2016 update of the ASAS-EULAR management recommendations for axial Spondyloarthritis

Désirée van der Heijde, Sofia Ramiro, Robert Landewé, Xenofon Baraliakos, Filip Van den Bosch, Alexandre Sepriano, Andrea Regel, Adrian Ciurea, Hanne Dagfinrud, Maxime Dougados, Floris van Gaalen, Pál Géher, Irene van der Horst-Bruinsma, Robert D. Inman, Merryn Jongkees, Uta Kiltz, Tore K. Kvien, Pedro Machado, Helena Marzo-Ortega, Anna Molto, Victoria Navarro-Compàn, Salih Ozgocmen, Fernando M. Pimentel-Santos, John Reveille, Martin Rudwaleit, Jochen Sieper, Percival Sampaio-Barros, Dieter Wiek, Jürgen Braun

Désirée van der Heijde, Leiden University Medical Center, Leiden, the Netherlands, mail@dvanderheijde.nl

Sofia Ramiro, Leiden University Medical Center, Leiden, the Netherlands, sofiaramiro@gmail.com

Robert Landewé, Amsterdam Rheumatology and Immunology Center, Amsterdam and Zuyderland Medical Center, Heerlen, the Netherlands, landewe@rlandewe.nl

Xenofon Baraliakos, Rheumazentrum Ruhrgebiet Herne, Ruhr-University Bochum, Germany, baraliakos@me.com

Filip Van den Bosch, Ghent University and Ghent University Hospital, department of Rheumatology, Ghent, Belgium, filip.vandenbosch@ugent.be

Alexandre Sepriano, Leiden University Medical Center, Leiden, the Netherlands; and NOVA Medical School, Universidade Nova de Lisboa, Lisboa, Portugal. alexsepriano@gmail.com

Andrea Regel, Rheumazentrum Ruhrgebiet, Herne, Ruhr-University Bochum, Germany, andrea-regel@web.de

Adrian Ciurea, Department of Rheumatology, University Hospital Zurich, Zurich Switzerland, Adrian.Ciurea@usz.ch

Hanne Dagfinrud, Diakonhjemmet Hospital, Oslo, Norway, h.s.dagfinrud@medisin.uio.no

Maxime Dougados, Paris Descartes University, Hôpital Cochin. Assistance Publique - Hôpitaux de Paris and INSERM (U1153), PRES Sorbonne Paris-Cité, PARIS, France, maxime.dougados@aphp.fr

Floris van Gaalen, Leiden University Medical Center, Leiden, the Netherlands, f.a.van_gaalen@lumc.nl

Pál Géher, Semmelweis University, Budapest, Hungary, geherpal@gmail.com

Irene van der Horst-Bruinsma, VU University Medical Center, Amsterdam, The Netherlands, ie.vanderhorst@vumc.nl

Robert D. Inman, University of Toronto, Toronto, Canada, robert.inman@uhn.ca

Merryn Jongkees, patient research partner, info@seaynmedical.nl

Uta Kiltz, Rheumazentrum Ruhrgebiet, Herne, Germany, Uta.Kiltz@elisabethgruppe.de

Tore K Kvien, Dept of Rheumatology, Diakonhjemmet Hospital, Oslo, Norway, t.k.kvien@medisin.uio.no

Pedro Machado, Centre for Rheumatology & MRC Centre for Neuromuscular Diseases, University College London, London, UK, pedrommcmachado@gmail.com

Helena Marzo-Ortega, NIHR Leeds Musculoskeletal Biomedical Research Unit, Leeds Teaching Hospitals Trust and Leeds Institute of Rheumatic and Musculoskeletal Disease, University of Leeds. Leeds, UK, H.Marzo-Ortega@leeds.ac.uk

Anna Molto, Paris Descartes University, Cochin Hospital, AP-HP, and INSERM (U1153), PRES Sorbonne Paris-Cité, Paris, France, anna.molto@aphp.fr

Victoria Navarro-Compàn, University Hospital La Paz, IdiPaz, Madrid, Spain, mvictoria.navarroc@gmail.com

Salih Ozgocmen, Division of Rheumatology, Department of Physical Medicine and Rehabilitation, Erciyes University, Faculty of Medicine, Kayseri, Turkey, sozgocmen@hotmail.com

Fernando M. Pimentel-Santos, NOVA Medical School, NOVA University of Lisbon, Lisboa, Portugal, pimentel.santos@gmail.com

John Reveille, The University of Texas-Health McGovern Medical School, Dallas, United States, John.D.Reveille@uth.tmc.edu

Martin Rudwaleit, Klinikum Bielefeld, Bielefeld, Germany, Gent University, Belgium, and Charité University Medicine, Berlin, Germany, martin.rudwaleit@charite.de

Joachim Sieper, Rheumatology, Campus Benjamin Franklin, Charité, Berlin, Germany, Joachim.Sieper@charite.de

Percival Sampaio-Barros, Faculdade de Medicina da Universidade de São Paulo, São Paulo, Brazil, pdsampaiobarros@uol.com.br

Dieter Wiek, EULAR PARE Patient Research Partner and Chair of EULAR PARE, dieter_wiek@web.de

Jürgen Braun, Rheumazentrum Ruhrgebiet and Ruhr University Bochum, Herne, Germany, juergen.braun@elisabethgruppe.de

Désirée van der Heijde, received consulting fees from AbbVie, Amgen, Astellas, AstraZeneca, BMS, Boeringer Ingelheim, Celgene, Daiichi, Eli-Lilly, Galapagos, Gilead, Janssen, Merck, Novartis, Pfizer, Regeneron, Roche, Sanofi, UCB and is Director of Imaging Rheumatology bv.

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Abstract

Aim: To update and integrate the recommendations for ankylosing spondylitis and the recommendations for the use of TNF-inhibitors (TNFi) in axial SpA (axSpA) into one set applicable to the full spectrum of patients with axSpA.

Methods: Following the latest version of the EULAR Standardised Operating Procedures two systematic literature reviews first collected the evidence regarding all treatment options (pharmacological and non-pharmacological) which were published since 2009. After a discussion of the results in the steering group and presentation to the task force overarching principles and recommendations were formulated, and consensus was obtained by informal voting.

Results: A total of 5 overarching principles and 13 recommendations were agreed on. The first 3 recommendations deal with personalised medicine including treatment target and monitoring. Recommendation 4 covers non-pharmacological management. Recommendation 5 describes the central role of non-steroidal anti-inflammatory drugs (NSAIDs) as first choice drug treatment. Recommendations 6 to 8 define the rather modest role of analgesics, and disprove glucocorticoids and conventional synthetic DMARDs for axSpA patents with predominant axial involvement. Recommendation 9 refers to biological DMARDs (bDMARDs) including TNF- and IL17-inhibitors (TNFi, IL17i) for patients with high disease activity despite the use (or intolerance/contraindication) of at least 2NSAIDs. In addition, they should either have an elevated CRP and/or definite inflammation on MRI and/or radiographic evidence of sacroiliitis. Current practice is to start with a TNFi. Switching to another TNFi or an IL-17i is recommended in case TNFi fails (recommendation 10). Tapering, but not stopping a bDMARD, can be considered in patients in sustained remission (recommendation 11). The final two recommendations (12,13) deal with surgery and spinal fractures.

Conclusion: The 2016 ASAS-EULAR recommendations provide up-to-date guidance on the management of patients with axSpA.

Introduction

Axial Spondyloarthritis (axSpA) is an inflammatory rheumatic disease with a diverse clinical presentation.[1] Chronic back pain is the leading symptom of the disease and often inflammatory in nature with pronounced stiffness and improvment of pain and stiffness with exercise. Other musculoskeletal manifestations of axSpA are arthritis, enthesitis and dactylitis. Extra-articular manifestations such as anterior uveitis, psoriasis and inflammatory bowel disease (in order of decreasing prevalence) are also characteristic for axSpA[2]. Historically, end-stage patients were recognised by a characteristic stooped posture and by the presence of syndesmophytes on radiographs of the spine. Later, radiographic sacroiliitis became a crucial finding in the diagnosis and classification of patients. The modified New York criteria for ankylosing spondylitis (AS) were most frequently used in studies and drug trials.[3] Only recently it has been properly acknowledged that radiographic sacroiliitis is a rather late finding in the disease course of many patients, that magnetic resonance imaging (MRI) may show signs of inflammation much earlier than radiographs show structural damage, and that patients can also be diagnosed based on a typical clinical pattern, even in the presence of normal imaging tests.[1,4] The term axSpA comprises the whole spectrum of patients with radiographic sacroiliitis (AS or radiographic axSpA) and without radiographic sacroiliitis (non-radiographic axSpA).[4]

