

# Italian evidence-based recommendations for the management of ankylosing spondylitis: the 3E Initiative in Rheumatology

S. D'Angelo<sup>1</sup>, A. Padula<sup>1</sup>, A. Nigro<sup>1</sup>, F. Cantini<sup>2</sup>, M. Matucci-Cerinic<sup>3</sup>, V. Modena<sup>4</sup>,  
L. Punzi<sup>5</sup>, C. Salvarani<sup>6</sup>, R. Scarpa<sup>7</sup>, I. Olivieri<sup>1</sup>

---

<sup>1</sup>Rheumatology Department of Lucania, San Carlo Hospital of Potenza and Madonna delle Grazie Hospital of Matera, Potenza, Italy; <sup>2</sup>Rheumatology Unit of the 2<sup>nd</sup> Division of Medicine of Prato Hospital, Prato, Italy; <sup>3</sup>Department of Biomedicine, Division of Rheumatology AOUC, Denoto Center, University of Florence, Florence, Italy; <sup>4</sup>Rheumatology Unit, Ospedale Le Molinette, Torino, Italy; <sup>5</sup>Academic Rheumatology Unit of the University of Padova, Padova, Italy; <sup>6</sup>Rheumatology Unit, Arcispedale Santa Maria Nuova, Reggio Emilia, Italy; <sup>7</sup>Academic Rheumatology Unit of the University Federico II, Napoli, Italy.

---

## Abstract Objective

The 3E (Evidence, Expertise, Exchange) Initiative is a multinational effort of rheumatologists aimed at developing evidence-based recommendations addressing specific questions relevant to clinical practice. The objective of the Italian part of the 3E Initiative was to develop new recommendations designed to help Italian rheumatologists in everyday clinical practice management of patients suffering from ankylosing spondylitis (AS).

## Methods

An international scientific committee selected a set of questions concerning the diagnosis, monitoring, and treatment of AS using a Delphi procedure. Evidence-based answers to each question were sought by a systematic literature search in MedLine for papers published up to August 2006. A panel of 55 Italian rheumatologists with expertise in the field of AS used the evidence thus gathered to develop recommendations, filling gaps in evidence with their expert opinion.

## Results

After discussion and votes, the panel developed 12 statements/recommendations: 3 concerning diagnosis (low back pain approach, early diagnosis, and GPs referral recommendations); 3 concerning monitoring (disease activity, severity, and prognosis), and 6 concerning treatment (bisphosphonates role; treatment of enthesitis; inter-agent safety/efficacy, long-term safety/efficacy, efficacy on different disease manifestations, and the role on inflammatory bowel disease flare precipitation of NSAIDs/COX-II inhibitors).

## Conclusion

Italian recommendations for the management of AS in everyday practice were developed. Their dissemination and implementation in daily clinical practice should help to improve practice uniformity and eventually optimize the management of AS patients.

## Key words

Ankylosing spondylitis, management, recommendations, evidence-based, expert opinion.

Salvatore D'Angelo, MD  
Angela Padula, MD  
Angelo Nigro, MD  
Fabrizio Cantini, MD  
Marco Matucci-Cerinic, MD  
Vittorio Modena, MD  
Leonardo Punzi, MD  
Carlo Salvarani, MD  
Raffaele Scarpa, MD  
Ignazio Olivieri, MD

*This study was supported by an unrestricted grant from Abbott International.*

*Please address correspondence and reprint requests to:*

*Dr. Ignazio Olivieri,  
Rheumatology Department of Lucania-San  
Carlo Hospital, Contrada Macchia Romana,  
Padiglione E, 85100 Potenza, Italy.  
E-mail: ignazioolivieri@tiscalinet.it*

*Received on August 17, 2007; accepted in  
revised form on May 19, 2008.*

© Copyright CLINICAL AND  
EXPERIMENTAL RHEUMATOLOGY 2008.

## Introduction

Ankylosing spondylitis (AS) is a chronic inflammatory disease which can lead to severe damage of the spine with functional impairment, disability and poor quality of life (1). With an estimated prevalence of 0.37% in Italy (2), AS is a significant health burden to the community.

AS is a rather heterogeneous disease: the typical feature is the axial involvement (sacroiliitis and spondylitis) that is frequently associated with peripheral skeletal involvement (peripheral arthritis and enthesitis) and extra-skeletal manifestations (*i.e.*, acute anterior uveitis).

