Concise report

Comparison of recommendations for the use of anti-tumour necrosis factor therapy in ankylosing spondylitis in 23 countries worldwide

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Abstract

Objective. To give an overview of the recommendations for the use of anti-TNF-α therapy in AS in 23 countries worldwide

Methods. The recommendations were collected, translated and a summary was checked by Assessment of SpondyloArthritis International Society (ASAS) members from the respective countries. The recommendations were compared with the ASAS recommendations (2006) on three aspects: patient selection for initiation of treatment (diagnosis, disease activity, previous treatment and contraindications), assessment of disease and assessment of response.

Results. The majority of the recommendations are similar to the ASAS recommendation with regard to patient selection, assessment of disease and treatment response. Additional objective assessments of disease activity are required in eight countries, leading to a more strict indication to start anti-TNF-α therapy.

Conclusion. Most national recommendations follow the international ASAS recommendations, suggesting that the latter are widely implemented. This might contribute to comparable access with anti-TNF-α treatment across countries. This article shows that general consensus exists about the use of anti-TNF-α therapy in AS across the world, although some countries require additional objective signs of inflammation and/or more pre-treatment, which limits access.

Key words: Ankylosing spondylitis, Anti-TNF therapy, ASAS, Recommendations.

Introduction

AS is a chronic, progressive inflammatory, rheumatic disease that generally starts in the second or third decade of life [1-3]. The most characteristic features of AS are inflammatory back pain (IBP) due to sacroiliitis and spondylitis, and the formation of syndesmophytes leading to ankylosis of the spine [1, 4]. In addition, AS is frequently associated with enthesitis, acute anterior uveitis, inflammatory bowel disease (IBD), psoriasis, peripheral (oligo)arthritis predominantly of the lower extremities, and cardiovascular and pulmonary abnormalities [1, 5, 6].

For decades, AS was mainly treated with NSAIDs, physiotherapy and to a lesser extent with DMARDs [3, 4]. And this is still the basis for treatment according to the Assessment of SpondyloArthritis International Society (ASAS)/European League Against Rheumatism (EULAR) recommendations for the management of AS [1]. Even though NSAIDs often give quick symptomatic relief [7], the effects on the long-term outcome are limited and there are reservations with safety in relation to long-term use [2, 7, 8]. Moreover, DMARDs are largely ineffective in axial AS and have limited efficacy on peripheral arthritis in AS [3, 7, 8]. The treatment armamentarium is broadened since the discovery of anti-TNF-α agents as an effective therapy. The anti-TNF-α agents infliximab [8, 9], etanercept [10, 11], adalimumab [12] and golimumab [13] have shown to be effective in the treatment of AS in short-term as well as intermediate to long-term evaluations [2, 14].
Anti-TNF-\(\alpha\) agents are very effective in the treatment of AS; nevertheless, they are associated with high costs and risks of side effects and might not be suitable for all patients. Therefore, it is important that recommendations are available to support the appropriate use of anti-TNF-\(\alpha\) agents within individual countries.

In 2003, the ASAS proposed recommendations for the use of anti-TNF-\(\alpha\) treatment in AS for rheumatologists and other experts in the management of AS, as well as payers [3, 14]. There was an update of the recommendations in 2006 [15]. Many countries developed national guidelines, whether or not based on the ASAS recommendations. The aim of the present report is to give an overview of the recommendations for the use of anti-TNF-\(\alpha\) therapy in AS in 23 countries worldwide, with a focus on the similarities and differences compared with the ASAS recommendations. In concordance with the advice of EULAR, we use the general term of recommendations throughout the manuscript, although some countries publish their recommendations as guidelines.

**Methods**

The recommendations of the following countries (presented alphabetically grouped by continent) were presented and translated: Australia, Hong Kong, Korea, Canada, Colombia, Mexico, Belgium, Czech Republic, Finland, France, Germany, Greece, Hungary, Italy, the Netherlands, Norway, Poland, Portugal, Slovakia, Spain, Sweden, Switzerland and the UK. A summary of the translated recommendations was sent to ASAS members from the specific countries included in this overview. They were asked to check the correctness of the summary. The recommendations were compared with the 2006 version of the ASAS recommendations [15] as a standard to be able to easily compare discrepancies.

