 45, peripheral disease manifestations (arthritis, dactylitis, enthesitis), confirmed acute anterior uveitis, positive family history, HLA-B27 positive, sacroiliitis/spondylitis by imaging.

Although chronic low back pain is present in many AS patients, the prevalence of AS among patients with any kind (e.g. inflammatory or not) of low back pain is only around 5% [11]. It is therefore reasonable that the diagnosis of AS, especially in the early stages, cannot be based solely on the presence of chronic back pain; other features are also needed. To this end, we analysed data on diagnostic properties of a set of different parameters (symptoms, signs and laboratory results).

Concerning early AS, in one uncontrolled study that prospectively followed 88 patients with possible AS for 10 yrs, HLA-B27 and elevated CRP at presentation had the highest sensitivity for AS (68.8% both), followed by peripheral arthritis (46.9%) [12].

Concerning established AS (Supplementary Table S2 available as supplementary data at *Rheumatology* Online), studies of patients with established disease were analysed; in some of them mechanical low back pain (MLBP) patients were used as controls, whereas in others the control population included a broader group of patients with other rheumatic diseases, healthy individuals, and MLBP. A high LR was found for HLA-B27 positivity (11.9 for Caucasians and 14.1 for all ethnic groups). Certain of the extra-spinal features [e.g. uveitis, inflammatory bowel disease (IBD), psoriasis, peripheral arthritis, enthesitis] have a high specificity albeit of low sensitivity. In reference to the diagnostic ability of symptoms relevant to AS, our pooled analysis showed better features for alternating buttock pain (LR 2.8, sensitivity 39.7% and specificity 85.8%) and morning stiffness (LR 2.8, sensitivity 72.6% and specificity 73.6%). The remaining of the parameters an LR around 1.

Statement 2: *For early diagnosis of AS, no additional imaging is required if definite radiographic changes of sacroiliitis are present. If radiographs of the sacroiliac (SI) joints are normal or equivocal, magnetic resonance imaging (MRI) is the best imaging modality to identify inflammation of the SI joints and spine. Computed tomography (CT) is a sensitive tool for identifying structural changes of the SI joints but the risks of radiation exposure need to be considered.*

Many studies have assessed X-ray findings of the spine—apart from SI joints—in patients with AS and evident sacroiliitis on X-rays (Supplementary Table S3 available as supplementary data at *Rheumatology* Online), as well as in patients with suspected sacroiliitis (Supplementary Table S4 available as supplementary data at *Rheumatology* Online). We also reviewed diagnostic properties of CT imaging both in established AS (Supplementary Table S3 available as supplementary data at *Rheumatology* Online) and in cohorts of suspected sacroiliitis (Supplementary Table S4 available as supplementary data at *Rheumatology* Online). Concerning MRI in early AS, only Brandt *et al.* [13] has assessed MRI in a group of 58 patients with a diagnosis of axial spondylarthropathy according to expert opinion, having MLBP patients as controls ($n = 68$). Active inflammatory changes in SI joints had both high sensitivity (87.9%) and specificity (98.5%), and thus an extremely high likelihood ratio (58.6). In the same study, sensitivity of MRI for active lesions in the spine was lower (40.9%). Analysis of data for the diagnostic properties of MRI in patients with established AS and suspected sacroiliitis is in Supplementary Tables S3 and S4, available as supplementary data at *Rheumatology* Online.

Statement 3: *Patients with chronic back pain of at least 3 months duration and features of inflammatory back pain (onset of symptoms before age 45 yrs, back pain at night, morning stiffness and*