AS requires a combined management (pharmacological and rehabilitation) and recently, the introduction of biological agents has positively changed the treatment scenario (3).

It has been estimated that a physician would need to read about 20 journal articles a day to keep abreast of all research relevant to a particular area of interest (4). This is clearly complicated. For this reason, in recent years, growing attention has been focused on the use of synthesized evidence resources such as systematic reviews, meta-analyses, and evidence-based clinical practice guidelines and recommendations. Within the field of research in spondylarthritis, there has been an increasing interest in proposing new sets of recommendations. Recently, by combining a systematic review of the literature and expert consensus, the ASsessment in Ankylosing Spondylitis (ASAS) International Working Group and the European League Against Rheumatism (EULAR) produced 10 recommendations for the management of AS (5). These recommendations are very useful in improving the knowledge of the disease, but some issues remain to be further investigated in order to facilitate the management of AS patients in daily practice.

The 3E (Evidence, Expertise, 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 this first effort, we addressed issues relevant to AS in the domains of diagnosis, monitoring, and treatment. The programme has involved a large number of rheumatologists working in different practice environments within 10 different countries (Australia, Austria, Belgium, Denmark, Germany, Greece, Italy, Norway, Spain, and Turkey). In addition to the developing process of the multinational recommendations (6), the project included a National level in order to reach recommendations appropriate in the context of resource and healthcare situation of the single participating countries.

This paper summarizes the Italian recommendations for the management of AS, based on literature research and expertise. The aim is to reach recommendations that are achievable in the real environment of a rheumatology practitioner and with the consensus of a large number of Italian rheumatologists. Moreover, the possible discrepancies existing between the multinational and the Italian recommendations will be analysed.

## Materials and methods

The methodology used in developing the recommendations included the combination of a rigorous analysis of the scientific literature with the opinion of experts in daily management of disease. The steps of the process are detailed elsewhere (6). In brief, the international steering committee, using the Delphi consensus procedure, prepared a set of questions for each of the 3 themes in AS management (diagnosis, monitoring, and treatment) (Table I). Questions concerning the treatment with biological agents were not considered since this topic has been already widely addressed by ASAS/EULAR group (7).

By combining keywords specific for each question, a literature search in PubMed was conducted for papers published up to August 2006 (6). The evidence from the literature search for the specific questions was then presented to national scientific committees. Each one in a national meeting formulated a set of propositions.

*Competing interests: none declared.*

**Table I.** Selected questions for the literature research.**Diagnosis**

- In case of back pain, which are the symptoms/signs/response to NSAIDs for considering the diagnosis of (early) AS?
- Imaging: what is the accuracy of imaging techniques to diagnose (early) AS?
- Based on which symptoms and other clinical data should the GP refer a patient to the rheumatologist?

**Monitoring**

- Which parameters (*e.g.*, symptoms, signs, metrology, biochemical, imaging, etc) are useful for assessing AS disease activity?
- Which parameters (*e.g.*, symptoms, signs, metrology, biochemical, imaging, etc) are useful for assessing AS disease severity?
- Which parameters (*e.g.*, symptoms, signs, metrology, biochemical, imaging, etc) are useful for assessing AS disease prognosis?

**Treatment (except biologics)**

- Is there any place for bisphosphonates for the treatment of AS?
- What is the optimal treatment of peripheral enthesitis/costochondritis?
- What is the exact place of NSAIDs in the management of AS patients?
  - What is the inter NSAIDs (low versus high dose, COX-II versus conventional, long vs. short half life) safety/efficacy profile?
  - What is the long-term safety (CV/GI) and efficacy profile of NSAIDs (concerning continuous or on demand treatment)? What's the evidence of DMARD properties of NSAIDs?
  - Is there any difference in the treatment usefulness with regard to the clinical presentation (axial/peripheral/enthesiopathy)?
  - Is there evidence that NSAIDs precipitate initial presentation and/or clinical flare-ups of IBD patients with AS?

**Table II.** Grading systems for category of evidence and strength of recommendation.**Category of evidence**

Ia: Meta-analysis of randomized controlled trials

Ib: Randomized controlled trial

IIa: Controlled study without randomization

IIb: Quasi-experimental study

III: Non-experimental descriptive studies, such as comparative, correlation, and case-control studies

IV: Expert committee reports or opinion and/or clinical experience of respected authorities, or both

**Strength of recommendation**

A: Category I evidence

B: Category II evidence or extrapolated from category I evidence

C: Category III evidence or extrapolated from category I or II evidence

D: Category IV evidence or extrapolated from category II or III evidence

Based on this information, the Italian scientific committees organised a consensus meeting that was held on December 15, 2006 in Rome, in order to provide written recommendations.

