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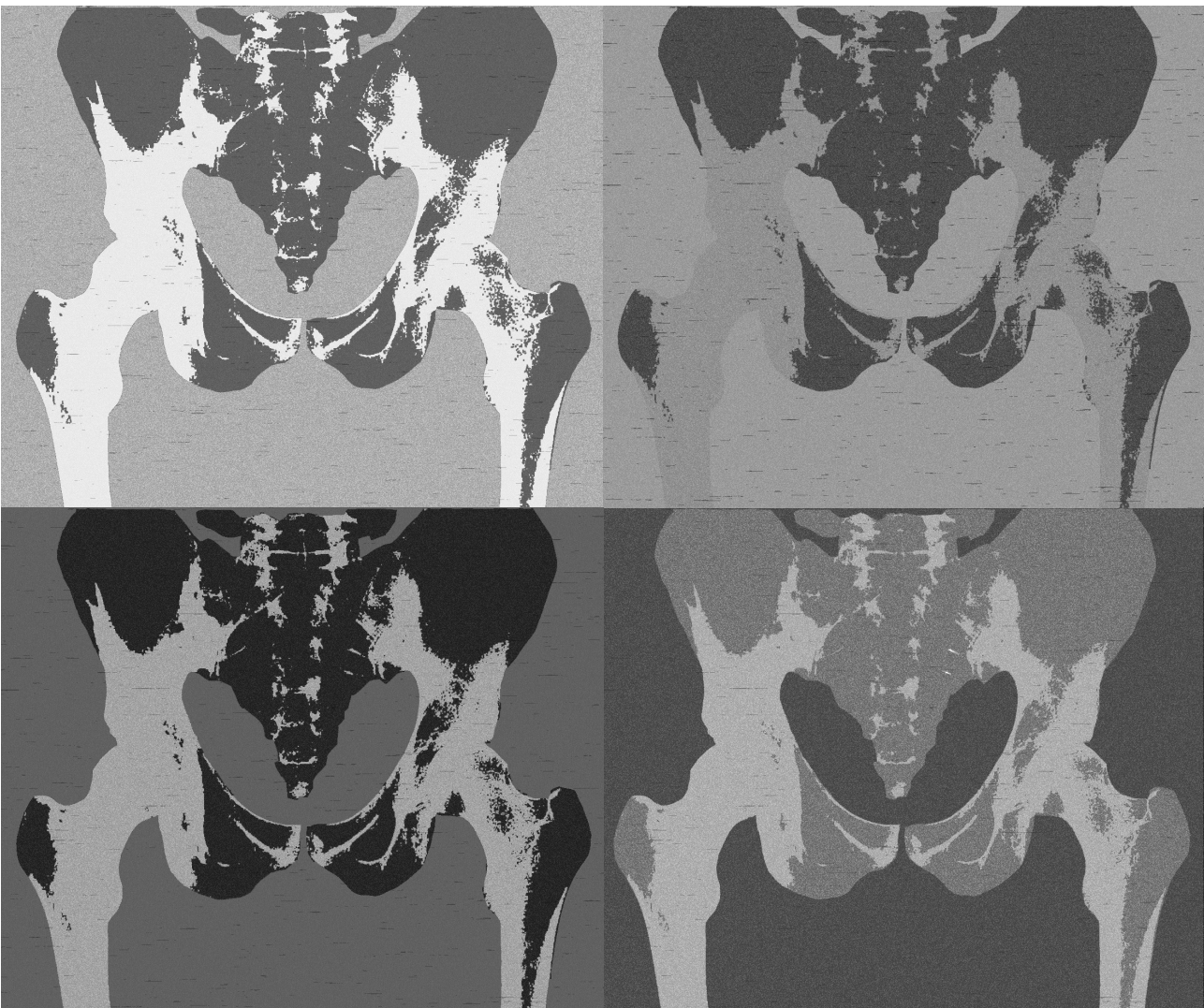
Summary and general discussion