There is still some debate as to whether radiographic and non-radiographic axSpA should be considered as two different entities or as a continuous disease spectrum. The currently prevailing opinion is that axSpA encompasses one disease spectrum in which single patients with non-radiographic axSpA may develop radiographic changes over time.[5] However, not all patients with non-radiographic axSpA will ultimately develop radiographic sacroiliitis. Similarly, not all patients with radiographic sacroiliitis will ultimately develop syndesmophytes. In fact, radiographic sacroiliitis artificially divides the spectrum of axSpA in two groups, and it is unlikely that the sole presence of radiographic sacroiliitis is relevant for the outcome of the disease. In addition, recent studies and trials have cast doubt on the reliability of establishing radiographic abnormalities.[6-10] Taken together, there is ample argument to use only the term axSpA in clinical practice.[11] Especially in the context of studies it may be of value to add certain characteristics to the profile of patients, such as the presence of radiographic sacroiliitis, the presence of inflammation on MRI, the presence of arthritis, of extra-articular manifestations, to describe in detail the type of patients included.[5]

Apart from historical reasons, drug development has played a major role in distinguishing patients based on the presence of radiographic sacroiliitis: TNF-inhibitor (TNFi) therapy was historically approved for patients with AS, and companies sought the additional regulatory approval for patients without radiographic sacroiliitis.[12-17] The newest draft guidance document of the European Medicines Agency now proposes to study patients with axSpA as one entity, which testifies of the progress in the field of axSpA.[18]

Historically, the Assessment of SpondyloArthritis international Society (ASAS) has drafted two sets of treatment recommendations, dating back to the time when TNFi were the only class of biological Disease Modifying Anti Rheumatic Drugs (bDMARDs) and the concept of axSpA was not yet well established. However, it

should be noted that there is no formal proof that TNF I are in fact disease modifying in axSpA. The first set included the ASAS recommendations for the use of TNFi therapy in patients with AS published first in 2003 and updated in 2006 and 2010.[19-21] In contrast to existing recommendations for the use of bDMARDs in rheumatoid arthritis (RA) and psoriatic arthritis (PsA), the ASAS recommendations on the use of TNFi in AS include specific definitions for the level of disease activity required before a TNFi can be installed.[22,23] The second set of recommendations that ASAS has drafted in collaboration with the European League Against Rheumatism (EULAR) included recommendations for the management of AS published first in 2006 and updated in 2010.[24,25] In line with a better delineation and acceptance of axSpA, in follow up of the advent and approval of another class of bDMARDs (IL17-pathway inhibitors, IL17i), and after the publication of studies with patients covering the entire spectrum of axSpA, it was felt timely to integrate all different aspects of management into one set of recommendations and update the recommendations accordingly.[26-28] However, we have to acknowledge that the term bDMARDs is not completely correct as the disease-modifying aspect has not yet been proven in axial SpA.

This document presents the 2016 ASAS/EULAR management recommendations for the management of patients with axSpA and details the process of their development.

Methods

This was a combined project endorsed and financed by both ASAS and EULAR. One aim of this update was to aggregate the existing ASAS-EULAR management recommendations of AS and the ASAS recommendations for the management of axSpA with TNFi into one set of recommendations. The objective of this aggregated set of recommendations is to give guidance on the non-pharmacological and pharmacological management of patients with axSpA.

The 2014 updated EULAR standardised operating procedures have been applied.[29] These prescribe that the process set out in AGREE II should be followed in order to design the recommendations and to write the manuscript.[29,30] The convenors formed first a task force with a steering committee. The steering committee included the convenor (DvdH), co-convenor (JB), methodologist (SR), two fellows who performed the SLRs (AS, AR), and three expert-rheumatologists (RL, XB, FvdB). The steering committee defined the research questions for the SLRs and prepared the one-day meeting of the task force. This task force included in addition to the steering committee 18 rheumatologists (two of them with axSpA), including 3 members of EMEUNET (AM, PM, VNC), one health professional (HD) and two patient partners (MJ, DW). The members of the task force represent 14 countries in Europe, North- and South America. All members of the task force disclosed their potential conflicts of interest before the start of the process.

Two fellows under the guidance of the methodologist performed two SLRs: one on non-pharmacological and non-biological pharmacological treatment (AR) and one on biological and targeted synthetic disease modifying antirheumatic drugs (DMARDs) (AS). These SLRs focused on the studies published after the locking date of the SLRs for the previous update, i.e. 2009. The two SLRs are published in detail

separately.[31,32] These SLRs and the current recommendations manuscript form an integral and inseparable part and should be read as such. Both SLRs addressed efficacy and safety, but because the literature on safety of specific drugs in axSpA was, as shown by the SLRs, somewhat limited, more extensive evidence collected on these drugs in SLRs for Rheumatoid Arthritis (RA) were also taken into account.[31-33] The evidence collected was presented in Summary of Findings (SoF) tables and included judgements about Risk of Bias, which was determined for every study.[34,35] SoF tables were presented to the Steering Committee in writing and by presentation, and served as the basis for the discussion in the full task force. When discussing the update of the recommendations, the evidence collected in the previous SLRs was also taken into consideration.[36-38]

In addition, the fellows performed an SLR on the research question whether Ankylosing Spondylitis Disease Activity Score (ASDAS) or Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) should be applied to best define disease activity for the start and continuation of bDMARDs (see Online Supplementary Text 1).

Based on the data obtained from the systematic literature search (SLR), the steering committee prepared wording for the update of the overarching principles and recommendations. The overarching principles and recommendations from the 2010 update were used as a basis and were updated if considered necessary. It was decided that recommendations could only be updated if there was new evidence available that justified such an update according to the task force.

The task force met for a one-day meeting. First, the results of the SLRs were presented to the participants. Thereafter, the updating process of the overarching principles and recommendations was done by discussion in the group. For every overarching principle and recommendation proposed formulations were presented, discussed and voted upon (informal voting). If at least 75% approved the new wording, this was accepted. If not, discussion was resumed and changes to the wording were proposed. In the second voting round a 67% majority was required to accept the recommendation. If this was not reached, a further round of discussion followed and completed with a vote in which a simple majority was deemed sufficient.

After the meeting, the levels of evidence (LoE) and grades of recommendation (GoR) derived from the SLRs following the standards of the Oxford Centre for Evidence Based Medicine were added to each of the recommendations.[39] In summary, level 1A refers to evidence stemming from a meta-analysis of RCTs, 1B corresponds to at least one RCT, 2A means that there was at least one controlled study without randomisation, 2B at least one type of quasi-experimental study, 3 corresponds to descriptive studies, such as comparative studies, correlation studies or case-control studies, and 4 means from expert committee reports or opinions and/or clinical experience of respected authorities. The grades of recommendation are A, which means consistent level 1 studies, B indicating consistent level 2 or 3 studies or extrapolations from level 1 studies, grade C meaning level 4 studies or extrapolations from level 2 or 3 studies and grade D reflecting level 5 evidence or troublingly inconsistent or inconclusive studies of any level. Finally, the overarching principles and recommendations were sent to the task force members and they were asked to add the level of agreement anonymously to each of the statements. This was done by numerical rating scale (NRS, 0-10) with the anchors ‘do not agree at all’ at 0 and

‘fully agree’ at 10. The average, standard deviation and range of the level of agreement per recommendation, as well as the percentage of participants with a score of at least 8, are presented.

The exact wording of the recommendations was considered final after the end of the one-day task force meeting. The final manuscript was drafted after the meeting, reviewed, revised and approved by all task force members, followed by final review and ratification by the EULAR Executive Committee and ASAS Executive Committee before submission to the journal.

Results

It was decided to use the same terminology for DMARDs as proposed recently: conventional synthetic (cs) DMARDs for drugs such as sulfasalazine and methotrexate; targeted synthetic (ts) DMARDs for drugs such as tofacitinib; and biological (b) DMARDs for drugs such as TNFi and IL-17i. bDMARDs can further be subdivided into bio-originator (bo) and biosimilar (bs) DMARDs. Only DMARDs that were approved in at least one country with an indication for axSpA were considered in the recommendations process.[40] However, all DMARDs were looked at in the SLRs.

The target-users of these recommendations are: “All health care professionals taking care of patients with axSpA”. While this definition will mainly include practicing rheumatologists, it may also include medical specialists of a different discipline, general practitioners, physical therapists and other health professionals, as well as medical students. These recommendations further aim at patients to be educated for informed / shared decision-making. The final target group is pharmaceutical industry in its broadest sense, national drug-agencies and policy makers, as well as health insurance companies.

The recommendations describe all aspects of the management of patients with a diagnosis of axSpA. Many of these patients will also fulfil the ASAS classification criteria for axSpA.[41] The focus of these recommendations is on the musculoskeletal signs and symptoms of the disease. But when appropriate and relevant, extra-articular manifestations such as psoriasis, uveitis and inflammatory bowel disease, as well as comorbidities including osteoporosis and cardiovascular diseases, will also be discussed. However, the actual management of these extra-articular manifestations and comorbid conditions are beyond the scope of these management recommendations. For the optimal management of these diseases, specific EULAR recommendations and respective medical specialists should be consulted.[42-44]

As the concept and term of axSpA is relatively new, the older studies in the literature are based only on patients with AS. This applies mainly to non-pharmacological treatments and to drugs that are already on the market for a long time, such as non-steroidal anti-inflammatory drugs (NSAIDs). However, the two SLRs revealed many trials that have included patients with the whole spectrum of axSpA, mainly trials with TNFi but also trials with NSAIDs and DMARDs. The task force agreed explicitly that these recommendations apply to all patients with axSpA.