This meeting was attended by 55 Italian rheumatologists with expertise in the field of AS. About 1 month before attending the meeting, each participant was provided by the detailed literature search. The panel of rheumatologists used evidence from the literature to develop recommendations for each question; gaps in evidence were filled with panelists' expert opinion.

**Results**

Details of the literature search results of each recommendation have been

published elsewhere (6). The level of evidence and the strength of recommendations were scored according to the same grading systems used by ASAS/EULAR group (5) and 3E multi-national group (6). In particular, for each selected paper, the level of evidence was categorised (Ia through IV) using the hierarchy suggested by Shekelle *et al.* (8). The level of evidence was then used to determine the strength (A to D) of each recommendation (Table II) (8). Each expert was asked to rate his agreement on final recommendations using a five-category Likert scale (strongly disagree, disagree, neither agree nor disagree, agree, strongly agree).

Table III shows the final 12 recommendations/statements.

**Diagnosis**

*Recommendation 1: In the case of back pain, the diagnosis of early AS should be considered if the back pain is inflammatory, especially if there are other features of spondyloarthritis including alternating buttock pain, anterior chest pain, limited spinal mobility, peripheral arthritis, peripheral enthesitis (heel enthesitis), dactylitis, acute anterior uveitis, positive HLA-B27, elevated acute phase reactants, rapid response to NSAIDs, and positive family history for spondyloarthritis or psoriasis or IBD.*

This is a grade C recommendation derived from level III evidence. The agreement (agree and strongly agree) among experts was 93%.

The panelists emphasized that the prevalence of AS among patients with low back pain (*i.e.*, inflammatory or not) is about 5% (9). Therefore, for the diagnosis of early AS other features (symptoms, signs, and laboratory results) should be considered.

The most significant difference between such recommendation and the corresponding multi-national one is the exclusion of radiological features. Italian rheumatologists consider that radiological signs of sacroiliitis and/or spondylitis become evident late thus they do not allow to made an early diagnosis of AS.

*Recommendation 2: Short tau inversion recovery (STIR)-magnetic resonance imaging (MRI) of the sacroiliac joints has a sufficient accuracy for the diagnosis of AS in the pre-radiographic phase.*

This is a grade C recommendation derived from level III evidence. The agreement (agree and strongly agree) among experts was 95%.

The diagnostic properties of MRI in early AS were reviewed (6). Active inflammatory changes in sacroiliac joints had both high sensitivity and specificity (10). STIR sequences are preferred for their excellent fat suppression and high signal intensity from areas of bone edema.

In contrast with the multinational recommendations, Italian rheumatologists prefer not to consider computed tomography of sacroiliac joints because it results to be less sensitive and safe (*i.e.*,