Summary and general discussion

Although our understanding of the expressions and mechanisms of SpA is far from complete, major advances have been made over the past decades. The need for earlier diagnosis was addressed by including MRI in the diagnostic process as well as by putting more emphasis on HLA-B27 in the diagnostic process. The development of new classification criteria, with the major objective to ensure the identification of non-radiographic types of SpA, is a further aid in classifying patients in early phases of the disease. The recently by ASAS proposed classification criteria sets for SpA included MRI for the first time [1, 2]. With the help of MRI, patients can be classified earlier in the disease stage since MRI can provide evidence of inflammatory sacroiliitis. Furthermore, in 2006 ASAS/EULAR published management recommendations to provide guidance for monitoring and treatment of AS patients. However, the performance of the ASAS classification criteria, including (the role of) imaging (both MRI and radiographs), required thorough evaluation. Moreover, as the number of clinical trials and publications on AS therapy has steadily increased over the first decade of the millennium, the ASAS/EULAR recommendations for the management of AS needed an update. The performed studies described in this thesis have contributed to the continuously developing field of SpA. The main results and conclusions are summarized and discussed in this chapter.

Part I: Early recognition and classification criteria of spondyloarthritis

The performance of the various developed classification criteria for SpA (mNY, Amor, ESSG, ASAS axial SpA, ASAS peripheral SpA, and the CASPAR criteria (for PsA only)) [1-6] was tested in a group of patients with predominantly axial complaints included in the SPondyloArthritis Caught Early (SPACE)-cohort (**chapter 2**) and in a group of patients with predominantly peripheral complaints (**chapter 4**) included in the Leiden Early Arthritis Clinic (EAC)-cohort [7]. In the EAC-cohort, patients diagnosed with PsA and peripheral SpA by the treating rheumatologist, and a control group matched on age, gender and symptom duration were selected and studied. In this group of PsA and peripheral SpA patients, the ASAS peripheral SpA criteria and CASPAR criteria had substantial overlap by classifying the same patients. In the peripheral SpA subgroup, the ASAS peripheral SpA criteria outperformed all other classification criteria, and in the PsA subgroup, the CASPAR criteria outperformed all other criteria. The diagnosis by the rheumatologist served as external standard. However, this setting is neither representative for all peripheral SpA patients nor for the whole concept of SpA since the EAC-cohort does not include patients with dactylitis or enthesitis or patients with predominantly axial complaints. This is reflected in the modest sensitivities of all classification criteria found in this analysis. Thus, in daily practice rheumatologists include a wider group of patients in the SpA disease spectrum than defined in the classification criteria, thereby underscoring the fact that classification criteria are not diagnostic criteria. Yet, it is very reassuring that the specificities of all criteria sets are in accordance with the reported specificities in the original validation cohorts [1-6]. This is especially of importance for the ASAS peripheral SpA criteria as these criteria are quite new and there was a fear that they might be insufficiently specific. Moreover, the results of **chapter 4** were recently confirmed in the ESPERANZA-cohort, which is developed in Spain to facilitate early diagnoses of SpA by creating early SpA units with standard operating procedures, and to improve the knowledge and practical skills of GPs and specialists in the field of SpA. Patients with complaints (IBP or asymmetrical arthritis (preferably in the lower limbs) or spinal/joint pain in combination with one other SpA-feature) were included. Thereby, a slightly different population is created than the population in the EAC-cohort and the ASAS validation cohort, but the sensitivity and specificity of the ASAS peripheral SpA criteria were very similar (sensitivity of 56%, specificity of 85%) [8].