**ASAS recommendations**

The ASAS recommendations are divided into the following three parts: patient selection for initiation of treatment including diagnosis, disease activity, previous treatment and contraindications; assessment of disease; and assessment of response (Table 1).

**Results**

Table 2 gives an overview of the recommendations of the 23 countries (references of the recommendations in appendix 1, available as supplementary data at Rheumatology Online). They are presented alphabetically grouped by continent. The recommendations of Canada, Mexico, France, Italy, Portugal, Spain and Sweden (n = 7) (Table 2) were developed by the professional rheumatologic community as treatment recommendations. In Australia, Hong Kong, Korea, Colombia, Belgium, Finland, Greece, Norway, Poland and Switzerland (n = 10) (Table 2), the recommendations were developed for reimbursement purposes. The recommendations of the Czech Republic, Germany, Hungary, the Netherlands, the UK and Slovakia (n = 6) (Table 2) were developed for both purposes.

**Diagnosis**

According to the ASAS recommendations, patients should normally fulfil the modified New York criteria for AS (Table 1) [15]. Most recommendations (n = 16) follow the ASAS recommendations and qualify patients for treatment if they fulfil the modified New York criteria [16]. In five recommendations, MRI and/or CT, instead of X-rays, are approved to reveal sacroiliitis [16]. In Hong Kong and Colombia, a diagnosis of SpA according to the Amor or ESSG criteria is sufficient for the diagnostic part for initiation of anti-TNF-\(\alpha\) therapy (Table 2).

**Disease activity**

The ASAS recommendations define active AS as having active disease for \(>4\) weeks based on a BASDAI score \(>4\) (scale 0–10) and an expert opinion of active AS (Table 1) [15]. According to all recommendations, except the Finnish recommendation, disease activity should be measured with the BASDAI. In 19 recommendations, the disease activity is qualified as high when the BASDAI is \(>4\). In two other recommendations (Hong Kong and Norway), the BASDAI is also used to measure disease activity, but no qualification of active disease is given. An expert opinion to determine disease activity is required in 13 countries (Table 2).

In eight recommendations, additional assessments of disease activity are required, such as laboratory parameters for inflammation (CRP and/or ESR), (spinal) pain [visual analogue scale (VAS)] (n = 4), patient and physician global health (n = 2 and n = 1, respectively), and/or inflammation on MRI (n = 1), or limitation in spinal mobility (n = 1) (Table 2). In particular, the request for additional elevated acute-phase reactants or inflammation on MRI increases the threshold to start a TNF-blocker substantially. In one instance (Hong Kong), a large increase is required (ESR \(>50\) mm/h or CRP \(>50\) mg/l). Moreover, the requirement for limitation in spinal mobility is remarkable, as this can be caused by the severity of the disease without active inflammation.

**Failure of standard treatment**

ASAS offers a description of conventional treatment failure specified for the predominant localization of the disease (axial, peripheral arthritis and enthesitis) (Table 1). Most recommendations follow the ASAS recommendations and give specified descriptions of treatment failure. In general, the recommendations describe failure of conventional treatment for predominantly axial localization as failure of two or more NSAIDs administered for a period of 1–3 months (n = 18). In Hong Kong, Canada and France, patients should fail at least three NSAIDs. Conventional treatment failure for a predominantly peripheral localization is in 18 recommendations described as a failure of one or two DMARDs (in most recommendations specified as MTX and/or SSZ) administered for a period of 2–3 months, and as a failure of IA injections of CSs.
**Table 1** International ASAS consensus statement for the use of anti-TNF-α agents in patients with AS