**Table III.** The Italian 3E Initiative recommendations/statements for the management of ankylosing spondylitis.

	Level of evidence	Strength of recommendation	Level of agreement
<i>Diagnosis</i>			
1) In case of back pain the diagnosis of early AS should be considered if the back pain is inflammatory especially if there are other features of spondyloarthritis including alternating buttock pain, anterior chest pain, limited spinal mobility, peripheral arthritis, peripheral enthesitis (heel enthesitis), dactylitis, acute anterior uveitis, positive HLA-B27, elevated acute phase reactants, rapid response to NSAIDs, and positive family history for spondyloarthritis or psoriasis or IBD.	III	C	93%
2) STIR-MRI of the sacroiliac joints has a sufficient accuracy for the diagnosis of AS in the pre-radiographic phase.	III	C	95%
3) The GP should refer every patient with inflammatory back pain to the rheumatologist.	IV	D	85%
<i>Monitoring</i>			
4) For the assessment of disease activity BASDAI and physician's global assessment are recommended. CRP and ESR could be useful. STIR-MRI is accurate but not feasible in daily practice, and should be used only in selected cases.	IV	D	91%
5) For the assessment of disease severity the following parameters are recommended: BASFI, chest expansion, modified Schober test, occiput-to-wall distance, hip involvement, presence of extra-articular manifestations, serial x-rays of spine and pelvis.	IV	D	92%
6) For the assessment of disease prognosis the following parameters are recommended: young age at onset, disease duration, hip arthritis, peripheral arthritis, BASDAI at onset, BASFI, rapid progression of radiological damage of spine and pelvis, poor efficacy of NSAIDs.	IV	D	90%
<i>Treatment (except biologics)</i>			
7) Intravenous pamidronate therapy could be considered in patients with NSAID-refractory disease.	Ib	C	78%
8) Local corticosteroid injections are recommended as first line treatment for peripheral enthesitis when only a few entheses are involved. In patients who respond inadequately to local corticosteroid injections and in patients with multiple peripheral enthesitis oral NSAIDs should be used. There is no evidence of efficacy of sulfasalazine and methotrexate for the treatment of peripheral enthesitis. The optimal treatment of costochondritis has not been established.	Ib	C	88%
9) Conventional NSAIDs and selective COX-II inhibitors are equally effective for pain control. In patients with increased GI risk conventional NSAIDs plus PPI agents or selective COX-II inhibitors should be used. Long half-life drugs could be preferred for their better efficacy profile.	Ib	B	81%
10) The continuous treatment with NSAIDs/COX-II inhibitors may offer a sustained effect on function and pain, and a possible slowing of radiographic disease progression. In patients with increased GI and/or CV risk such an approach should be used with caution.	Ib	B	95%
11) NSAIDs/COX-II inhibitors are effective on different ( <i>i.e.</i> , axial/articular/enthesal) clinical manifestations of disease even though spinal pain seems to better respond to this treatment.	Ib	A	93%
12) Despite of the lack of evidence that COX-II inhibitors induce clinical flare-ups of IBD manifestations, both NSAIDs and COX-II inhibitors should be used with caution in AS patients with IBD.	IIa	C	89%

radiation exposure) when compared to MRI.

Furthermore, the panelists felt that the use of MRI in everyday practice raises some practical problems: availability of MRI in Italy is still limited; the cost is high; no standardised criteria exist for interpreting results.

**Recommendation 3:** *The GP should refer every patient with inflammatory back pain to the rheumatologist.*

This is a grade D recommendation derived from level IV evidence. The agreement (agree and strongly agree) among experts was 85%.

The literature contains poor evidence regarding criteria according to a patient should be referred to a rheumatologist for further evaluation of possible AS.

However, early referral recommendations have recently been proposed (11), but prospective studies are needed to assess their performance among primary care physicians.

Choosing a clinical parameter for referral of AS patients is very favourable because it is not expensive. Chronic back pain, the leading symptom of AS, is very common in the general population. Therefore, using this parameter as referral criteria the number of patients to be seen by the rheumatologist to make the diagnosis in one patient will be too large. On contrary, using inflammatory back pain as referral parameter a diagnosis of AS can be made in about 1/7 patients seen by the rheumatologist (11). This recommendation, even

though more concise, does not substantially differ from the corresponding multinational one.

#### *Monitoring*

**Recommendation 4:** *For the assessment of disease activity BASDAI and physician's global assessment are recommended. CRP and ESR could be useful. STIR-MRI is accurate but not feasible in daily practice, and should be used only in selected cases.*

This is a grade D recommendation derived from level IV evidence. The agreement (agree and strongly agree) among experts was 91%.

Parameters assessing symptoms, metrology, laboratory, and imaging studies were reviewed. The only available



publications dealing with this feature are based on expert opinion such as the ASAS core set of variables to be used in clinical record keeping (12).

The most significant difference between such recommendation and the corresponding multi-national one is the inclusion of a smaller number of clinical parameters to be assessed. According to Italian panelists a limited number of assessments is needed in order to allow the recommendation to be feasibly applied in a clinical practice setting.

*Recommendation 5: For the assessment of disease severity the following parameters are recommended: BASFI, chest expansion, modified Schober test, occiput-to-wall distance, hip involvement, presence of extra-articular manifestations, serial x-rays of spine and pelvis.*

This is a grade D recommendation derived from level IV evidence. The agreement (agree and strongly agree) among experts was 92%.

Parameters assessing irreversible damage like metrology and imaging were reviewed. There is no published evidence accurately addressing this feature. Thus, the experts' opinion filled the gaps of evidence producing this recommendation.

This recommendation does not substantially differ from the corresponding multi-national one with the exception of phrasing differences.