We also tested the existing classification criteria in patients with predominantly axial complaints included in the SPACE-cohort. The SPACE-cohort is an ongoing prospective longitudinal observational cohort including patients with back pain ≥3 months but ≤2 years with the onset of symptoms <45 years, which is extensively described in **chapter 2**. At baseline, all patients in the SPACE-cohort undergo a diagnostic work-up including imaging (MRI and radiographs of the SI-joints and spine), laboratory tests (including HLA-B27 testing) and physical examination and history taking. In **chapter 2** we showed that at baseline almost 60% of the patients in the SPACE-cohort fulfilled any classification criteria set (mNY, Amor, ESSG, ASAS axial SpA criteria) [2-5]; almost 40% fulfilled the ASAS axial SpA criteria [2]. The ASAS axial SpA criteria outperformed all other sets (including modifications of Amor and ESSG by adding MRI) with respect to sensitivity, specificity, positive and negative likelihood ratio (LR+ and LR-). Again, the diagnosis by the rheumatologist served as external standard. As the percentage of patients with axSpA according to the ASAS axSpA criteria in the SPACE-cohort appears to be high, it could be argued that our observed prevalence of axSpA is influenced by referral bias; e.g. that due to increased awareness among referring physicians about the SPACE cohort over time, patients from areas other than the Leiden area are referred to the LUMC or that only patients with a high suspicion of axSpA are referred.

However, the percentage of axSpA among all referred patients over the years was similar, and the percentage of referrals from outside the Leiden area was also similar over time. Moreover, 33 of the 157 patients (21.0%) included at baseline had none or only one less specific SpA feature. This indicates, but does not prove, that there is no referral bias, thereby suggesting that the observed prevalence of axSpA could be generalized to primary care (**chapter 2**). Moreover, very similar results regarding the performance of the ASAS axial SpA criteria are recently found in another study, also including patients with back pain ≥3 months, onset <45 years, conducted by Moltó *et al.* among rheumatologists working in office-based and hospital-based practices in France [9].

As there are indications that not all rheumatologists as well as registration authorities (U.S. Food and Drug Administration (FDA)) [10, 11] do appreciate the validity of the clinical arm of the ASAS axial SpA criteria as similar to the imaging arm, we compared patients fulfilling the clinical arm to patients fulfilling the imaging arm (both patients with radiographic sacroiliitis and patients with inflammatory sacroiliitis on MRI) in **chapter 2**. Noteworthy, patients in both arms were remarkably similar with respect to the presence of most SpA-features and level of disease activity (BASDAI and ASDAS). Similar comparisons were made in the DESIR-cohort and in the ABILITY-1 trial. The latter is a randomized controlled trial performed in patients with nr-axSpA (fulfilling the ASAS axSpA criteria but not fulfilling the mNY criteria) to evaluate the efficacy and safety of adalimumab in those patients [12]. The results of these studies were comparable to the results we found in the SPACE-cohort that patients fulfilling the clinical arm and patients fulfilling the imaging arm are very similar [12, 13]. Nevertheless, the level of confidence about the diagnosis indicated by the rheumatologist in the SPACE-cohort is lower in patients fulfilling the clinical arm than in patients fulfilling the imaging arm (**chapter 2**). This seems to indicate that rheumatologists heavily base their diagnosis on positive imaging. This concept is confirmed in the study by Moltó *et al*. mentioned above, pointing out that (radiographic) sacroiliitis has the highest LR+ on the diagnosis of SpA according to rheumatologists [9].

For further analyses in the SPACE-cohort, patients are classified as no-SpA or axial SpA based on the ASAS axSpA criteria (the best performing classification criteria) as classification criteria are by definition exactly defined and therefore reproducible while the diagnosis of the rheumatologist is not. Of the axSpA patients, approximately 80% have IBP, and the other way around, 56.7% of the patients without SpA have IBP, thereby showing that - at least in the SPACE-cohort - IBP is not a very useful feature to discriminate between axSpA patients and patients without SpA (**chapter 2**). These results are in line with results reported

before [14, 15]. Nevertheless, IBP history taking is cheap and can be useful in the diagnostic process in combination with other SpA-features (the more clinical items suggestive of SpA, the more likely the diagnosis) [16]. Moreover, some items of IBP, like age at onset ≤35 years, are more important than other items by having a higher calculated LR+ on the diagnosis of axial SpA [17]. However, the interpretation of (items) of IBP differ from person to person, reflected in low agreement on whether a patient is suffering from IBP or not [14, 18].