Overarching principles

As in the 2010 update, the recommendations start with overarching principles, which are considered so generic and implicit in nature that they serve as a basis for the state-of-the-art management of patients with axSpA. As such, they reflect the state of practice rather than the state of science. There are in total 5 overarching principles; 4 are identical to the previous version and one new overarching principle was formulated. Only the order of the previous overarching principles 3 and 4 was switched. We present the LoA of each overarching principle in table 1.

1. Axial Spondyloarthritis (axSpA) is a potentially severe disease with diverse manifestations, usually requiring multidisciplinary management coordinated by the rheumatologist

This overarching principle is important, not only because it stresses that musculoskeletal manifestations of the disease may importantly interfere with patients' daily living, but also because it points to the fact that patients with axSpA frequently experience extra-articular manifestations: approximately 40% of the patients experience at least one extra-articular manifestation during the course of the disease.[2,45]. Some of these extra-articular manifestations require the immediate consultation of other experts, pointing to the presence of multidisciplinary networks for the best care of patients with axSpA. Some of the available (biological) drugs are efficacious for both musculoskeletal and the extra-articular manifestations, while others have effects limited to the musculoskeletal symptoms. These factors should be taken into account when choosing a drug. Since the treating rheumatologist should have extensive knowledge of the entire disease spectrum, it is crucial that the rheumatologist is the coordinator in a multidisciplinary network of care for patients with axSpA. In this network, other medical specialists and care professionals do of course also have their place.

2. *The primary goal of treating the patient with axSpA is to maximise long term health related quality of life through control of symptoms and inflammation, prevention of progressive structural damage, preservation/normalisation of function and social participation*.

Management should aim at the best possible health-related quality of life. Many studies have clearly shown that patients with axSpA have a reduced quality of life in comparison to the non-diseased population[46,47]. Problems experienced by patients with axSpA can be summarised according to the International Classification of Functioning, Disability and Health and can be assessed using the ASAS Health Index, which is based on the ICF.[48-50] As axSpA is an inflammatory disease, suppression of inflammation by drugs has a prominent place, in order to relieve symptoms, preserve physical function and maintain quality of life. And indeed, data have accrued that suggest a direct relation between clinical disease activity and syndesmophyte formation and between disease activity and function.[51-53] Moreover, patients who have inactive disease have a better health-related quality of life.[54]

3. The optimal management of patients with axSpA requires a combination of non-pharmacological and pharmacological treatment modalities.

This overarching principle is identical to number 4 in the 2010 set of recommendations.

In comparison to other chronic inflammatory rheumatic diseases such as RA and PsA, non-pharmacological management has a relatively important place in the management of patients with axSpA. While this will be highlighted in the separate recommendations, the task force wanted to draw attention to the importance of non-pharmacological treatment by formulating it as an overarching principle.

4. Treatment of axSpA should aim at the best care and must be based on a shared decision between the patient and the rheumatologist.

This is an unchanged principle but is now listed as the fourth overarching principle. 'Best care' is an important concept and closely relates to overarching principle 2: 'to maximise health related quality of life'. But 'best care' here refers to the 'best possible care' for individual patients, and still prevails when costs of treatment are taken into account, as indicated in the following fifth overarching principle.

'Shared decision making' is the second important concept in this overarching principle and refers to the formal and informal relationship between patient and rheumatologist, that partner during all phases of their encounters, in order to collectively decide upon the best possible management, given all factors that may be relevant for such a decision. 'Shared decision' does not only refer to the choice of a particular drug but pertains to all phases of the process: defining a treatment-goal (target), investigating potential barriers to achieve that target, choosing the best strategy to achieve the target (given the potential barriers), considering alternative strategies if the target is not reached or the treatment is not tolerated, considering tapering strategies if a target is 'sustained', etcetera. Shared decision making requires sufficient education about the disease, appropriate information (that means: comprehensible risk communication) about risks and benefits of separate treatment options and the design of a feasible management plan, as well as strategies to monitor treatment success. In this process of shared decision making, rheumatologists and patients have different roles and responsibilities that ideally should merge into one management plan with full commitment from patient and care-giver, so that the likelihood of treatment success and good compliance is highest.

5. AxSpA incurs high individual, medical and societal costs, all of which should be considered in its management by the treating rheumatologist.

This is a new overarching principle which has been taken from the EULAR recommendations on RA and PsA.[22,23] This overarching principle first points to the fact that there are high costs associated with the disease itself and with its treatment. This relates to the patient (individual costs) and can be seen as monetary costs, but also as burden of the disease. When assessing the financial burden for society, the direct medical costs as well as indirect costs due to work productivity loss should be taken into account. And when evaluating the cost-effectiveness of (potentially expensive) treatments, all these aspects should be considered.[55]

AxSpA is a disease for which the treatment options rapidly increase. Some of them are very cheap; others are very expensive. When a choice between treatments has to be made in clinical practice, costs in its broadest sense are relevant factors. This should only be done taking ‘best care’ as worded in overarching principle number 4 into account. Consequently, only if the outcome for the patient is expected to be similar under either treatment, healthcare costs can drive the choice This is an important principle in light of the fact that in many (Western) countries the pressure to reduce cost of healthcare through cuts on drug expenditure has increased significantly. Several task force members, including patients, expressed major concerns regarding this overarching principle, because of the historical -but currently untenable- premise that physicians should not be influenced by drug costs when making decisions, and because of the fear to be hindered in choosing the treatment that may provide ‘best care’. Nevertheless, the vast majority (see LoA) of task force members were supportive of this principle after highlighting the fact that the principle of ‘best care’ (and that of shared decision making) should always prevail. An appropriate example of the above mentioned discussion could be the choice between a cheaper bsDMARD and a (likely) more expensive boDMARD. In this scenario similar (efficacy and safety) outcomes can be reasonably expected, and the price of the drug may become a prevailing argument, provided that the patient is fully informed and agrees with this choice under the premise of ‘shared decision making’. Moreover, drug costs as well as costs of treatment can vary tremendously not only across countries, but between different regions within the same country (e.g. due to price negotiations among payers). It is therefore strongly recommended to consider costs of treatment in the context of the local situation.

The task force is keen to point out that although no dedicated SLR on cost-effectiveness was performed, costs have been taken into account at all times during the development of these recommendations.

Recommendations

A total of 13 recommendations have been formulated (Table 1). Two of these (#3, #11) are new from previous publications, one recommendation was split into two (old #9 into new #9, #10) and one recommendation has been deleted (old #4). The deleted recommendation dealt with the management of extra-articular manifestations and comorbidities. The task force decided that these aspects were already sufficiently covered by the overarching principles and by other recommendations. Comparing to the 2010 recommendations, the new recommendations are far better formulated as recommendations. In hindsight, the 2010 recommendations represented in realilty ‘statements’, which were based on findings of evidence in the literature and/or on expert opinion. The current recommendations are far more specific and prescribe what should be done in particular clinically relevant situations. These improvements reflect a general tendency of moving insight into recommendation development over the last decade. Moreover, LoE and GoR are now clearly added to each recommendation (Table 1).

Recommendation 1
The treatment of patients with axSpA should be individualised according to the current signs and symptoms of the disease (axial, peripheral, extra-articular

manifestations) and the patient characteristics including comorbidities and psychosocial factors.

The content of the first recommendation is largely unchanged, and indicates the importance of personalized management in a disease with a very heterogeneous phenotype. All the factors mentioned in the body of the text may play a role in making decisions about aspects of management. It also points to the fact that group-level results of trials in patients with axSpA often suggest a certain level of homogeneity, but that individual patients with axSpA in clinical practice may deviate from this supposedly homogeneous pattern. Rheumatologists should take this principle of generalizability into consideration when treating patients with axSpA.

Recommendation 2
Disease monitoring of patients with axSpA should include patient reported outcomes, clinical findings, laboratory tests and imaging, all with the appropriate instruments and relevant to the clinical presentation. The frequency of monitoring should be decided on an individual basis depending on symptoms, severity, and treatment.