*Recommendation 6: For the assessment of disease prognosis the following parameters are recommended: young age at onset, disease duration, hip arthritis, peripheral arthritis, BASDAI at onset, BASFI, rapid progression of radiological damage of spine and pelvis, poor efficacy of NSAIDs.*

This is a grade D recommendation derived from level IV evidence. The agreement (agree and strongly agree) among experts was 90%.

The optimal study to assess AS prognosis would be a prospective study of patients with early disease to whom prognosis would be assessed after a long-term follow-up. A prospective observational study assessing long-term prognosis at 10 years was reviewed (13). Recently, one study has reported data for 90 patients with early AS followed over a 2-year period (14).

When compared with the corresponding multi-national recommendation, this recommendation includes some additional parameters which do not substantially distinguish the two recommendations.

#### Treatment

*Recommendation 7: Intravenous pamidronate therapy could be considered in patients with NSAID-refractory disease. This is a grade C recommendation derived from level Ib evidence. The agreement (agree and strongly agree) among experts was 78%.*

In one controlled trial (15) intravenous pamidronate resulted to be efficacious in AS patients refractory to NSAIDs. However, the number of treated patients was low and treatment effect was modest (mean BASDAI reduction 2.2) and thus larger controlled trials confirming these results are needed.

This recommendation is substantially different from the corresponding multi-national one. In particular, Italian rheumatologists give to bisphosphonates a possible role in the treatment of active AS while in the multi-national recommendation these drug are considered to be useful only for the management of osteoporosis in AS.

*Recommendation 8: Local corticosteroid injections are recommended as first line treatment for peripheral enthesitis when only a few entheses are involved. In patients who respond inadequately to local corticosteroid injections and in patients with multiple peripheral enthesitis oral NSAIDs should be used. There is no evidence of efficacy of sulfasalazine and methotrexate for the treatment of peripheral enthesitis. The optimal treatment of costochondritis has not been established.*

This is a grade C recommendation derived from level Ib evidence. The agreement (agree and strongly agree) among experts was 88%.

Although only case reports addressing local corticosteroid injections of specific enthesial involvement were reported, the panelists considered that such treatment may be useful when only a few entheses are involved.

In controlled studies that assessed enthesitis as an outcome parameter,

NSAIDs/COX-II inhibitors resulted to be efficacious (16, 17) while traditional DMARDs (sulfasalazine, methotrexate) had contradictory results (18-20).

This recommendation, even though more detailed, does not substantially differ from the corresponding multi-national one.

*Recommendation 9: Conventional NSAIDs and selective COX-II inhibitors are equally effective for pain control. In patients with increased GI risk conventional NSAIDs plus PPI agents or selective COX-II inhibitors should be used. Long half life drugs could be preferred for their better efficacy profile.*

This is a grade B recommendation derived from level Ib evidence. The agreement (agree and strongly agree) among experts was 81%.

NSAIDs have been recommended by ASAS/EULAR as the first line drug to improve pain and stiffness (5).

The analysis of data from randomized controlled trials concerning the efficacy of NSAIDs or COX-II inhibitors in AS did not reveal consistent differences between the different traditional NSAIDs and between the NSAIDs and COX-II inhibitors (6). As regards the safety, a meta-analysis showed that etoricoxib had a better safety profile (major gastrointestinal events) compared to conventional NSAIDs (21). The efficacy and safety profiles were not consistently different between different doses of NSAIDs or COX-II inhibitors or between long and short half-time agents (6).

Therefore, the available data do not permit definitive conclusions concerning the choice of one agent over another in terms of efficacy. In patients with increased GI risk COX-II inhibitors showed a better safety profile. The panelists considered that long half-time agents could be preferred for their better efficacy profile.

The most significant difference with the corresponding multi-national one is that Italian rheumatologists between short and long half-life drugs prefer the latter for their better efficacy profile.

*Recommendation 10: The continuous treatment with NSAIDs/COX2 inhibitors may offer a sustained effect on function and pain, and a possible slowing of radiographic disease progression.*

*In patients with increased GI and/or CV risk such an approach should be used with caution.*

This is a grade B recommendation derived from level Ib evidence. The agreement (agree and strongly agree) among experts was 95%.

In AS patients NSAIDs are usually administered in intermittent regimens according to patient symptoms and aiming to fewer adverse events.