Nonetheless, in the previously developed ESSG criteria but also in the diagnostic Berlin algorithm, IBP was used as (one of the) entry criteria [4, 19]. As the Berlin algorithm is the only available diagnostic tool, this challenged us to propose two modifications of the Berlin algorithm, presented in **chapter 3**. In modification 1, the first step of the algorithm – fulfillment of the ASAS IBP criteria – was slightly changed. Instead of ≥4 out of the 5 criteria, patients need to fulfill ≥3 out 5 criteria. Modification 2 slightly changed the structure and the set of SpA-features by deleting IBP as obligatory entry criterion and adding it as a SpA-feature. This resulted in three entry groups based on the requirement of ≥4, 2-3 and 0-1 SpA-features. The performance of the (modified) algorithms, was tested against fulfillment of the ASAS axSpA criteria, the disease probability based on the likelihood ratio product [19, 20] and the diagnosis by the rheumatologist as external standard due to the lack of a true gold standard. Modification 1 resulted in a major increase in sensitivity, at the cost of little specificity. With modification 2, the number of missed axSpA diagnoses by the algorithm even further decreased. Additional adjustments that might improve the diagnostic algorithm even more could be contemplated; rheumatologists could consider performing an MRI in HLA-B27 negative patients who do have 2-3 other SpA-features, especially male patients [21, 22]. As it is now stated in the algorithm, those patients leave the algorithm ('consider other diagnosis'), however, if the MRI is positive they would fulfill the ASAS axSpA criteria. Moreover, as this algorithm is developed to guide rheumatologists in the diagnostic process, it will often be applied in patients with relatively short symptom duration. The usefulness of performing conventional radiographs of the SI-joints as a first step could therefore be challenged, reflected by the high number of negative radiographs in both the SPACE-cohort and the ASAS-cohort. Nevertheless, modification 2 of the algorithm might be a useful tool for rheumatologists in daily practice. The Dutch Society for Rheumatology (Nederlandse Vereniging voor Reumatologie (NVR)) recently published new guidelines for the diagnosis and treatment of axSpA in which the modified algorithm is included [23].

Although the tools available to rheumatologists for classification and diagnostic purposes improved a lot over the last years, one of the unmet needs is the referral of the most appropriate patients by physicians and health professionals to the rheumatologist. Referring physicians have only limited knowledge of manifestations belonging to SpA [24], illustrated by the poor agreement regarding the evaluation of IBP by referring physicians and rheumatologists (κ=0.04 to κ=0.20) [14, 18]. Therefore, it is a challenge for referring physicians to recognize patients with a suspicion of having SpA who should be referred to a rheumatologist. Several (complex) referral strategies have been developed in order to early identify patients with possible SpA. All strategies performed well in research settings with instructed GPs, yielding 24% to 45% SpA patients [14, 25-28]. However, the limited knowledge of referring physicians poses a challenge on successful implementation of referral strategies in the common daily primary care setting [24]. Hence, it might be useful to consider an easy referral structure instead of complex strategies, by just referring patients with back pain ≥3 months with the onset of symptoms <45 years, like the eligibility criteria of the ASAS axSpA criteria. At least in the SPACE-cohort - with the additional restriction of a maximum symptom duration of ≤2 years - and in the study by Moltó *at al*. these criteria yield high percentages of SpA (41.4% and 35.1%, respectively) (**chapter 2**) [9]. However, it remains to be seen whether this would be successful in other centers or in countries with other healthcare systems, and therefore more research is needed.

Another important related question is which patients are erroneously not referred to the rheumatologist by applying these referral strategies [14, 25-28]. We tried to answer this question by testing the performance of various referral strategies in the SPACE-cohort, even though the SPACE-cohort might not be ideal to sort out this question as patients already had been referred [29, 30]. Remarkably, almost all non-referred patients that fulfilled the ASAS axSpA criteria had (radiographic) sacroiliitis [29, 30].