TABLE 1. Summary of recommendations/statements

Statement number	Statement	Level of evidence	Strength of recommendation	Compiled agreement (%)
Diagnosis				
1	In chronic back pain of at least 3 months duration, the presence of several of the following features makes the diagnosis of AS likely: inflammatory back pain, alternating buttock pain, response to NSAIDs, onset of symptoms before age 45, peripheral disease manifestations (arthritis, dactylitis, enthesitis), confirmed acute anterior uveitis, positive family history, HLA-B27 positive, sacroiliitis/spondylitis by imaging.	III	C	85.4
2	For early diagnosis of AS, no additional imaging is required if definite radiographic changes of sacroiliitis are present. If radiographs of the SI joints are normal or equivocal, MRI is the best imaging modality to identify inflammation of the sacroiliac joints and spine. CT is a sensitive tool for identifying structural changes of the SI joints but the risks of radiation exposure need to be considered.	IIb	B	89.8
3	Patients with chronic back pain of at least 3 months duration and features of inflammatory back pain (onset of symptoms before age 45 yrs, back pain at night, morning stiffness and improvement with exercise) should be referred to a rheumatologist for further evaluation of possible AS.	IV	D	77.6
Monitoring				
4	Useful parameters to assess disease activity in AS include: BASDAI, overall pain, pain at night, patient's global assessment, ESR and/or CRP, daily function (BASFI, working ability), extra-articular manifestations, peripheral arthritis. MRI of SI joints and/or spine can be considered in selected cases.	IV	D	72
5	Useful parameters to assess disease severity in AS include: structural damage assessed by X-ray, metrological evaluation such as BASMI, measures of function such as BASFI, hip involvement, extra-articular manifestations.	IV	D	84
6	Predictors of a poor prognosis in AS include: radiographic structural changes of the spine at initial assessment, hip involvement, young age at disease onset, persistently elevated acute phase reactants, persistently high disease activity.	IV	D	90.9
Treatment				
7	There are insufficient data to support the use of bisphosphonates in the treatment of active AS. However, bisphosphonates may be useful for the management of osteoporosis in AS.	Ib	B, D	92.9
8	NSAIDs can be used for the treatment of enthesitis in patients with AS. Local corticosteroid injections may be the preferred treatment in selected cases.	Ib	A, D	97.7
9	NSAIDs are the first-line treatment for relief of pain and improvement of daily function in AS. NSAIDs should be used as needed in AS for symptoms of active disease. There is no significant difference in efficacy between short-acting and long-acting agents or between COX-II selective and non-selective agents.	Ib	B	88.1
10	AS patients with persistently active disease may require continuous use of NSAIDs but this may increase the risk of side-effects including cardiovascular toxicity. In patients at higher risk of gastrointestinal side effects, a selective COX-II agent or a non-selective NSAID in combination with a gastroprotective agent should be considered.	Ib	B	88.1
11	NSAIDs are effective for axial, peripheral and enthesal features of AS although axial symptoms are most responsive.	Ib	A	86
12	There is limited evidence that NSAID use in AS precipitates first presentations of IBD or flares of pre-existing disease. IBD patients treated with NSAIDs should be monitored closely together with a gastroenterologist.	IIa	C	88.4

improvement with exercise) should be referred to a rheumatologist for further evaluation of possible AS.

AS is among the rheumatic diseases with the longest delay in diagnosis, with an average of about 8 yrs [5]. Early referral recommendations have only recently been proposed [14], thus there are no studies assessing their impact in improving AS outcome.

However, there exist early data on the performance of the aforementioned early referral recommendations in clinical practice. Approximately 45% of the patients referred because of HLA-B27 positivity and sacroiliitis on imaging (MRI or X-rays) had a diagnosis of AS, irrespective of the presence of inflammatory back pain (IBP). On the contrary, the presence of isolated HLA-B27 positivity or IBP was rarely associated with AS (19 and 17%, respectively).

To identify an indirect measure of the quality of candidate parameters for early referral counselling, we searched for studies of patients with certain parameters and assessed the frequency of AS in these cohorts. Generally the prevalence of AS in these populations was <25%. The higher prevalence was found among patients with psoriasis (23%, $n=48$) [14], HLA-B27 positivity (18%, $n=365$) [16–19] and acute anterior uveitis (17%, $n=1120$) [15, 20–24], while it was lower among patients with positive family

history and HLA-B27(+) (13%, $n=61$) [1] and IBP (11%, $n=903$) [11, 25–27].