Only few studies supporting the effect of long-term continuous use on disease outcome have been published. Two controlled studies of 1-year continuous treatment with NSAIDs/COX-II inhibitors showed a significant improvement of function and pain (22, 23). Recently, a 2-year study has showed that a strategy of continuous use of NSAIDs/COX-II inhibitors reduces radiographic progression (24). This study addressed issues on safety of long-term treatment of NSAIDs/COX-II inhibitors, showing a mild increase, although the difference was not statistically significant, in GI toxicity together with similar cardiovascular toxicity of continuous compared to intermittent therapy. However, panelists preferred to put a warning concerning long-term use of NSAIDs/COX-II inhibitors in AS patients with increased GI and/or CV risk.

This recommendation does not substantially differ from the corresponding multi-national one.

**Recommendation 11:** *NSAIDs/COX-II inhibitors are effective on different (i.e., axial/articular/enthesal) clinical manifestations of disease even though spinal pain seems to better respond to this treatment.*

This is a grade A recommendation derived from level Ib evidence. The agreement (agree and strongly agree) among experts was 93%.

Studies reporting data of efficacy on the different AS clinical manifestations showed that, although NSAIDs/COX-II inhibitors have a clinically relevant symptomatic effect on all 3 main involvements (axial/articular/enthesal), spinal improvement appeared to be greater (16, 23).

This recommendation does not substantially differ from the corresponding multi-national one.

**Recommendation 12:** *Despite the lack of evidence that COX-II inhibitors induce clinical flare-ups of IBD manifestations, both NSAIDs and COX-II inhibitors should be used with caution in AS patients with IBD.*

This is a grade IIa recommendation derived from level C evidence. The agreement (agree and strongly agree) among experts was 89%.

No published studies have produced data on IBD flares occurring in AS patients treated with NSAIDs. In 2 prospective, randomized placebo-controlled trials of IBD patients, COX2 inhibitors were not associated with increased flares of IBD (25, 26).

This recommendation substantially differs from the corresponding multi-national one since Italian rheumatologists are more favourable in using COX-II inhibitors in AS patients with IBD.

## Discussion

An improvement of the prognosis of AS can be achieved not only by therapeutic advances (i.e., anti-TNF- $\alpha$  agents) but also by a better standardization of the management of the disease (7, 12, 27).

The 3E (Evidence, Expertise, Exchange) Initiative in Rheumatology is a multinational effort of rheumatologists with the aim to develop evidence-based recommendations addressing specific questions relevant to clinical practice. In contrast to previously proposed recommendations/guidelines developed by a limited panel of experts in the field of AS, the 3E initiative has involved a total of 509 rheumatologists from 10 countries (6). These are the first recommendations for the management of AS in clinical practice obtained combining a systematic literature review together with the opinion of a large number of experts and practicing rheumatologists. The objective of the Italian part of the 3E Initiative was to develop new recommendations designed to help Italian rheumatologists in everyday clinical practice management of AS patients. The 3E Italian recommendations have dealt directly with specific practical issues, and are thus designed to complement not conflict with ASAS/EULAR recommendations. The aim is to utilize

them in daily practice to further the standard of care in AS.

There are only few differences between the 3E Italian and the corresponding multinational recommendations. In particular, Italian rheumatologists consider that conventional radiography and computed tomography are less useful than MRI in making an early diagnosis of AS. The differences regarding AS treatment substantially consist of a more favourable approach in using bisphosphonates in active AS patients, long vs. short half-life NSAIDs, and COX-II inhibitors in AS patients with IBD.

These recommendations are based on evidence from the literature combined with expert opinion used to fill gaps in evidence. This approach is particularly useful when, such as in our case, the literature does not offer satisfactory evidence (category III and IV).

Most recommendations are grade C and D. This could depend on the high level of expertise and knowledge of literature in the field of AS of the international steering committee members. They could have selected questions that they consider difficult to answer and, consequently the following literature search has often resulted lacking.

It is noteworthy that the level of agreement between members was very high (mean 89%, range 78-95%). However, such result could be depended on the fact that the level of agreement was derived from the same experts who developed the recommendations. Further investigations are needed to evaluate the level of agreement among Italian rheumatologists who did not participate to the 3E initiative.

The target audience for these recommendations is the entire community that is interested in AS – clinicians, clinical and basic researchers, regulatory bodies, and patients. It is important to specify that these are recommendations and not guidelines aiming to do not restrict the autonomy of treating physicians.