Although major improvements have been achieved in classifying and diagnosing patients, more research and education is needed, starting with warranted improvements in referring the right patients to the rheumatologist. This could be achieved by (further) educating referring physicians about SpA-features. Furthermore, both referring physicians and rheumatologists could be trained in acknowledging that axSpA should not be ruled out if IBP is absent. If performance of the current strategies appears to be insufficient - even after educating referring physicians - eventually the development of new referral strategies could be considered. These strategies offer the possibility of referring patients with positive imaging without the necessity of performing imaging in daily practice (a proxy for positive imaging is needed), since with the current strategies precisely imaging positive patients are often not referred.

Moreover, only diagnostic tool for rheumatologists, the ASAS modified Berlin algorithm, is not validated in other cohorts than the two validation cohorts yet. In addition to this necessary validation, other improvements of the algorithm could be considered. For example, it could be investigated whether it is useful to make a distinction in the group of HLA-B27 negative patients with 0-1 SpA-features to decide on whether or not performing MRI. Patients with 1 feature could fulfill the ASAS axSpA criteria if imaging is positive while the patients without any SpA-features will never fulfill the ASAS axSpA criteria. Moreover, performing conventional radiographs of the SI-joints after medical history taking and physical examination - instead of before - could be considered.

Moreover, long-term follow-up studies are required in order to study outcomes in patients fulfilling the clinical arm and patients fulfilling the imaging arm of the ASAS axSpA criteria, and to compare the long-term outcomes of patients in both groups. This will help in understanding the disease and in concluding on whether it was the right decision to include the clinical arm in the ASAS axSpA criteria. The clinical arm was included as it gave the best balanced sensitivity and specificity compared to including the imaging arm only [2]. Moreover, more knowledge will assist in considering potential adjustments of the ASAS axSpA criteria like weighting the various SpA-features (as in the ASAS modified Berlin algorithm) since some SpA-features, such as a 'positive family history for SpA' and 'HLA-B27 positivity' are more strongly correlated than others.

Part II: The role of imaging in the early diagnosis of spondyloarthritis

MRI has proven its usefulness in diagnosing and classifying SpA patients over the last years. Nevertheless, the newly acquired prominent role of MRI as well as the role of conventional radiographs are currently under debate. The discussion regarding the role of radiographic sacroiliitis has its origin in the knowledge that it is challenging to recognize radiographic sacroiliitis. The undulating articular surface and the complex anatomy of the SI-joints by a 2-dimensional imaging technique can result in misinterpretations [31, 32]. Recently, the poor reliability of evaluating conventional radiographs was emphasized in post-hoc analyses on the data of the ABILITY-1 and RAPID-axSpA pivotal clinical trials for the registration of TNF-blockers in patients with nr-axSpA [12,33-35]. The analysis in ABILITY-I pointed out that 37% of the patients classified as nr-axSpA by local readers were reclassified as AS by fulfilling the mNY criteria according to central readers [12, 34]. In the RAPID-axSpA trial a similar analysis resulted in reclassification of 36% of the patients; 26% of the nr-axSpA patients according to local readers were reclassified as fulfilling the mNY criteria according to central readers,

and 10% of the mNY fulfilling patients by local readers were reclassified as nr-axSpA based on the central reading [33, 35].

We performed similar analyses in the DESIR-cohort (**chapter 5** and **chapter 6**), in which imaging evaluations by both local readers and central readers are available. In daily practice the diagnosis of AS is based on the judgment of local radiologists and/or rheumatologists, while in cohorts and clinical trials the radiographs are usually judged by one or more trained central readers. The comparison described in **chapter 5** on the presence/absence of radiographic sacroiliitis by local readers versus central readers revealed that the agreement was only moderate (κ=0.55). The local readers primarily overrated sacroiliitis in comparison with central readers as external standard, resulting in an unacceptably high percentage (41.5%) of false-positive diagnoses of AS in daily practice. Only a small minority of patients with a classification of AS according to central readers is not recognized in daily clinical practice (7.5%). Even in patients with bilateral involvement and patients with at least one fused SI-joint major discrepancies are seen between local readers and central readers. Moreover, interreader agreement between the two central readers was also only moderate (κ=0.54), indicating that evaluating SI-joints on radiographs is very difficult and that training does not improve the agreement substantially. But where misclassification by local readers almost exclusively consisted of overclassification of positive cases, the disagreement between the two central readers was more balanced in two directions.