Monitoring

Statements 4 and 5: *Useful parameters to assess disease activity in AS include: Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), overall pain, pain at night, patient's global assessment, ESR and/or CRP, daily function (BASFI, working ability), extra-articular manifestations, peripheral arthritis. MRI of SI joints and/or spine can be considered in selected cases.*

Useful parameters to assess disease severity in AS include: structural damage assessed by X-ray, metrological evaluation such as Bath Ankylosing Spondylitis Metrology Index (BASMI), measures of function such as Bath Ankylosing Spondylitis Functional Index (BASFI), hip involvement, extra-articular manifestations.

Parameters used for monitoring in clinical practice should be easily performed, related to disease prognosis and have definite limits of severity that may guide clinical decisions. Concerning the monitoring of AS disease activity, we reviewed parameters assessing symptoms, metrology, laboratory and imaging studies; for monitoring AS disease severity we reviewed parameters assessing

irreversible damage like metrology and imaging as well as symptoms. The strongest evidence for a parameter as a monitoring tool for clinical practice would be that patients followed by this parameter would have a better prognosis. We found no trials addressing this question.

We also assessed data concerning the OMERACT filter qualities of the selected parameters. Although the OMERACT filter characteristics are typically used for assessing the quality of a parameter for clinical trials, we used them as a marker of the quality of these parameters (see Supplementary Tables S5 and S6, available as supplementary data at *Rheumatology* Online).

Experts have formulated proposals on methods for following patients. Thus the ASAS working group has proposed the core set of variables to be used in clinical record keeping and in clinical trials [28]. This core set of variables proposed for clinical records consists of physical function, pain, spinal mobility, spinal stiffness, patient's global assessment, peripheral joints/enthesitis and acute phase reactants.

Statement 6: Predictors of a poor prognosis in AS include: radiographic structural changes of the spine at initial assessment, hip involvement, young age at disease onset, persistently elevated acute phase reactants, persistently high disease activity.

The optimal study for the evaluation of a parameter to predict AS prognosis would be a prospective study of patients with early disease and minimal damage, for whom prognosis would be assessed after a long-term follow-up.

Investigators of the GESPIC cohort (German Spondylarthrit Inception Cohort) have reported, in abstract form, data for 90 patients with early AS (mean symptom duration 5.2 ± 2.5 yrs) [29]. Patients with definite radiographic damage at baseline (mean mSASSS change 3.3 ± 3.8) had a higher degree of radiographic progression than patients with no radiographic damage at baseline (mean mSASSS change 0.6 ± 1.0 , $P < 0.001$ between groups).

We also found data from two prospective, observational studies assessing long-term prognosis at 10 (328 patients) and 5 yrs (97 patients), respectively [30, 31] (Supplementary Table S7 available as supplementary data at *Rheumatology* Online) and two cross-sectional studies (529 and 1538 patients) (Supplementary Table S8, available as supplementary data at *Rheumatology* Online) [32, 33]. Among the factors associated with adverse prognosis were hip arthritis, young age at onset, poor efficacy of NSAIDs and baseline BASDAI.

Treatment

Statement 7: There are insufficient data to support the use of bisphosphonates in the treatment of active AS. However, bisphosphonates may be useful for the management of osteoporosis in AS.

Intravenous pamidronate has been assessed in one controlled [34] and five uncontrolled AS trials [35–39]. Although efficacious, the treatment effect was generally modest (mean BASDAI reduction 2.2) [34]. On the other hand, there is adequate evidence for the efficacy of bisphosphonates in the treatment of osteoporosis in patients with rheumatic diseases treated with steroids [40]. Although they have not been assessed in the treatment of osteoporosis of AS, the members of 3E Initiative considered that bisphosphonates may be used for the management of Osteoporosis (OP) in AS.

Statement 8: NSAIDs can be used for the treatment of enthesitis in patients with AS. Local corticosteroid injections may be the preferred treatment in selected cases.