In conclusion, the 3E Initiative has confirmed that important aspects of disease management, including early diagnosis, monitoring and treatment, are based on suboptimal evidence. These evidence-

and expert-based recommendations should facilitate and standardize the care of AS patients.

Future steps will include the dissemination and implementation of these recommendations in order to improve the management of AS.

### Acknowledgements

We acknowledge the project coordinator Maxime Dougados and the international research fellows Prodromos Sidiroopoulos, Gulen Hatemi, In-Ho Song, and Jerome Avouac for their crucial contribution.

We express our appreciation to Carlo Pasetto, Michela Ferri, and Marina Capasso from Abbott Italy for their support in every phase of the 3E initiative. We are grateful to the Italian rheumatologists who gave their knowledge and experience to participate in developing these recommendations:

Altomonte Lorenzo (Roma), Bagnato Gianfilippo (Messina), Bambara Lisa Maria (Verona), Bellisai Francesca (Siena), Bezzi Alessandra (Rimini), Bianchi Gerolamo (Genova), Bracci Massimo (Roma), Buticchi Gianni (Parma), Canesi Bianca (Milano), Cantatore Francesco Paolo (Foggia), Carrabba Mario (Milano), Cattaneo Roberto (Brescia), Ceralli Fabrizio (Roma), Di Matteo Luigi (Pescara), Fantini Flavio (Milano), Ferraccioli Gianfranco (Roma), Ferri Clodoveo (Modena), Filippini Davide (Milano), Giacomelli Roberto (L'Aquila), Lapadula Giovanni (Bari), Leardini Gianni (Venezia), Malavolta Nazzarena (Bologna), Marchesoni Antonio (Milano), Mathieu Alessandro (Cagliari), Meroni Pierluigi (Milano), Minisola Giovanni (Roma), Montecucco Carlomaurizio (Pavia), Muratore Maurizio (Lecce), Numo Raffaele (Bari), Palazzi Carlo (Chieti), Passiu Giuseppe (Monserato), Perpignano Giuseppe (Cagliari), Perricone Roberto (Roma), Riente Lucrezia (Pisa), Rossini Maurizio (Verona), Sacco Stefania (Udine), Scarpellini Magda (Magenta), Sinigaglia Luigi (Milano), Spadaro Antonio (Roma), Triolo Giovanni (Palermo), Trotta

Francesco (Ferrara), Valentini Gabriele (Napoli), Vinci Maria (Catania), Vitali Claudio (Piombino), Zaccari Giuseppe (Roma).