| Patient selection Diagnosis | Patients normally fulfilling modified New York criteria for definitive AS
| Diagnosed | Modified New York criteria 1984:
| | Radiological criterion: sacroiliitis, Grade > II bilaterally or Grades III–IV unilaterally
| | Clinical criteria (two of the following three): back pain and stiffness for >3 months, which improves with exercise but is not relieved by rest; limitation of motion of the lumbar spine in both the sagittal and frontal planes; limitation of chest expansion relative to normal values correlated for age and sex
| Active disease | Active disease for >4 weeks
| | BASDAI > 4 (0–10) and an expert opinion
| Treatment failure | All patients should have had adequate therapeutic trials of at least two NSAIDs. An adequate therapeutic trial is defined as:
| | Treatment for at least 3 months at maximum recommended or tolerated anti-inflammatory dose unless contraindicated
| | Treatment for <3 months where treatment was withdrawn because of intolerance, toxicity or contraindications
| Contra-indications | Women who are pregnant or breastfeeding; effective contraception must be practiced
| | Active infection
| | Patients at high risk of infection including:
| | Chronic leg ulcer
| | Previous tuberculosis (note: please follow local recommendations for prevention or treatment)
| | Septic arthritis of a native joint within the past 12 months
| | Sepsis of a prosthetic joint within the past 12 months, or indefinitely if the joint remains in situ
| | Persistent or recurrent chest infections
| | Indwelling urinary catheter
| | History of lupus or multiple sclerosis
| | Malignancy or pre-malignancy states excluding:
| | Basal cell carcinoma
| | Malignancies diagnosed and treated >10 years previously (where the probability of total cure is very high)
| Assessment of disease | Physical function (BASFI or Dougados functional index)
| ASAS core set for daily practice | Pain (VAS, past week, spine at night, from AS andVAS, past week, spine, from AS)
| | Spinal mobility (chest expansion and modified Schober and occiput to wall distance and lateral lumbar flexion)
| | Patient’s global assessment (VAS, past week)
| | Stiffness (duration of morning stiffness, spine, past week)
| | Peripheral joints and entheses [number of swollen joints (44 joints count), enthesitis score such as developed in Maastricht, Berlin or San Francisco]
| | Acute-phase reactants (ESR or CRP)
| | Fatigue (VAS)
| BASDAI | VAS overall level of fatigue/tiredness, past week
| | VAS overall level of AS neck, back or hip pain, past week
| | VAS overall level of pain/swelling in joints other than neck, back or hips, past week
| | VAS overall discomfort from any areas tender to touch or pressure, past week
| | VAS overall level of morning stiffness from time of awakening, past week
| | Duration and intensity (VAS) of morning stiffness from time of awakening (up to 120 min)
| Assessment of response | BASDAI: 50% relative change or absolute change of 20 mm (on a scale between 0 and 100) and expert opinion in favour of continuation
| Responder criteria | Between 6 and 12 weeks
| Time of evaluation | 8The expert is a physician, usually a rheumatologist, with expertise in IBP and the use of biological agents. Expert should be locally defined. 9The expert should consider clinical features (history and examination), serum acute-phase reactant levels and/or imaging results, such as radiographs demonstrating rapid progression or MRI indicating ongoing inflammation. 2SSZ: treatment for at least 4 months at standard target dose or maximally tolerated dose unless contraindicated or not tolerated. Treatment for <4 months, where treatment was withdrawn because of intolerance or toxicity or contraindicated.
<table>
<thead>
<tr>
<th>Country</th>
<th>Diagnosis</th>
<th>Disease activity</th>
<th>Treatment failure</th>
<th>Assessment of disease</th>
<th>Assessment of response</th>
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<tbody>
<tr>
<td>Asia Pacific Region</td>
<td>Australia&lt;sup&gt;a&lt;/sup&gt; [R1] Sacroiliitis (X-ray) Grade II bi- or Grade III unilateral</td>