Concerning enthesitis, it was anticipated that the most relevant clinical problem for physicians is the treatment of a specific enthesitis, but we found only case reports addressing treatment of specific enthesial involvement. We found one systematic review and six RCTs of DMARDs or NSAIDs that assessed

enthesitis as an outcome parameter. In three randomized controlled trial (RCTs) (528 patients on sulphasalazine, 551 on placebo), the ES for enthesopathy was mild (0.11) and the NNH (withdrawals because of toxicity) was 46 [41–43]. In a small study (51 patients, 12 months), methotrexate (MTX) had contradictory results compared with naproxen [44]. Finally, a higher ES was found in two controlled studies of NSAIDs/COX-II inhibitors (ES 0.6 up to ES 1.6) with a rather higher toxicity than in other NSAIDs trials (NNH = 9) [45, 46].

Statement 9: NSAIDs are the first-line treatment for relief of pain and improvement of daily function in AS. NSAIDs should be used as needed in AS for symptoms of active disease. There is no significant difference in efficacy between short-acting and long-acting agents or between COX-II selective and non-selective agents.

NSAIDs have been considered as the cornerstone of medical treatment of AS, and have been recommended by ASAS/EULAR as the first-line drug to improve pain and stiffness [9]. Notably, apart from ASAS/EULAR-published recommendations based on systematic literature research [9, 47], there is only one published review of literature of the NSAIDs studies in AS [48], while two meta-analyses of NSAIDs/COX-II inhibitors assessed upper gastrointestinal (GI) events [49] and cardiovascular events [50], respectively in patients with AS, RA or OA and not separately in AS.

Inter-NSAIDs efficacy profile. Of 32 randomized controlled trials of NSAIDs or COX-II inhibitors in AS, nine compared different NSAIDs and/or COX-II inhibitors with placebo. In four of them that had data to assess ES for pain and BASFI, no constant differences between the different agents over placebo was found (see Supplementary Table S9, available as supplementary data at *Rheumatology* Online) [51–54]. Similarly, analysis of data for NSAIDs and COX-II inhibitors did not reveal consistent differences between the two classes of agents. Furthermore, the small total number of patients does not permit firm conclusions favouring one agent over another (Supplementary Table S9 available as supplementary data at *Rheumatology* Online) [53, 54]. Similarly, no consistent differences between different doses of NSAIDs or COX-II inhibitors were found [51, 52, 54], nor between long and short half-life agents [55–59].

Inter-NSAIDs safety profile. We analysed data from 20 studies, applying withdrawals due to toxicity as a surrogate marker of toxicity in order to compare data from different studies. An acceptable safety profile (NNH = 77) was found from combined analysis of nine studies (2477 NSAIDs, 898 placebo). When we analysed studies comparing coxibs to non-selective NSAIDs in AS patients, no consistent differences favouring one class over the other were found [53, 54]. However, in a meta-analysis of 10 multinational etoricoxib trials in different patient groups (5441 patients with OA, RA or AS), etoricoxib had a better safety profile compared with conventional NSAIDs [NNH = 80 concerning withdrawals due to rather major gastrointestinal events (perforation, bleeding and ulcers)] [49]. Similarly, no consistent differences favouring the safety profile of low vs higher doses of NSAIDs were found [51, 52, 54]. The safety profile was not consistently different between long and short half-life agents; in studies favouring long half-life agents NNH ranged from 6 up to 129, compared with those favouring short half-life agents (NNH 6 up to 87) [46, 55–57, 59–69].

Statement 10: AS patients with persistently active disease may require continuous use of NSAIDs but this may increase the risk of side-effects including cardiovascular toxicity. In patients at higher risk of gastrointestinal side-effects, a selective COX-2 agent, or a non-selective NSAID in combination with a gastroprotective agent should be considered.

Most physicians recommend intermittent use of NSAIDs according to patient symptoms, aiming at fewer adverse events. Data supporting the effect of long-term use on disease outcome are limited. We searched the literature for long-term studies (≥ 1 yr) of continuous or intermittent NSAIDs use, assessing the impact of the drugs on diseases outcome; we considered long-term outcomes of function and structural damage to be valid.

van der Heijde D *et al.* [28] reported evidence of disease-modifying properties of NSAIDs for the first time. Statistical analysis showed significant differences between continuous and on-demand treatment on progression of damage. Two additional studies of continuous long-term (1 yr) NSAIDs/COX-II inhibitors treatment, reported a significant improvement of function (ES 1.1) and pain (ES 0.5–0.66) compared with placebo [52, 54].