Due to the heterogeneous presentation of the disease, monitoring should include a broad variety of assessments. In principle, the ASAS core set for monitoring in clinical practice is still guiding.[56] This includes questionnaires for levels of pain, disease activity (BASDAI), and physical function (Bath Ankylosing Spondylitis Functional Index, BASFI), swollen joint counts, spinal mobility and assessment of extra-articular manifestations if appropriate.[56] Acute phase reactants now play a more prominent role in monitoring patients with axSpA than before. The ASDAS is a relatively new disease activity score, which combines patient reported outcomes and C-reactive protein (CRP) (or erythrocyte sedimentation rate - ESR) into one index.[57] It has been proven that there is a longitudinal relationship between ASDAS and subsequent syndesmophyte formation, while such a relationship between BASDAI (even if combined with CRP in the model) and syndesmophytes was far weaker.[51] Although not (yet) included in the ASAS core set (which was defined before the development of the ASDAS), ASDAS seems a relevant measure to assess disease activity.
MRI is an imaging modality that can provide information on inflammation. Both MRI of the sacro-iliac (SI) joints and of the spine can be used for this purpose. In early disease MRI of the SI joints may be most relevant, while in later stages especially the MRI of the spine may be informative.[28,58] However, the correlation between clinical disease activity measures and MRI inflammation is modest at best.[59-62] To date, the role (if any) of MRI in monitoring the disease remains unclear. Apart from the fact that the meaning of MRI inflammation in patients who have clinically inactive disease (they are free of symptoms) is unclear and that it is unknown if residual MRI inflammation can and should be treated, it is simply not feasible in most settings and far too expensive to repeat MRIs frequently. This explains why MRI is currently not recommended for monitoring. However, MRI can be used to define the level of present inflammation, and may add arguments to the global opinion to start or continue a particular treatment in a particular patient.

Radiographs of the SI joints are useless to monitor the disease course, but may be necessary to define if a patient is fulfilling criteria for a bDMARD start (see later). In contrast, radiographs of the spine provide important information about the presence of syndesmophytes, and about the prognosis of an individual patient, since

evidences show that this is a risk factor for developing more syndesmophytes.[51,53] However, monitoring the disease by consecutive spinal radiographs is of limited value, because of the very slow rate of progression in the majority of patients. If applied, it should not be performed more frequently than once every 2 years.

Recommendation 3
Treatment should be guided according to a predefined treatment target.

This is an important aspect of the treat-to-target concept and is newly added to the recommendations. For the first time in the history of SpA-research, evidence has been accrued to suggest the value of 'targetting disease activity' because disease activity leads to new syndesmophytes in patients with axial SpA.[51,53] As described in the overarching principles, a target should be a shared decision between patient and rheumatologist, taking all relevant situational factors into consideration. Treatment, once started, should be monitored in order to investigate if the target is reached. While amply discussed, the task force did not want to establish a preferred target (as has been done in RA and PsA). In principle, inactive disease is the ultimate goal, but depending on the phase of the disease and the treatments already used previously, it was felt that the required treatment for reaching this target (including its inherent risks) could imply an unrealistic goal. So after discussion it was decided that it is important to recommend that a target should be defined and documented, but refrain from mentioning the content of such target.

Recommendation 4
Patients should be educated about axSpA and encouraged to exercise on a regular basis and stop smoking; physical therapy should be considered.

Education is an important aspect of management, it is essential for patients to make informed shared decisions and has been proven to be efficacious[63-65]. In axial SpA, it is known that home exercises are efficacious and these are therefore recommended to patients.[66] However, physical therapy is proven to be more efficacious than home exercises.[66] Physiotherapy is certainly more expensive and less feasible than home exercises but may be required in some patients. Consequently, it is recommended that rheumatologists always consider if physical therapy could be beneficial for a particular patient. While quitting smoking likely has favourable health effects for every individual, it is of particular interest for axSpA patients, since there is an established association between smoking and disease activity, inflammation on MRI, and syndesmophyte formation.[67-69] In spite of these positive associations, to date there are no data showing a beneficial effect of smoking cessation on signs and symptoms of patients with axSpA.

Recommendation 5
Patients suffering from pain and stiffness should use an NSAID as first line drug treatment up to the maximum dose, taking risks and benefits into account. For patients who respond well to NSAIDs continuous use is preferred if symptomatic otherwise.

The most important aspect of this 2010-recommendation on the use of NSAIDs as first line drug was maintained in the text of this recommendation. All task force members were still convinced of the virtues of NSAIDs administered in a full anti-inflammatory dosage. This can for example be based on the ASAS20 response of above 70%, an ASAS40 response in more than 50% of the patients starting with an

NSAID in early disease or 35% of patients in ASAS partial remission.[70] Important consideration however needs to be given to the potential side effects of NSAIDs, especially when administered chronically. NSAIDs should therefore only be prescribed if patients are symptomatic. If so, treatment should be advised to the maximum tolerated dose, continuously weighing the risks against the benefits. Moreover, while there is much discussion on the long-term safety of NSAIDs especially in relatively young patients data from two studies have suggested that lack of exposure to NSAIDs is associated with an increase in mortality.[71,72] This argues against a major or important safety problem associated with the use of NSAIDs.

Given the risks of long-term NSAID use, the question about which patients require continuous NSAID treatment is valid: trial data have suggested that the continuous use of NSAIDs in patients with an elevated CRP results in reduced progression of structural damage in the spine in comparison to on demand use only.[73,74] Similar results were found in a in a cohort study comparing high and low dose NSAID use.[75] However, a recent randomised trial did not confirm this effect, casting doubts on the potential structural effects of NSAIDs.[76] It was suggested during the task force discussions that the protective effects of NSAIDs may be specific for certain NSAIDs.[76] In the absence of equivocal evidence, it was finally decided to base a decision of continuous use of NSAIDs to the symptoms of the patient rather than on a possible protective effect regarding structural progression: if symptoms recur after stopping or dose reduction of an NSAID, continuous use should be advised. This was accepted by a two third majority in the second round of voting. Whether continuous NSAID use may be beneficial in patients with risk factors for syndesmophyte progression (presence of syndesmophytes, elevated CRP, longstanding disease, spinal inflammation on MRI) remains a topic on the research agenda.[51,53,67,74,75,77-80]

Recommendation 6
Analgesics, such as paracetamol and opioid-(like) drugs, might be considered for residual pain after previously recommended treatments have failed, are contraindicated, and/or poorly tolerated.

This recommendation remained unchanged. It is formulated as a rather weak recommendation since formal evidence that analgesics are efficacious in axSpA is lacking (not tested). Nevertheless, common sense justifies a statement that analgesics may relieve painful conditions, but only if positively recommended treatments for axSpA, including bDMARDs when indicated, have failed.

Recommendation 7
Glucocorticoid injections directed to the local site of musculoskeletal inflammation may be considered. Patients with axial disease should not receive long-term treatment with systemic glucocorticoids.

This recommendation combines, as in the previous version, two means of glucocorticoid use: local and systemic. The formulation about the use of local injections is unchanged and indicates that the task force is still of the opinion that injections with glucocorticoids may be an option to treat arthritis and enthesitis, although direct evidence is lacking. The formulation about the use of systemic glucocorticoids has changed slightly. While systemic glucocorticoids were not specifically discouraged entirely in previous recommendations, positive data were also lacking. New data now have suggested that short-term high dose of

glucocorticoids (50mg/day) may have a very modest effect on signs and symptoms in patients with axial disease.[81] However, the task force still had the conviction that patients with axial disease should not be treated long-term with systemic glucocorticoids irrespective of the dose.

Recommendation 8
Patients with purely axial disease should normally not be treated with csDMARDs; Sulfasalazine may be considered in patients with peripheral arthritis.

Again this recommendation consists of two parts: The first part refers to patients with purely axial disease and the second part to patients with peripheral arthritis. The latter remained identical: sulfasalazine as a treatment option in patients with peripheral arthritis. The statement pertaining to patients with axial disease has been reworded into a real recommendation, while the previous version was rather a statement on the lack of efficacy of csDMARDs in patients with axial SpA. There were no new studies on csDMARDs in axSpA. Already in the SLR informing the previous version of the recommendations, and on the basis of older studies, it had been shown that csDMARDs were not efficacious in axSpA.

The word ‘normally’ in the text of the recommendation created a lot of argument. Only in the third round of voting, 65% of the participants voted in favour of adding the word ‘normally’. In principle, the task force was of the opinion that patients with purely axial disease should not be treated with csDMARDs. While there is evidence that sulfasalazine, methotrexate and leflunomide are not efficacious for axial symptoms, there may be exceptional situations in which there is no other pharmacological treatment option left for a particular patient for reasons of toxicity, contraindications or costs.[82-84] In such exceptional (‘not normal’) situations, a shared decision could be to try a csDMARD for a limited period of time. This policy violates the (ethical) principle of ‘best care’, knowing the low likelihood of treatment success, but not the principle of ‘shared decision making’ since the patient should be fully informed about the low likelihood of treatment success and the likelihood of side effects, before the decision is made. This reasoning convinced the majority of the task force to accept the wording of the recommendation in such a manner that the use of csDMARDs in patients with purely axial disease can only exceptionally be defended.