### References

1. SIEPER J, BRAUN J: Ankylosing spondylitis. *Lancet* 2007; 369: 1379-90.
2. SALAFFI F, DE ANGELIS R, GRASSI W: Prevalence of musculoskeletal conditions in a Italian population sample: results of a regional community-based study. I. The MAP-PING study. *Clin Exp Rheumatol* 2005; 23: 819-28.
3. BRANDT J, MARZO-HORTEGA H, EMERY P: Ankylosing spondylitis: new treatment modalities. *Best Pract Res Clin Rheumatol* 2006; 20: 559-70.
4. DAVIDOFF F, CASE K, FRIED PW: Evidence-Based Medicine: Why all the fuss? *Ann Intern Med* 1995; 122: 727.
5. ZOCHLING J, VAN DER HEIJDE D, BURGOS-VARGAS R *et al.*: ASAS/EULAR recommendations for the management of ankylosing spondylitis. *Ann Rheum Dis* 2006; 65: 442-52.
6. SIDIROPOULOS PI, HATEMI G, SONG IH *et al.*: 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. *Rheumatology* 2008; 47: 355-61.
7. BRAUN J, DAVIS J, DOUGADOS M *et al.*: First update of the international ASAS consensus statement for the use of anti-TNF agents in patients with ankylosing spondylitis. *Ann Rheum Dis* 2006; 65: 316-20.
8. SHEKELLE PG, WOOLF SH, ECCLES M *et al.*: Clinical guidelines: developing guidelines. *BMJ* 1999; 318: 593-6.
9. CALIN A, KAYE B, STERNBERG M *et al.*: The prevalence and nature of back pain in an industrial complex: a questionnaire and radiographic and HLA analysis. *Spine* 1980; 5: 201-5.
10. BOLLOW M, FISCHER T, REIBHAUER H *et al.*: Quantitative analyses of sacroiliac biopsies in spondyloarthropathies: T cells and macrophages predominate in early and active sacroiliitis - cellularity correlates with the degree of enhancement detected by magnetic resonance imaging. *Ann Rheum Dis* 2000; 59: 135-40.
11. SIEPER J, RUDWALEIT M: Early referral recommendations for ankylosing spondylitis (including pre-radiographic and radiographic forms) in primary care. *Ann Rheum Dis* 2005; 64: 659-63.
12. VAN DER HEIJDE D, BELLAMY N, CALIN A *et al.*: Preliminary core sets for endpoints in ankylosing spondylitis. Assessments in Ankylosing Spondylitis Working Group. *J Rheumatol* 1997; 24: 2225-9.
13. AMOR B, SANTOS RS, NAHAL R *et al.*: Predictive factors for the longterm outcome of spondyloarthropathies. *J Rheumatol* 1994; 21: 1883-7.
14. RUDWALEIT M, BARALIAKOS X, LISTING J *et al.*: The course of radiographic spinal lesions in patients with early ankylosing spondylitis over a 2-year follow-up period. *Ann Rheum Dis* 2005; 64 (Suppl. III): 335.
15. MAKSYMOWYCH WP, JHANGRI GS, FITZGERALD AA *et al.*: A six-month randomized, controlled, double-blind, dose-response comparison of intravenous pamidronate (60 mg versus 10 mg) in the treatment of nonsteroidal antiinflammatory drug-refractory ankylosing spondylitis. *Arthritis Rheum* 2002; 46: 766-73.
16. GOSSEC L, VAN DER HEIJDE D, MELIAN A *et al.*: Efficacy of cyclo-oxygenase-2 inhibition by etoricoxib and naproxen on the axial manifestations of ankylosing spondylitis in the presence of peripheral arthritis. *Ann Rheum Dis* 2005; 64: 1563-7.
17. SYDNES OA: Comparison of piroxicam with indomethacin in ankylosing spondylitis: a double-blind crossover trial. *Br J Clin Pract* 1981; 35: 40-4.
18. CLEGG DO, REDA DJ, WEISMAN MH *et al.*: Comparison of sulfasalazine and placebo in the treatment of ankylosing spondylitis. A Department of Veterans Affairs Cooperative Study. *Arthritis Rheum* 1996; 39: 2004-12.
19. DOUGADOS M, BOUMIER P, AMOR B: Sulfasalazine in ankylosing spondylitis: a double blind controlled study in 60 patients. *Br Med J (Clin Res Ed)* 1986; 293: 911-4.
20. ALTAN L, BINGOL U, KARAKOC Y *et al.*: Clinical investigation of methotrexate in the treatment of ankylosing spondylitis. *Scand J Rheumatol* 2001; 30: 255-9.
21. RAMEY DR, WATSON DJ, YU C *et al.*: The incidence of upper gastrointestinal adverse events in clinical trials of etoricoxib vs. non-selective NSAIDs: an updated combined analysis. *Curr Med Res Opin* 2005; 21: 715-22.
22. 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.
23. VAN DER HEIJDE D, BARAF HS, RAMOS-REMUS C *et al.*: Evaluation of the efficacy of etoricoxib in ankylosing spondylitis: results of a fifty-two-week, randomized, controlled study. *Arthritis Rheum* 2005; 52: 1205-15.
24. WANDERS A, VAN DER HEIJDE D, LANDEWE R *et al.*: Nonsteroidal antiinflammatory drugs reduce radiographic progression in patients with ankylosing spondylitis: a randomized clinical trial. *Arthritis Rheum* 2005; 52: 1756-65.
25. EL MIEDANY Y, YOUSSEF S, AHMED I *et al.*: The gastrointestinal safety and effect on disease activity of etoricoxib, a selective cox-2 inhibitor in inflammatory bowel diseases. *Am J Gastroenterol* 2006; 101: 311-7.
26. SANDBORN WJ, STENSON WF, BRYNSKOV J *et al.*: Safety of celecoxib in patients with ulcerative colitis in remission: a randomized, placebo-controlled, pilot study. *Clin Gastroenterol Hepatol* 2006; 4: 203-11.
27. ZOCHLING J, BRAUN J: Remission in ankylosing spondylitis. *Clin Exp Rheumatol* 2006; 24 (Suppl. 43): S88-92.