<td>BASDAI ≥ 4 and abnormal lab tests (ESR &gt; 25, CRP &gt; 10)</td>
<td>In the preceding 3 months: two different NSAIDs and a specified exercise programme (both stretching and daily aerobic exercise)</td>
<td>At least two out of three: LBP and stiffness ≥ 3 months relieved by exercise but not by rest; ↓ lumbar flexion sagittal and frontal planes as a score of at least 1 on relevant measures in BASMI; ↓ chest expansion</td>
<td>↓ BASDAI ≥ 2 points and normalized lab tests (or 20% ↑ on baseline lab tests) 12 weeks</td>
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<td></td>
<td>Korea&lt;sup&gt;a&lt;/sup&gt; [R3] According to ASAS</td>
<td>BASDAI ≥ 4</td>
<td>Two DMARDS or NSAIDS, 3 months</td>
<td>According to ASAS</td>
<td>According to ASAS 12 weeks</td>
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<td></td>
<td>Colombia&lt;sup&gt;a&lt;/sup&gt; [R5] According to ASAS, or Amor or ESSG</td>
<td>According to ASAS, duration not specified</td>
<td>According to ASAS and not measuring infiltration intra-steroids in peripheral arthritis and ≥ 2 CSs injections in enthesitis</td>
<td>According to ASAS and not measuring fatigue and stiffness and extra chest radiography</td>
<td>According to ASAS and assessment of safety</td>
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<td></td>
<td>Mexico&lt;sup&gt;b&lt;/sup&gt; [R6] According to ASAS</td>
<td>According to ASAS</td>
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<tr>
<td>Europe</td>
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<tr>
<td>Belgium</td>
<td>Modified NY criteria and expert opinion</td>
<td>BASDAI &gt; 4 and elevated CRP</td>
<td>Insufficient response on at least ≥2 NSAIDs, optimum dosage ≥3 months or contraindication for NSAIDs</td>
<td>Not mentioned</td>
<td>↓ BASDAI ≥50% or 2 points ENT and ADA &lt; 14 weeks IFX &lt; 12 weeks.</td>
</tr>
<tr>
<td>Czech Rep.</td>
<td>According to ASAS, or MRI instead of X-ray</td>
<td>BASDAI &gt; 4 and CRP ≥10 at two consecutive FU visits separated by ≥4 weeks</td>
<td>According to ASAS</td>
<td>According to ASAS</td>
<td>According to ASAS</td>
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<tr>
<td>Finland</td>
<td>Not mentioned</td>
<td>Active disease not specified</td>
<td>Two NSAIDs and MTX and SSZ 6-12 months and intolerance/lack of efficacy DMARDs</td>
<td>Not mentioned</td>
<td>Expert opinion</td>
</tr>
<tr>
<td>France</td>
<td>According to ASAS, or MRI/CT instead of X-ray or cervical syndesmophytes without any sacroiliac structure lesion</td>
<td>According to ASAS and peripheral: TJC and SJC (≥3 of 76-78 joints)</td>
<td>According to ASAS and ≥3 NSAIDs instead of two NSAIDs and enthesitis not specified</td>
<td>According to ASAS</td>
<td>Axial: ↓ BASDAI &gt; 2 points Peripheral: &gt;30% decrease TJC and SJC FU varies with drug and route of administration</td>
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<tr>
<td>Germany</td>
<td>Secured diagnosis of AS</td>
<td>According to ASAS and disease symptomatic ≥6 months</td>
<td>According to ASAS and enthesitis not specified</td>
<td>Clinical rheumatologic findings using validated scores</td>
<td>If there is no response (not specified) after 3 months, no continuation treatment</td>
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<tr>
<td>Greece</td>
<td>Clinical and laboratory and radiological findings</td>
<td>According to ASAS</td>
<td>According to ASAS and MTX &gt; 2 months in peripheral arthritis and ≥2 topical infusions of Cs in enthesitis</td>
<td>According to ASAS</td>
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<tr>
<td>Hungary</td>
<td>According to ASAS</td>
<td>According to ASAS</td>
<td>According to ASAS and ≥2 IA steroid injections, SSZ or other DMARD ≥4 months in peripheral arthritis</td>
<td>BASDAI</td>
<td>According to ASAS</td>
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<td>Italy</td>
<td>According to ASAS</td>
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<tr>
<td>Netherlands</td>