Recommendation 9
bDMARDs should be considered in patients with persistently high disease activity despite conventional treatments (box 1); current practice is to start with TNFi therapy.

The previous recommendation 9 only included TNFi therapy, because no other class of bDMARDs was available. Moreover, the details about the use of TNFi therapy was discussed in the separate ASAS recommendations. Now both are integrated in the current recommendations. The first part of the recommendation remained essentially unchanged: bDMARDs (in general and not limited anymore to TNFi therapy) should be considered in patients with persistently high disease activity despite conventional treatments. These conventional treatments obviously include non-pharmacological management as well as NSAIDs. And in patients with (mainly) peripheral symptoms ‘conventional management’ may also include a local glucocorticoid injection (if considered appropriate) and normally a treatment with sulfasalazine (in case of peripheral arthritis). This recommendation emphasises that a treatment ‘should be

considered' and the outcome of this process of consideration is dependent on an evaluation of the risks and benefits to be expected. As always, shared decision making is key.

Box 1 is summarizing the different requirements before a bDMARD could be started. The first step is the diagnosis of axSpA by a rheumatologist. Only formally fulfilling classification criteria (such as the ASAS axSpA criteria) does not suffice. A knowledgeable rheumatologist should make a diagnosis based on the full evaluation of all clinical, laboratory and imaging information, and should also exclude other potentially more likely diagnoses. While the large majority of these patients will also fulfil the ASAS axSpA criteria, the opposite is not necessarily true: solely checking and ticking boxes in order to test fulfilment of separate elements is inappropriate and obsolete.

The next step is to judge if a patient fulfils 'labelling criteria': elevated CRP, the presence of inflammation on MRI of the SI joints and/or spine, or the presence of radiographic sacroiliitis (defined as according the modified New York grading: at least grade 2 bilaterally or at least grade 3 unilaterally). The clarification of the content and order of this step is as follows:

TNFi therapy is approved in many countries for patients with radiographic axSpA (AS) without further limitations, and in patients with non-radiographic axSpA only if there is an elevated CRP and/or inflammation on MRI. This means that if a patient with axSpA has radiographic sacroiliitis or when this patient has either an elevated CRP or inflammation on MRI, the patient formally complies with the requirements for bDMARD therapy mentioned in the label of the respective drugs. While not brought up as a limitative factor, the task force was of the opinion that many studies have now suggested that also patients with radiographic axSpA that have an increased CRP have the highest likelihood of treatment success.[85,86] In addition, recent observational studies, as well as re-evaluations of clinical trials, have cast doubts on the reliability of the finding of radiographic sacroiliitis by (untrained) single evaluators.[6,7] Elaborating on this principle, one may argue that –albeit formally justifiable- a sole finding of radiographic sacroiliitis in a patient without further indication of objective disease activity may be too meagre to justify proper bDMARD treatment in the spirit of 'best possible care' as defined in overarching principle number 4. Therefore, the task force decided to start with 'elevated CRP' as being the strongest predictor of a good response to TNFi therapy, both in patients with radiographic axSpA and non-radiographic axSpA.[15,87] In addition, inflammation on MRI appeared to be second-best predictor of response to TNFi therapy, again irrespective of the presence of radiographic sacroiliitis.[13,15,17] The task force hopes that rheumatologists will take CRP and (when available) MRI into consideration when deciding about the appropriateness of starting a bDMARD, irrespective of whether radiographic sacroiliitis is present or not.[13,15,17,87] Radiographic sacroiliitis is not a predictor of response: a study stratified on radiographic sacroiliitis has shown that patients with radiographic and non-radiographic sacroiliitis have similar response rates.[28] But there is one proviso here: while this box pertains to treatment with bDMARDs, currently the use of IL17i therapy and of infliximab in patients with non-radiographic axSpA is not approved by the agencies and therefore for IL17i therapy and infliximab radiographic sacroiliitis is mandatory.

Step 3 refers to the failure of standard treatment as explained above. A treatment with sulfasalazine should be evaluated after 3 months of treatment reaching a dose of 3g per day if tolerated. This is different in comparison to the 2010 ASAS recommendations, as in those recommendations MTX was also advocated as a possible treatment for patients with peripheral symptoms. As there are no data proving the efficacy of MTX and there are with regard to sulfasalazine, this was changed back to sulfasalazine in accordance with earlier recommendations.[20,21]

Step 4 is to define the level of disease activity. Historically, active disease has been defined by a BASDAI level of at least 4. But ASDAS is a better index than BASDAI (see below), and active disease can also be defined by ASDAS of at least 2.1[88]. ASDAS is placed first, as it is the preferred measure. This decision was based on data from the SLR of the fellows and on expert opinion (Online Supplementary Text 1). The BASDAI is a fully patient reported outcome while the ASDAS is a combination of patient reported outcomes and CRP. BASDAI and physicians' opinion on disease activity only correlate weakly, while ASDAS correlates far better with both patients' and physicians' level of disease activity.[57,89] Another argument is that increased ASDAS may lead to syndesmophyte formation, while this has not been proven for BASDAI alone (BASDAI works only if combined with CRP).[51] Moreover, a high BASDAI appeared to be a predictor for stopping TNFi therapy, while a high ASDAS was a predictor for continuation of TNFis, which can be seen as a surrogate outcome for efficacy.[85] Frequently, there is concordance between a BASDAI $\geq$4 and ASDAS $\geq$2.1, but in discordant cases an elevated ASDAS was more predictive of a good response than an elevated BASDAI.[90,91] Finally, the ASDAS cut-offs for disease activity states and response criteria were based on a thorough validation process, while the BASDAI cut-offs were arbitrarily chosen.[88]

In addition to the level of high disease activity, the rheumatologist should be convinced that in a particular patient there is a favourable benefit/risk profile before a treatment with a bDMARD is started. In order to construct this profile intuitively, the rheumatologist can take 'positive factors' such as inflammation on MRI, into consideration, but should also weigh potential contraindications such as risk for side effects, or compliance. Ultimately, only a shared decision between patient and rheumatologist will result in the start of a bDMARD.

The second part of recommendation 9 refers to 'current practice' in which it is normal to start with TNFi therapy. TNFis registered for the indication of axSpA are (in alphabetical order) adalimumab, certolizumab pegol, etanercept, golimumab and infliximab. The wording for this recommendation was borrowed from previous EULAR recommendations for RA at the time that TNFi were already on the market for a long time; there was extensive experience with the use of TNFi; TNFi were also used in clinical practice in a wide variety of patients; registry data suggested positive long term safety.[22] This is exactly how the situation is in axSpA in 2016. For the first time there is a different class of bDMARDs on the market with a different mode of action: an IL17-pathway inhibition. Currently, only secukinumab is approved, but several other agents are far in their development. To date, only trial data on IL17i in radiographic axSpA are available and data in patients with non-radiographic axSpA are still lacking. So it is obvious that the body of experience with TNFi in axSpA on efficacy, safety and variety of indications greatly outweighs that with IL17-pathway inhibition, both in terms of volume and time of follow up. This is why the task force has decided to recommend TNFi as the first bDMARD, use the wording 'current

practice' to justify that choice, and implicitly give endorsement to this practice. Moreover, the use of IL17i therapy should be avoided in patients with active IBD, as secukinumab in comparison to placebo was not efficacious in Crohn's disease and resulted in more adverse events.[92] Secukinumab has proven efficacy for the treatment of psoriasis.[93] Apart from IL17i therapy there is no other non-TNFi bDMARD on the market. Various IL-6is have been tried in well-designed trials but were proven not efficacious.

Several TNFi have been approved for axSpA. All, except infliximab, have indications for both radiographic and non-radiographic axSpA. Their efficacy with regards to musculoskeletal signs and symptoms seems very comparable, although no head-to-head comparisons are available. However, there seems to be a difference in efficacy with regards to extra-articular manifestations. Monoclonal antibodies (infliximab, adalimumab, certolizumab, golimumab) are efficacious in the treatment of IBD and in preventing the recurrence of uveitis (no data on golimumab) and, whereas etanercept has shown contradictory results for uveitis and no efficacy in IBD.[94-103] Etanercept seems to be less efficacious for psoriatic skin involvement than other TNFi, although no head-to-head comparisons are available.[23]

In this entire document, we refer to both boDMARDs as well as bsDMARDs when we mention TNFi therapy. The price of a bDMARD should be taken into account when choosing a particular drug. The choice is very much dependent on local situations, and general recommendations cannot be made, but given the similar expected safety and efficacy with regard to alleviating musculoskeletal symptoms, cost is potentially an important consideration in making a choice between a boDMARD and a bsDMARD. In many countries and regions within countries this choice is increasingly determined by payers based on cost considerations rather than by individual rheumatologists and their patients.