Thus far, there is no data on this aspect for sacroiliitis on MRI, except for the data of the DESIR-cohort presented in **chapter 6**. In contrast to the moderate agreement regarding radiographic sacroiliitis, agreement regarding sacroiliitis on MRI between the two central readers as well as between the local readers and the central readers is substantial (κ=0.73 and κ=0.70, respectively). Potentially 163/582 patients (28.0%) in whom the MRI and/or radiograph reading was different between the local readers and central readers, could have been classified differently according to the ASAS axSpA criteria. Yet, only 46/582 patients (7.9%) were classified differently. These results point out the robustness of the ASAS axSpA classification criteria to differences in reading of the images. This is mainly due to the clinical arm; patients fulfilling the clinical arm will always fulfil the clinical arm, regardless of the imaging results, as HLA-B27 status will not change.

Given the only moderate reliability in conventional radiograph reading and the substantial reliability in MRI reading, some experts in the field argue that the option of leaving out conventional radiographs completely and conducting MRI only should be considered. As the current definition of a positive MRI is based on the presence of inflammatory lesions only, this discussion is becoming even more interesting if structural lesions (erosions, ankylosis and sclerosis) on MRI are taken into account as well. To be able to evaluate the potential additive value of adding structural lesions to the definition of a positive MRI, it is first important to know whether structural lesions can be detected reliably on MRI. Therefore, the performance of MRI in the detection of structural lesions in the SI-joints was tested against the conventional radiographs as gold standard. Agreement varied from κ=0.11 to κ=0.15 for erosions, from κ=0.16 to κ=0.46 for sclerosis, and from κ=0.08 to κ=0.85 for ankylosis (partial or total) in the GESPIC-cohort and SPACE-cohort [36, 37]. Overall, agreement is poor; more erosions and less sclerotic lesions are detected on MRI compared to conventional radiographs [36, 37]. These comparisons should be extended and repeated with an alternative external standard such as CT.

The incorporation of various combinations of structural lesions and fatty depositions on the definition of a positive MRI is presently being investigated in both the SPACE-cohort and the DESIR-cohort, but should be investigated and validated in other cohorts as well, especially in patients with longer symptom duration. Before we can conclude on the role of conventional radiographs and structural lesions on MRI, we will have to wait for the results of these studies. In the meantime, we investigated in the DESIR-cohort the possible consequences

of this proposal of leaving out conventional radiographs and using the current definition of a positive MRI based on inflammatory lesions only (**chapter 6**). Taking into account the complete ASAS axSpA criteria including the clinical arm, this would result in only 11 to 14 missed patients (1.9-2.4%using either the local reading or the central reading) as those patients only fulfill the imaging arm by having radiographic sacroiliitis only (and not inflammatory sacroiliitis on MRI). However, it should be stated immediately that this is in an early cohort and this may be different in patients with more advanced disease.

MRI is also used to quantify inflammation in the SI-joints and spine, for example by using the SPARCC-score. We tested the metric properties of the SPARCC-score of the sacroiliac joints in the SPACE-cohort in **chapter 7.** We found out that a SPARCC-score of 2 as cut-off value is the best equivalent of the ASAS definition of a positive MRI. This cut-off value can be used (in clinical trials) to create a dichotomous MRI variable of potential prognostic interest. Additionally, we calculated smallest detectable changes (SDCs), which in this study were close enough to the proposed minimally important change (MIC) of 2.5 SPARCC-units to add credibility to a cut-off level of 2.5 units representing a true change rather than only measurement error. A large proportion of the SPARCC-score changes seen in the patients in the SPACE-cohort could be considered as noise as these changes are smaller than the calculated SDCs (62.9% and 45% (3 months, campaign 1 and 2) and 39.1% (1 year in campaign 2)). Surprisingly, true (>SDC) changes in SPARCC-score over time (both increases and decreases) were frequently observed while patients are on stable treatment. This observation strongly suggests that MRI-activity fluctuates over time.