Concerning the safety of long-term treatment in AS patients, we found an increase in overall GI toxicity of continuous compared with intermittent therapy [odds ratio (OR) 4.2, 95% CI 1.9, 9.5] but comparable cardiovascular toxicity (OR 1.2, 95% CI 0.5, 2.8) [70]. Concerning upper GI events in general, an increased risk was found with NSAIDs compared with placebo (OR 2.2, 95% CI 1.3, 4.9) [52]. Interestingly, a rather comparable safety profile between etoricoxib and naproxen-concerning GI events was shown (perforation, ulcers, bleeding – PUB) (OR 0.4, 95% CI 0.08, 1.7) [54]. Concerning cardiovascular thrombotic serious events, five were recorded with etoricoxib and none with naproxen [54].

Statement 11: *NSAIDs are effective for axial, peripheral and enthesal features of AS although axial symptoms are most responsive.*

Although axial skeletal involvement is the hallmark of AS, a considerable number of patients have peripheral arthritis (up to 68%) [71] or enthesopathy (25–58%) [72]. We identified three studies reporting on peripheral arthritis and/or enthesitis [46, 54, 64]. In addition, Gossec *et al.* [45] reported a *post hoc* analysis based on the results of van der Heijde *et al.* [54]. In the most recent study, two doses of etoricoxib ($n = 195$) were assessed compared with naproxen ($n = 99$) and placebo ($n = 93$) [54]. Active treatment significantly reduced axial disease and moderately peripheral arthritis and enthesopathy (ES 1.1–2.3, 0.6 and 0.5–0.6 for spinal pain, peripheral pain and enthesial pain, respectively). The authors concluded that although NSAIDs and COX-II inhibitors have a clinically relevant symptomatic effect on axial AS irrespective of the presence of peripheral arthritis, spinal improvement appeared to be greater in patients without peripheral disease.

Statement 12: *There is limited evidence that NSAID use in AS precipitates first presentations of IBD or flares of pre-existing disease. IBD patients treated with NSAIDs should be monitored closely together with a gastroenterologist.*

In case reports, treatment with non-selective NSAIDs in IBD patients has been reported to lead to frequent disease exacerbation [73–75]. In two prospective, randomized placebo-controlled trials of IBD patients, coxibs were not associated with increased flares of IBD (celecoxib OR 0.7; 95% CI 0.2, 0.4, etoricoxib OR 0.9; 95% CI 0.3, 2.6) [76, 77]. In three retrospective, case-control studies, of non-selective NSAIDs that reported on IBD flares no constant increased risk was found [OR from 0.5 (95% CI 0.2, 1.2) up to 1.7 (95% CI 1, 3)].

Discussion

In this systematic literature search, we reviewed a total of 2699 papers and selected 467 for detailed analysis. The final set of recommendations was formulated following extensive discussions and votes in two rounds, the first in 10 national meetings and the second in the final international meeting (Table 1). The final level

of agreement between members of the initiative was excellent (mean 86.7%, range 72–97.7%). These are the first recommendations for the management of AS based on the opinion of both experts and practising rheumatologist, which focus on practical issues of everyday clinical practice; thus, they should be considered supplementary to the ASAS/EULAR recommendations. They should aid physicians in clinical decision making and optimize the care of AS patients. To this end, efficient dissemination and implementation of the recommendations are of paramount importance.

The diagnosis of AS is based upon a combination of clinical, laboratory and radiological findings. Sacroiliitis, the hallmark of the disease, develops after a variable period from the onset of symptoms. Furthermore, restriction of spinal mobility, a characteristic finding of axial involvement, may be absent in early stages. To overcome this delay in diagnosis, and in order to increase the likelihood of the diagnosis of AS, we recommend the use of a group of nine parameters to be used in combination with chronic back pain.