Finally, box 2 clarifies when and how should efficacy of bDMARDs be evaluated and in which circumstances it is recommended to continue. First, the wording has changed from 'stopping' a bDMARD in the previous versions of the ASAS recommendations to 'continuation' in the current recommendations. The response should be defined by the same outcome used to initiate: either ASDAS or BASDAI. For ASDAS a clinically important improvement of $\geq$1.1 is required, while this is $\geq$2.0 for BASDAI. Importantly, such an evaluation should coincide with the positive opinion from the rheumatologist, who will take all potential risks and benefits into consideration, before deciding together with the patient whether treatment with a bDMARD should be continued.

Recommendation 10
If TNFi therapy fails, switching to another TNFi or an anti-IL17 therapy should be considered.

With the advent of a second class of bDMARDs available, there is a potential choice after failure of TNFi therapy. Data suggest that a second TNFi (after failure of the first TNFi) can still be efficacious, although the level of efficacy may be lower than with the first TNFi.[104] IL17i therapy has proven efficacy in patients that had failed a TNFi but this was also less than in TNFi-naïve patients.[26,27] In patients with a primary nonresponse to the first TNFi, it may be more rational to switch to another class of drugs, i.e. an IL17i. However, before doing so, it is important to reconsider if the indication for the start of the first TNFi was indeed correct. Rather than drug

failure, primary failure can also be the consequence of an incorrect diagnosis, in which no clinical efficacy can be expected. The task force was of the opinion that true primary failure is an infrequent observation in correctly diagnosed axSpA patients with active disease.

Toxicity to a TNFi may also be a reason to switch directly to an IL17i. Data proving whether a TNFi is efficacious in patients who have failed IL17i therapy are still lacking. Therefore, evidence-based guidance cannot be provided, but the task force felt it reasonable to assume that a TNFi in this situation makes sense. It is important to formally investigate the efficacy of a TNFi after failure of an IL17i (research agenda).

Figure 1 summarises all the various phases of treatment in a graphical representation.

Recommendation 11
If a patient is in sustained remission, tapering of a bDMARD can be considered.

This recommendation is a completely new one. Since the SLR in 2009 new data have become available that suggest the possibility of successful tapering of bDMARDs and acceptable efficacy after restart.[105,106] However, complete discontinuation of bDMARDs seems to lead to a high percentage of patients that experience flares.[107,108] Given the high costs of long-term bDMARD-use it is considered appropriate to slowly taper bDMARDs in patients who are in sustained remission Although remission is not defined here ASDAS inactive disease is a clinical remission-like definition, which could be used. Currently, it is unclear what the definition of 'sustained' should be, but the task force was of the opinion that this should be at least 6 months, possibly longer. Data should be collected that provide insight on predictors of a flare after tapering treatment. It is, for instance, important to know if residual inflammation on MRI may predict a flare or if there is an association between the length of time in remission and likelihood of flare. In principle, tapering can be done by either dose reduction or increasing the interval ('spacing'). Again it is unclear if one method is better than the other, but 'spacing' seems to be the most practical approach. Although tapering can theoretically be continued until zero (discontinuation), it is recommended to do this only very slowly and assuring a sufficient period of time remaining in remission after the previous step of tapering. Shared decision making is pivotal in tapering. This opinion was specifically expressed by the patients since they fear that the need for cost reduction will outweigh principles of 'best care' as the most important driving factor. Needless to say that -for the quality of life of patients with axSpA- principles of 'best care' and 'shared decision making' should outweigh cost considerations, but the latter remain significant.

Recommendation 12
Total hip arthroplasty should be considered in patients with refractory pain or disability and radiographic evidence of structural damage, independent of age; spinal corrective osteotomy in specialised centres may be considered in patients with severe disabling deformity.

The old recommendation on surgery consisted of the above aspects on total hip arthroplasty and corrective osteotomy, which remained unchanged for the current recommendation. However, a third item, referring to the consultation of a spinal

surgeon in case of an acute vertebral fracture, was deleted. It was broadly felt that this item is already sufficiently covered by the last recommendation. Hip involvement is a frequent problem in patients with axSpA.[109] In case of symptoms and a compatible radiograph with destruction, patients at any age should be considered candidates for a total hip arthroplasty. Especially in young patients, cementless prostheses are preferred. Corrective spine osteotomy is available only in specialised centres, and patients with severe deformities could consult a specialised spinal surgeon to discuss risks and benefits of this procedure.[110]

Recommendation 13
If a significant change in the course of the disease occurs, causes other than inflammation, such as a spinal fracture, should be considered and appropriate evaluation, including imaging, should be performed.

The final recommendation was kept unchanged. Frequently, axial symptoms in patients with axSpA are caused by inflammation, but other causes should always be considered. This is especially important if a patient is not responding to pharmacological treatment and if there is a major, frequently sudden, change in the course of the disease. In this case, a spinal fracture should be suspected, since these are more prevalent than often expected.[111] They may occur with neurological symptoms but most frequently are without neurological symptoms and can even occur without preceding trauma. In case of suspicion, proper imaging such as MRI and/or CT scanning should be performed, and an experienced spinal surgeon may need to be consulted.[112]

Discussion

The 2010 ASAS-EULAR recommendations on the management of AS and the 2010 ASAS recommendation on the use of TNFi in axSpA, have not only been updated but also aggregated into one set of management recommendations intended for patients with axSpA. The integrated set is more ‘user friendly’ and clearer to users than two separate sets. There are two major novelties: 1) Unlike the previous sets, these recommendations not only apply to patients with radiographic axSpA (AS) but to all patients with axSpA, irrespective of the presence of radiographic sacroiliitis; 2) These recommendations include a new class of bDMARDs, IL17-pathway inhibiting therapy, which recently has become available for the treatment of patients with (radiographic) axSpA. Both aspects are integrated into one Box explaining requirements to start a bDMARD. As a first step, there is emphasis on the fact that a proper diagnosis is key, that such a diagnosis should be made by an expert rheumatologist, and that classification criteria do not suffice to make a diagnosis. On the contrary, a proper diagnosis of axSpA includes a credible pattern of axSpA and exclusion of more likely diagnoses.

Thereafter, the various aspects that are mentioned in the labelling of bDMARDs are combined. All TNFis except infliximab have been approved for the treatment of patients with AS (radiographic sacroiliitis) and for patients with non-radiographic axSpA. But in this latter group, the presence of an elevated CRP or inflammation on MRI is mandatory. By combining this into one step as a requirement in addition to a diagnosis of axSpA, we have integrated two separate lines of drug registration (bDMARDs for AS and bDMARDs for non-radiographic axSpA) into one workable

definition with profound predictive validity: While increased CRP is formally not required to indicate a patient with AS for a treatment with a bDMARD, ample evidence suggests that elevated CRP (and to a lesser extent: inflammation on MRI) predisposes to clinical efficacy, both in radiographic and non-radiographic axSpA.

It may even be questioned if patients with radiographic sacroiliitis only (without syndesmophytes), normal CRP and no inflammation on MRI are good candidates for bDMARD therapy. Given the lack of reliability of assessing SI-joints for radiographic sacroillitis, misdiagnosis could be an important aspect in this group of patients and more information on the efficacy of bDMARDs in these patients is warranted.[6,7]

It needs to be stressed that this formulation formally does not apply to IL17i therapy, which has been approved for axSpA with radiographic sacroiliitis only.[26,27]

Another new aspect is the use of ASDAS to assess the level of disease activity, the response to bDMARDs, and the decision on continuation of the bDMARD. Taking several aspects as discussed into account, the ASDAS is likely to be the preferred assessment. Although the task force has decided to include a treat-to-target principle and has formulated one recommendation on the definition of a target, it was considered too early to give a recommendation on the content of the target. A task force that is updating the current treat-to-target recommendations for SpA will further work on this aspect.

Although a lot of attention is paid to the use of bDMARDs, it is important to stress that non-pharmacological management remains an important aspect of management in patients with axSpA. This applies to all phases of the disease, and is irrespective of the pharmacological treatment. In addition, NSAIDs continue to be the first line drug in axSpA.

For the first time, cost considerations received a prominent place in the axSpA recommendations. The task force considers this an important aspect, given the extreme drug costs for individual patients and society, and feels a responsibility to help minimising total health care expenditures for patients with axSpA. However, here lies also a clear responsibility for the pharmaceutical industry.[113] But it is clearly stated in this document that this should not go at the cost of access to ‘best possible care’. In case of similar efficacy and safety, the cheapest treatment option can be chosen. Tapering of a bDMARD is also recommended as an option, but again under the condition of maximising health related quality of life.

For an easier understanding and presentation, the recommendations are presented in a table, two boxes and a figure. However, we like to underline these cannot be read and interpreted without the accompanying text. Furthermore, the text of the current manuscript cannot be well understood without the accompanying SLRs, which form an integrated whole.[31,32] Even the SLRs of the previous recommendations need to be consulted in order to be informed about the complete body of evidence published in the literature.[36-38] The SLRs give also information on the quality of the publications, for example by presenting the risk of bias estimates.