Other intriguing matter is the hypothesis of inflammation being the inciting cause of structural lesions including ossification. Prospective long-term follow-up data is necessary to study the possible relationship between inflammation and structural lesions in more detail [38, 39], in both the SI-joints and spine. To get more insight in why some patients do develop spinal lesions and others do not, information is needed on the prevalence of spinal lesions (inflammatory and structural), especially in patients without (radiographic) sacroiliitis. Several studies already addressed this question, but the results are inconclusive as the prevalence of spinal lesions varies with age and disease duration [40-45]. In addition, it is questioned whether the results of MRI of the spine should be taken into account in the diagnostic and/or classification process, which could be of particular interest in patients without (radiographic) sacroiliitis. To address these research questions as well as other questions, long-term follow-up data is currently being collected in, among others, the SPACE-cohort and DESIR-cohort.

Part III: Treatment of spondyloarthritis and ankylosing spondylitis

ASAS together with EULAR published recommendations for the management of AS in 2006. As the number of clinical trials and publications on AS therapy is increasing, ASAS developed an update of the first recommendations for the management of AS. These recommendations are described in **chapter 11**, based on systematic literature reviews (**chapter 9** and **chapter 10**) as recommended by the EULAR standard operating procedures for management recommendations [46]. In the title, ASAS has restricted the recommendations to AS since the evidence from trials in axSpA patients is currently limited and this was an update of the previous recommendations on AS (and not axSpA). Nevertheless, the project group unanimously agreed that these recommendations could equally be applied to patients with axSpA. First because AS is part of the total group of axSpA, and second because all available data indicated that efficacy was at least as good in patients with nr-axSpA as in patients with AS. And indeed, this has been confirmed in all trials that have been published since. As described in **chapter 11**, ASAS recommend tailored treatment, taking into account all aspects of the disease including peripheral and extra-articular manifestations, level of disease activity, gender, and comorbidities etc. Disease should be

monitored regularly, according to the clinical presentation as well as the ASAS core set for assessment in clinical practice [47]. Treatment should consist of non-pharmacological and pharmacological treatment. Non-pharmacological treatment is the cornerstone, comprising patient education and regular exercise. The review on non-pharmacological treatment and non-biological drugs described in **chapter 9** pointed out that home exercises have positive effects on physical function (BASFI), patient reported disease activity (BASDAI), pain and spinal mobility, but that physical therapy with supervised exercises, either land or water based, either individually or in a group, are more effective than home exercises. This is adopted in the ASAS recommendations (**chapter 11**).

NSAIDs, including coxibs, are recommended as first line drug to relief pain and stiffness for both short-term and prolonged periods of treatment (**chapter 9** and **chapter 11**), and these should be taken in an anti-inflammatory dose [48]. ASAS recommends patients with persistently active, symptomatic disease to use NSAIDs continuously (**chapter 11**) as continuous therapy may be superior to on-demand therapy on the prevention of new bone formation [49]. After the update of the ASAS recommendations was published, a post-hoc analysis was conducted in this randomized trial comparing continuous to on-demand NSAID treatment, revealing that solely patients with elevated acute phase reactants will benefit from continuous treatment with NSAIDs [50]. Additionally, a study was recently performed in the German Spondyloarthritis Inception Cohort (GESPIC), investigating the influence of NSAIDs intake on radiographic spinal progression over 2 years in both AS and nr-axSpA patients. The results showed that a high NSAIDs intake is associated with retarded radiographic spinal progression in AS patients while this effect was less evident in nr-axSpA patients, probably due to a low grade of new bone formation in the spine at this stage [51].

Analgesics might be considered for residual pain after previously recommended treatments have failed, are contraindicated and/or poorly tolerated. Glucocorticoid injections directed to the local site of musculoskeletal inflammation may be considered, but systemic glucocorticoid use for axial disease is not supported by evidence. There is no evidence for the efficacy of DMARDs, including sulfasalazine and methotrexate, for the treatment of axial disease, however, sulfasalazine may be considered in patients with peripheral disease (**chapter 11**).