<td>Conventional diagnosis Prescription from department with ≥2 specialists (rheumatologists) Approval based on disease history, previous treatment and current status</td>
<td>ESR/CRP, clinical status and imaging, Peripheral arthritis: joint counts and disease activity indices</td>
<td>Axial: 2 NSAIDs and peripheral arthritis: DMARD if relevant: IA steroid injections</td>
<td>According to ASAS</td>
<td>According to ASAS</td>
</tr>
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<td>Norway</td>
<td>According to ASAS</td>
<td>According to ASAS</td>
<td>Axial: BASDAI and BASFI, Both axial and peripheral: pain, fatigue and globals on VAS (not specified)</td>
<td>According to ASAS</td>
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<tr>
<td>Poland[^b] [R17]</td>
<td>According to ASAS</td>
<td>Two of three following parameters: BASDAI &gt; 4, pain VAS &gt; 4, CRP &gt; 10 mg/dl in 12 weeks interval on stable treatment One or more parameters limited in 1-month interval: chest expansion, occiput-to-wall distance, Schober test</td>
<td>According to ASAS and &gt;2 IA glucocorticosteroids injections in peripheral arthritis</td>
<td>BASFI and BASMI and BASDAI and spinal pain (VAS) and CRP/ESR</td>
<td>↓ BASDAI &lt; 4 No time frame</td>
</tr>
<tr>
<td>Portugal[^b] [R18]</td>
<td>According to ASAS, or MRI/CT instead of X-ray</td>
<td>According to ASAS and in case of BASDAI &lt; 4: expert opinion</td>
<td>According to ASAS and 4 weeks instead of 3 months</td>
<td>Physical function (BASFI) and pain and patient’s global assessment and stiffness and BASDAI</td>
<td>↓ BASDAI &gt; 50% or ≥ ASAS 20% improvement 12 weeks</td>
</tr>
<tr>
<td>Slovakia[^a,b] [R19]</td>
<td>According to ASAS, or MRI instead of X-ray</td>
<td>BASDAI &gt; 4 and CRP &gt; 10 at two consecutive FU visits separated by ≥ 4 weeks</td>
<td>According to ASAS</td>
<td>According to ASAS</td>
<td>According to ASAS 12 weeks</td>
</tr>
<tr>
<td>Spain[^b] [R20]</td>
<td>Expert opinion</td>
<td>BASDAI &gt; 4 and one out of three: spinal pain or patient global assessment (VAS &gt;4) or ↑ ESR/CRP, for &gt; 3 months</td>
<td>According to ASAS and any DMARD (pref. SSZ) instead of only SSZ</td>
<td>Pain and patient physician global assessment and physical function and structural damage</td>
<td>↓ BASDAI &gt; 50% and 50% or 2 points (VAS) ↓ in patient’s general assessment, and/or ESR/CRP 3–4 months</td>
</tr>
<tr>
<td>Sweden[^b] [R21]</td>
<td>According to ASAS</td>
<td>According to ASAS Expert opinion</td>
<td>According to ASAS</td>
<td>According to ASAS</td>
<td>According to ASAS Expert opinion, IFX after 6 weeks, ADA after 12 weeks, ETN unlimited</td>
</tr>
<tr>
<td>Switzerland[^a] [R22]</td>
<td>Expert opinion</td>
<td>Expert opinion and mandatory consent of the consultant physician of the health insurance company</td>
<td>Not mentioned</td>
<td>Not mentioned</td>
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<tr>
<td>UK[^a,b] [R23]</td>
<td>According to ASAS</td>
<td>BASDAI &gt; 4 and spinal pain (VAS &gt;4) on two occasions &gt;4 weeks apart and no change in treatment</td>
<td>&gt;2 NSAIDs for 4 weeks</td>
<td>Not mentioned</td>
<td>According to ASAS and ↓ spinal pain (VAS &gt; 2 cm) 6–12 weeks</td>
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[^a]Reimbursement recommendation;[^b]professional recommendation. R1–R23: references of the recommendations are available as supplementary data available at Rheumatology Online; SJC: swollen joint count; TJC: tender joint count; IFX: infliximab; ADA: adalimumab; ETN: etanercept; FU: follow-up; GH: gene VAS, visual analogue scale; SJC, Swollen joint count; TJC, Tender joint count; ESR, Erythrocyte sedimentation rate; CRP, C-reactive protein; MTX, methotrexate; SSZ, sulfasalazine; IFX, infliximab; ADA, adalimumab; ETN, etanercept; NSAID, non-steroidal anti-inflammatory drugs; DMARD, disease modifying anti-rheumatic drugs; MRI, magnetic imaging resonance; CT, computed tomography; FU, follow-up; GH, general health; LBP, low back pain.
(n = 16). Conventional treatment failure of CS injections for enthesitis is described in 12 recommendations (Table 2).