The ACR and SPARTAN have published recommendations for the treatment of AS and nonradiographic axSpA in 2015.[114] While these have been developed according to the GRADE methodology, and our recommendations have applied the

Oxford levels of evidence to assess the evidence of the literature, the overall recommendations are very similar. Differences are mainly in those areas where strong evidence is lacking (e.g. corrective osteotomy, injections with glucocortiocids). The presentation, though, is fundamentally different. The ACR-SPARTAN recommendations are grouped for various stages and presentations of the disease (e.g. patients with AS with active disease, with stable disease, with various extra-articular conditions) while the ASAS-EULAR recommendations are more condensed and integrated. The ACR-SPARTAN set of recommendations comprises 38 separate recommendations and the ASAS-EULAR set comprises 13 recommendations. A few of the unique aspects of the ASAS-EULAR recommendations are: treatment according to a target, the explicit conditions in which a bDMARD should be started, tapering of a bDMARD, the use of IL17i, taking aspects of costs into account, and treating axial SpA as one continuum of the disease.

The 2016 ASAS-EULAR recommendations for the management of axSpA provide in a single set of recommendations guidance for the management of patients from the whole spectrum of the disease, including radiographic and non-radiographic axSpA, and address the whole disease management, including non-pharmacological and pharmacological treatment. While this aspect can be seen as a facilitator of these recommendations, a potential barrier is that it implies acceptance of the concept of axSpA. There are clear signs confirming that this is the world-spread movement, but still some challenges remain. Efforts shall be made towards the implementation of these recommendations, namely through dissemination across national societies, websites, and presentations made in congresses, as well as in educational sessions to physicians. Both ASAS and EULAR will lead these efforts, and support implementation efforts at a national level, preferably involving all the stakeholders, namely patient groups, national rheumatologist societies and policy-makers.

This was the first update since 2010 and this relatively long period could be explained by an absence of new treatment options until recently. The next update will be undertaken when there are sufficient new data on existing treatments or when data on new treatment options will become available. Until then, we hope that the current recommendations will be useful for health professionals taking care of patients with axSpA, for patients themselves, for the pharmaceutical industry and for payers.

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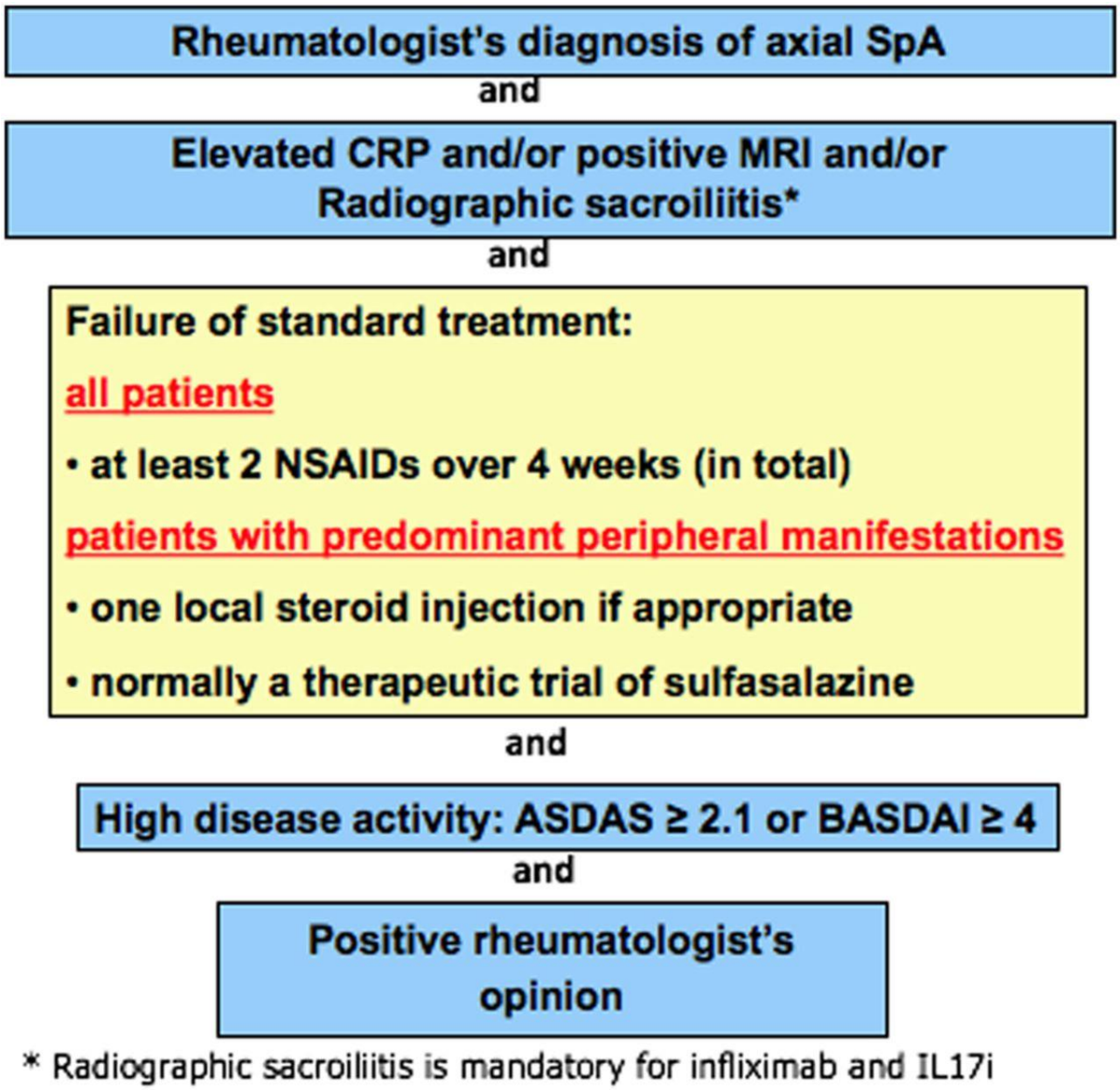
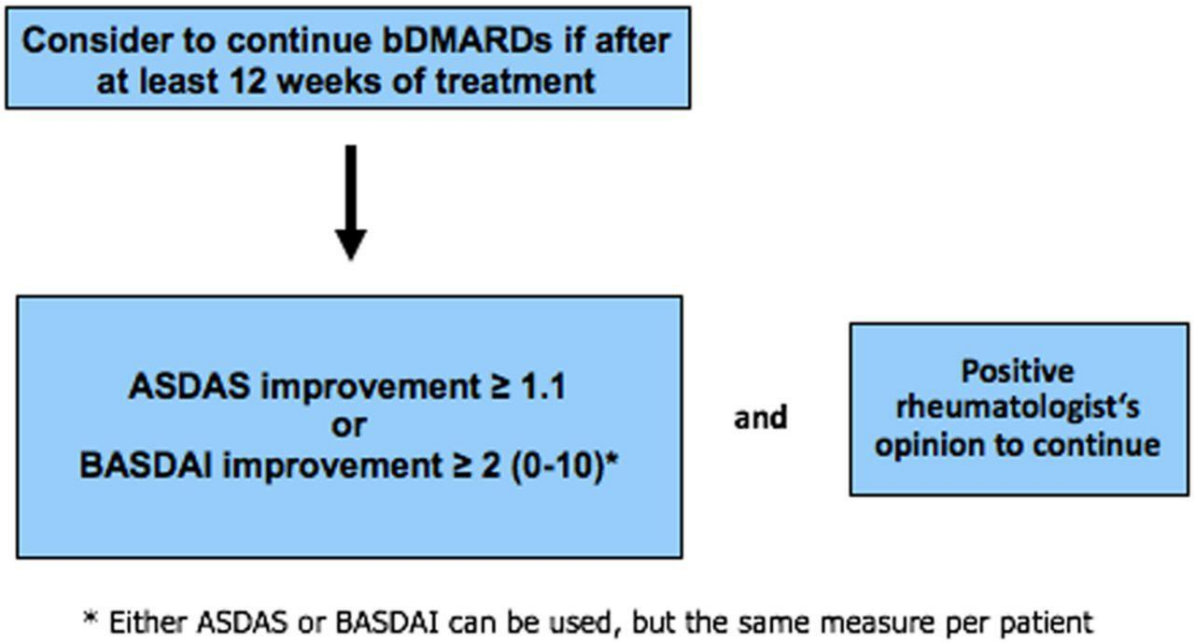
Figure 1 - Algorithm based on the ASAS-EULAR recommendations for the management of axial spondyloarthritis



ASDAS: Ankylosing Spondylitis Disease Activity Score; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; bDMARD: biological disease modifying antirheumatic drug; TNFi: tumor necrosis factor inhibitor; IL17-inhibitor: interleukin17 inhibitor