Our recommendations for early AS diagnosis and referral by general practitioners to rheumatologists are in line with the proposed confidence intervals algorithm for early axial SpA diagnosis by Rudwaleit *et al.* [78]. They propose that primary care physicians may refer cases of chronic low back pain to rheumatologists in the presence of either inflammatory characteristics of back pain or HLA-B27 positivity [14].

MRI represents a significant advance in the diagnosis of AS during the pre-radiographic stage. Active inflammation in SI joints is depicted by MRI years prior to plain radiography [79–81]. From the literature search, only Brandt *et al.* [26] have studied patients at a pre-radiographic stage and found a high sensitivity (88%) and specificity (99%) for active inflammatory changes by MRI. Thus, we propose MRI imaging for those cases of early AS where radiographs of the SI joints are normal or equivocal. High cost and limited availability are major disadvantages of MRI at present.

The existence of valid prognostic factors helps rheumatologists to rationalize aggressive, expensive and potentially toxic treatments for those patients who would benefit the most. At this point, studies with early AS patients to whom baseline parameters were prospectively assessed for outcome are lacking. Early data—in abstract form—from the GESPIC cohort of early AS, suggest that radiographic damage evident at first assessment correlates with an increased rate of progression at 2 yrs [29].

Our combined analysis confirmed previously reported results of the effectiveness of NSAIDs/COX-II inhibitors for pain control and for function [47]. Concerning the potential of differential efficacy for different classes of NSAIDs, we found no consistent results supporting any superiority of one class of NSAIDs over another. Although of proven symptomatic efficacy, long-term NSAID therapy is limited because of safety concerns, mainly gastrointestinal, but also renal and cardiovascular. Thus, most physicians recommend intermittent use titrating to the patients' symptoms. Our analysis showed an increased GI toxicity with continuous compared with on-demand therapy (OR 4.2, 95% CI 1.9, 9.5) [70]. Nevertheless, these are data which stem from one study only and should be interpreted cautiously.

Recently, the association of cardiovascular events with the use of COX-II inhibitors and traditional NSAIDs has been extensively investigated; data for increased risk with rofecoxib from earlier [82] and recent meta-analyses [83] have confirmed data from randomized controlled trials [84] and pharmaco-epidemiological studies [85–88]. Furthermore, observational studies have linked diclofenac [83, 89–91] and ibuprofen [91] with cardiovascular events. Regarding cardiovascular toxicity, data from AS patients are limited to only two studies [54, 70]. AS patients, similar to patients with other chronic inflammatory arthritides, are at an increased risk for cardiovascular diseases [92]. Thus, although data from AS studies are limited, physicians

should use NSAIDs/coxibs cautiously, especially in those patients with concomitant risk factors for cardiovascular diseases. Data supporting that long-term use could affect disease outcome are limited to one study of celecoxib and therefore need verification in larger cohorts [70].

The question of whether NSAIDs increase the risk for IBD flare is important, since spondylarthropathies are among the most common extra-intestinal manifestations of patients with IBD, with a prevalence up to 22% [93]. Our analysis of 24 studies with a total of 5556 AS patients revealed that symptoms of IBD were reported in 5.8% of the patients. We conclude that although the available data do not support that NSAIDs increase IBD symptoms, IBD patients treated with NSAIDs should be monitored closely for early detection of IBD flares.

In summary, our analysis has demonstrated previous findings that important aspects of disease management, including early diagnosis, monitoring and treatment, are based on suboptimal evidence. This study combined systemic literature review together with expert opinion revealing the daily practice perspective with the inclusion of a large number of practising rheumatologists. These recommendations should facilitate the care of AS patients without restricting the autonomy of treating physicians. Increasing the familiarity of practising rheumatologists with available evidence, together with a critical overview of its strengths and weaknesses, may facilitate their implementation in clinical practice. Longitudinal studies are needed to document the effect of these recommendations in curbing unjustified variation in clinical practice and in reducing health-related costs.

Rheumatology key messages

- Recommendations for the management of AS have been formulated based on both Systematic Literature Research and international experts' opinion'.
- They aim to facilitate "Translating Research into Practice-TRIP" in AS.

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Supplementary data

Supplementary data are available at *Rheumatology* Online.

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