Contraindications
To minimize treatment risks, ASAS has specified a list of contraindications (Table 1) basically similar to contraindications of the treatment of anti-TNF-α therapy for other indications [15]. Almost all recommendations (n = 17) list active infections, especially tuberculosis (TB), as contraindications. Several recommendations mention some types of malignancy or pre-malignancy (n = 10), a history of lupus (n = 8), multiple sclerosis or other demyelinating diseases (n = 11) and pregnancy/breastfeeding (n = 9) as contraindications, in accordance with the ASAS recommendations. A frequently mentioned contraindication (n = 11) not referred to in the ASAS recommendations [15] is heart failure Stages 3–4 as defined by the New York Heart Association (NYHA) [17].

Remarkably, the recommendations of the Czech Republic and Slovakia report that an advanced or terminal radiographic stage of the disease is a contraindication for applying anti-TNF-α therapy. Four recommendations do not mention contraindications at all.

Monitoring and withdrawal
ASAS recommends using the ASAS core set for daily practice [18] and the BASDAI to assess the activity of the disease (Table 1) [15]. Most countries (n = 19) recommend the ASAS core set for daily practice as well, or at least a part of the ASAS core set. However, four countries do not specify how to assess the disease (Table 2).

An assessment of the treatment response should be conducted 6–12 weeks after the start of the treatment, according to ASAS (Table 1) [15]. In 16 recommendations, the same time frame is advised. However, in seven recommendations the response is assessed after >12 weeks (range 14–16 weeks).

At this assessment point, a decision should be made about either continuation or discontinuation of anti-TNF-α therapy. ASAS advises considering discontinuation in patients not showing a 50% relative or absolute change of 2 cm (scale 0–10 cm) in the BASDAI score [15]. Eighteen recommendations use these criteria to determine a good treatment response. In some recommendations other criteria to assess response to treatment are obligatory, such as normalized or improved lab tests (n = 3) and improvement in pain (n = 2) or BASDAI <4 (n = 1). Furthermore, ASAS advises a positive opinion by the expert to continue treatment. This criterion is used in 14 recommendations as well.

Discussion and conclusion
This report provides an overview of the recommendations developed in 23 countries across the world. ASAS developed recommendations for the management of anti-TNF-α therapy in patients with AS [3, 15]. As internationally developed recommendations, the ASAS recommendations might contribute to comparable access with anti-TNF-α treatment across countries [19].

Indeed, this aim is (largely) reached, since the recommendations in AS are quite similar worldwide, in contrast to the recommendations in RA, which vary greatly between countries in Europe [19]. This can be explained by the lack of European guidance for initiation of anti-TNF-α therapy in RA [19], unlike the situation in AS [15]. Another explanation might be the considerably varying goals of RA treatment with anti-TNF-α agents [19]. Other possible explanations for the differences in recommendations across countries that apply to both RA and AS are variations regarding different methods for funding health-care provision and the level of recognition of recommendations [19].

Despite the similarities between the recommendations in AS across countries, differences exist. These differences are mostly based on the fact that some countries use objective assessment, such as acute-phase reactants, to measure disease activity for initiation and to monitor treatment response. This puts a major limitation on access to TNF-α blockers for patients in these countries, as only about half of the patients with active disease have elevated acute-phase reactants [20]. Although patients with elevated acute-phase reactants have a higher likelihood to show response, this difference is too small to withhold patients with a normal acute-phase reactant treatment with TNF-α blockers. Other differences exist in the required pre-treatment for NSAIDs (more and/or longer) and DMARDs (also required in axial disease and not only SSZ in peripheral disease). Moreover, several countries evaluate the efficacy of treatment after >12 weeks.

In conclusion, it can be said that despite some differences, there is general consensus about the recommendations to use anti-TNF-α therapy in AS across the world, except for the stricter requirement of objective signs of inflammation in some countries. The observation that most national recommendations follow the international ASAS recommendations seems to indicate that the latter are widely accepted and implemented. The information acquired by this comparison will also been taken into account in the next update of the ASAS recommendations.

<table>
<thead>
<tr>
<th>Rheumatology key messages</th>
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<tbody>
<tr>
<td>• Recommendations for use of anti-TNF-α therapy in patients with AS are similar across the world.</td>
</tr>
<tr>
<td>• The ASAS recommendations might have contributed to similarities between anti-TNF-α therapy recommendations across the world.</td>
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</table>

Acknowledgements
the correctness of the (translated) summaries of the national recommendations.

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Supplementary data

Supplementary data are available at Rheumatology Online.

References