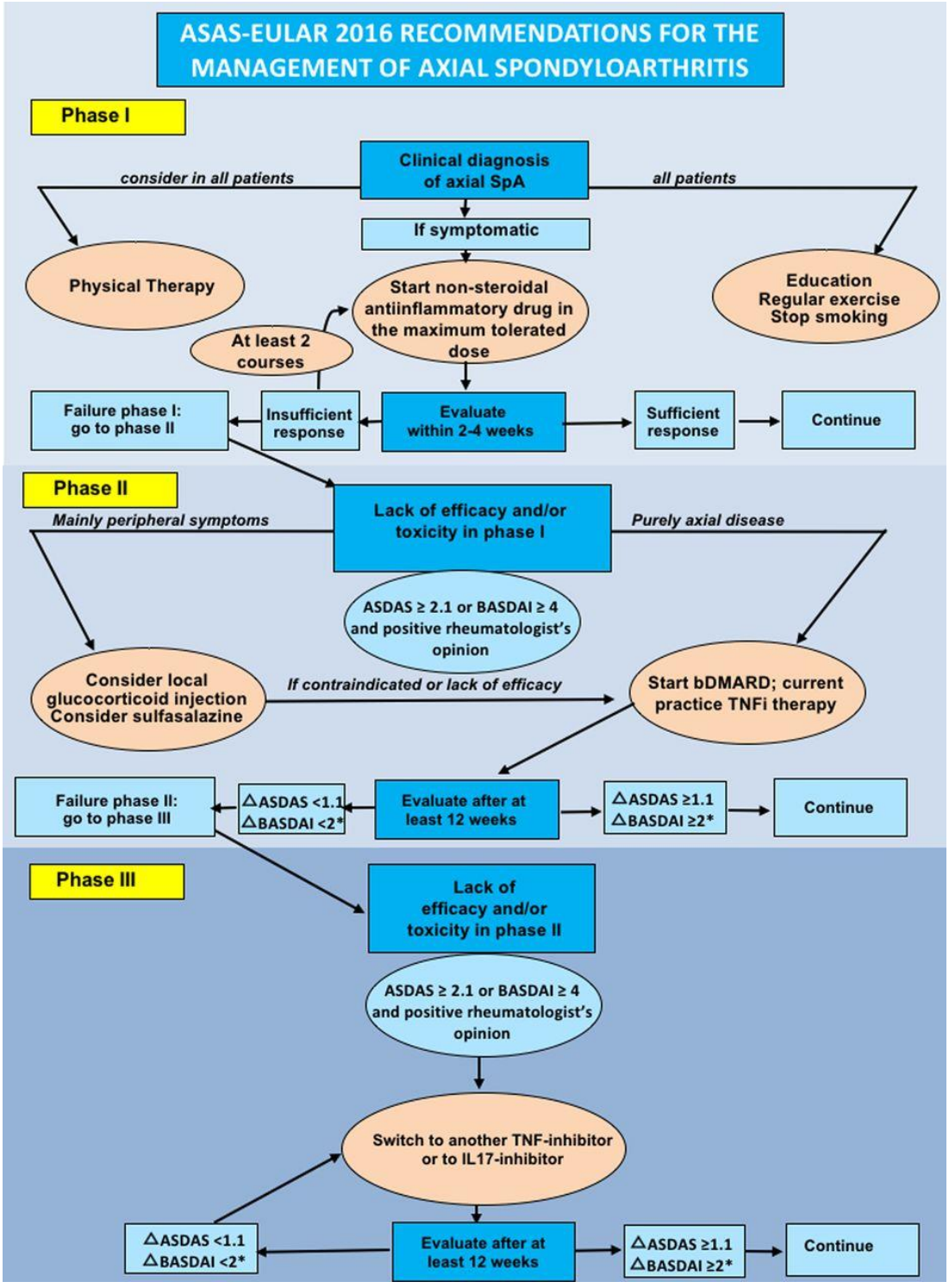
* Either BASDAI or ASDAS, but the same outcome per patient

Figure 2 – ASAS-EULAR recommendations for the continuation of bDMARDs.



ASDAS, Ankylosing Spondylitis Disease Activity Score; axSpA, axial spondyloarthritis; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; bDMARD, biological disease modifying anti-rheumatic drug.

Figure 3 - Algorithm based on the ASAS-EULAR recommendations for the management of axial spondyloarthritis.



ASDAS, Ankylosing Spondylitis Disease Activity Score; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; bDMARD, biological disease-modifying antirheumatic drug; TNFi, tumor necrosis factor inhibitor; IL17-inhibitor, interleukin-17 inhibitor. *Either BASDAI or ASDAS, but the same outcome per patient.

Box 1 - ASAS-EULAR recommendations for the treatment of patients with axSpA with bDMARDs

	Overarching principles	**LoE**	**GoR**	**LoA (0–10)**
1	axSpA is a potentially severe disease with diverse manifestations, usually requiring multidisciplinary management coordinated by the rheumatologist			9.9 (0.31) 100% ≥8
2	The primary goal of treating the patient with axSpA is to maximise health-related quality of life through control of symptoms and inflammation, prevention of progressive structural damage, preservation/normalisation of function and social participation			9.8 (0.47) 100% ≥8
3	The optimal management of patients with axSpA requires a combination of non-pharmacological and pharmacological treatment modalities			9.8 (0.45) 100% ≥8
4	Treatment of axSpA should aim at the best care and must be based on a shared decision between the patient and the rheumatologist			9.5 (0.91) 100% ≥8
5	axSpA incurs high individual, medical and societal costs, all of which should be considered in its management by the treating rheumatologist			9.3 (1.17) 97% ≥8
	Recommendations			
1	The treatment of patients with axSpA should be individualised according to the current signs and symptoms of the disease (axial, peripheral, extra-articular manifestations) and the patient characteristics including comorbidities and psychosocial factors	5	D	9.7 (0.65) 100% ≥8
2	Disease monitoring of patients with axSpA should include patient-reported outcomes, clinical findings, laboratory tests and imaging, all with the appropriate instruments and relevant to the clinical presentation. The frequency of monitoring should be decided on an individual basis depending on symptoms, severity and treatment	5	D	9.6 (0.78) 100% ≥8
3	Treatment should be guided according to a predefined treatment target	5	D	8.9 (1.45)

	Overarching principles	LoE	GoR	LoA (0–10)
				93% ≥8
4	Patients should be educated* about axSpA and encouraged to exercise* on a regular basis and stop smoking‡; physical therapy† should be considered	2* 5‡ 1a†	B* D‡ A†	9.6 (0.78) 100% ≥8
5	Patients suffering from pain and stiffness should use an NSAID as first-line drug treatment up to the maximum dose, taking risks and benefits into account. For patients who respond well to NSAIDs continuous use is preferred if symptomatic otherwise	1a	A	9.4 (0.94) 100% ≥8
6	Analgesics, such as paracetamol and opioid-(like) drugs, might be considered for residual pain after previously recommended treatments have failed, are contraindicated, and/or poorly tolerated	5	D	8.8 (0.94) 100% ≥8
7	Glucocorticoid injections* directed to the local site of musculoskeletal inflammation may be considered. Patients with axial disease should not receive long-term treatment with systemic glucocorticoids‡	2* 5‡	B* D‡	9.4 (0.78) 100% ≥8
8	Patients with purely axial disease should normally not be treated with csDMARDs§; sulfasalazine† may be considered in patients with peripheral arthritis	1a†	A	9.2 (0.78) 100% ≥8
9	bDMARDs should be considered in patients with persistently high disease activity despite conventional treatments (**figure 1**); current practice is to start with TNFi therapy	1a (TNFi); 1b (IL-17i)	A	9.6 (1.09) 93% ≥8
10	If TNFi therapy fails, switching to another TNFi* or IL-17i** therapy should be considered	2* 1b**	B* A**	9.6 (0.95) 97% ≥8
11	If a patient is in sustained remission, tapering of a bDMARD can be considered	2	B	9.1 (1.57) 97% ≥8
12	Total hip arthroplasty should be considered in patients with refractory pain or disability and radiographic evidence of structural damage, independent of age; spinal corrective osteotomy in specialised centres may be considered in patients with severe disabling deformity	4	C	9.4 (0.82) 100% ≥8

	Overarching principles	LoE	GoR	LoA (0–10)
13	If a significant change in the course of the disease occurs, causes other than inflammation, such as a spinal fracture, should be considered and appropriate evaluation, including imaging, should be performed	5	D	9.9 (0.31) 97% ≥8

- **§1a (sulfasalazine; methotrexate); 1b (leflunomide); 4 other csDMARDs.**
- **axSpA, axial spondyloarthritis; bDMARD, biological disease-modifying antirheumatic drug; csDMARD, conventional synthetic disease-modifying antirheumatic drug; GoR, grade of recommendation; IL-17i, interleukin-17 inhibitor; LoA, level of agreement; LoE, level of evidence; NSAIDs, non-steroidal anti-inflammatory drugs; TNFi, tumour necrosis factor inhibitor.**