The results of the systematic literature review on biologics are described in **chapter 10**. TNF-α inhibitors should be given to patients with persistently high disease activity despite conventional treatments according to the ASAS recommendations [52]. Overall, all TNF-α inhibitors available for AS have proved to be effective on BASDAI, BASFI and BASMI, both in AS patients with established disease as well as in nr-axSpA patients, especially in patients with elevated CRP and/or inflammation on MRI. In the presence of IBD, a difference in gastrointestinal efficacy needs to be taken into account. There is no evidence to support the obligatory use of DMARDs before or concomitant with TNF-α inhibitors in patients with axial disease. Switching to a second TNF-α inhibitors might be beneficial, especially in patients that lost response (**chapter 10** and **chapter 11**).

Moreover, ASAS recommend considering total hip arthroplasty in case of refractory pain or disability and radiographic evidence of structural damage, independent of age. In case of severe disabling deformity, spinal corrective osteotomy may be considered (**chapter 9** and **chapter 11**).

Despite the fact that there is conclusive evidence that TNF-α inhibitors can dramatically improve disease activity (including inflammation on MRI) and functional capacity, its use is associated with high costs and is not suitable for all patients in terms of safety and increased risk of infections. Therefore, ASAS developed recommendations for the use of TNF-α inhibitors in 2003 [53]. Those recommendations have been updated twice already [52, 54]. Moreover, many countries developed national guidelines for the use of TNF-α inhibitors, either or not based on the ASAS recommendations. In **chapter 8**, the national guidelines of 23 countries worldwide

were compared, revealing that despite some differences, there is general consensus about the use of TNF-α inhibitors in AS. In addition, there is evidence that patients with nr-axSpA show good responses to TNF-α inhibitors, although the number of trials is limited and the sample sizes in those trials are relatively small [12, 33, 42, 43, 55]. Furthermore, only patients with high disease activity and/or elevated acute phase reactants and/or a positive MRI were included in those trials [11, 31, 40, 41, 51]. High disease activity as measured by the ASDAS, elevated acute phase reactants and a positive MRI are all identified as predictors for good response to treatment with TNF-α inhibitors [56]. Recently, adalimumab and certolizumab are approved by the European Commission for the treatment of adults with severe nr-axSpA, who have had an inadequate response to, or are intolerant to NSAIDs, but only in those nr-axSpA patients that show objective signs of inflammation by elevated CRP and/or MRI [57, 58]. Still, in many countries, patients with active, severe axSpA refractory to NSAIDs are only eligible for treatment with TNF-α inhibitors if imaging shows signs of sacroiliitis. However, the only difference between nr-axSpA and axSpA/AS is the presence of (radiographic) sacroilitis, which is proven to be challenging to reliably evaluate (**chapter 5** and **chapter 6**) [32]. Therefore, more research is warranted on the (long-term) effects of TNF-α inhibitors in early nr-axSpA patients, including patients without a positive MRI. In addition, long-term outcomes of head-to-head comparisons of different treatments are needed, focusing on the development of structural lesions. For example, head-to-head comparisons of the different available TNF-α inhibitors could be studied, with or without concomitant use of, amongst others, NSAIDs. In the same manner, TNF-α inhibitors could be compared directly to other types of drugs, like NSAIDs and bisphosphonates [59]. Moreover, the effect of various treatment strategies, like ASDAS-steered treatment, could be investigated. Furthermore, as there is evidence that a recent onset of symptoms is associated with higher response rates, and, importantly, a greater likelihood of a very good response, the existence of a 'window of opportunity' could be investigated [56, 60]. If a 'window of opportunity' exists, it would be favorable in achieving clinical and biological benefits as well as preventing structural damage, especially in recent-onset, active axSpA patients with MRI or laboratory signs of inflammation [60].

In conclusion, patients with SpA can be recognized earlier with the recent developments, thereby offering better treatment options and thus better outcomes. However, in order to further improve care of SpA patients, we cannot afford to stand still, but we have to keep on moving, just like patients with SpA.

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