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Axial spondyloarthritis including ankylosing spondylitis

AS is a prevalent rheumatic condition with incidence rates varying from 0.44 to 0.73/100 000 and prevalence rates of 0.007 to 1.7% [1], and it shows some variability related to aspects such as the genetic background of the population and regional factors [2]. It belongs to the spectrum of spondyloarthritis (SpA), of which axial SpA (axSpA) and PsA are the main diseases [3]. According to the Assessment of SpondyloArthritis international Society (ASAS) 2009 criteria [4], AS can be classified into two subgroups: radiographic axSpA and non-radiographic axSpA (nr-axSpA) [5].

AxSpA is a complex immune-mediated health condition with characteristic clinical features such as enthesitis, sacroiliitis and spondylitis, and extra-articular manifestations such as anterior uveitis, psoriasis and IBD [4]. The pathogenesis of axSpA is incompletely understood, but genetics plays a major role. AS is strongly associated with inheritance of the HLA allele B27 (*HLA-B27*) [6], but other genetic factors influencing antigen presentation and the IL-23/17A pathway are also very likely to be involved [7]. This is dealt with in detail in the contribution of Simone and colleagues in this supplement. Importantly, they stress that effective therapeutic interventions use targets of inflammatory cytokines (e.g. TNF-α, IL-17 A) that are produced by innate and adaptive immune cells.

AxSpA is now considered to be one disease [7] and this terminology alone is sufficient for diagnosis. There are some interesting differences between axSpA and nraxSpA: for example, established AS is more common in men than in women, whereas there is a female predominance of nr-axSpA [5]. Furthermore, patients with AS, in comparison with patients with nr-axSpA, have more inflammation (as shown by increased CRP levels and on MRI) and more structural changes (syndesmophytes, ankylosis). The diagnosis of axSpA is often delayed as symptoms can be confused with other more common but usually less serious disorders such as non-specific chronic low back pain—a frequent complaint that patients have when visiting general practitioners, orthopaedists and physiotherapists [7]. Furthermore, typical radiological changes of the sacroiliac joints may only become visible after some time, often years, of ongoing inflammation [7]. However, 20–30% of patients with axSpA develop structural changes within the first 2 years of disease [7, 8]. The main clinical symptoms of patients with axSpA are pain and stiffness of the back—predominantly the lower back and pelvis, although any part of the spine can be involved [7, 9]. The most characteristic symptom of axSpA is inflammatory back pain, which can only be clinically defined (i.e. it cannot be defined by laboratory tests such as CRP or ESR). Patients with axSpA complain about morning back stiffness, which improves with exercise but not with rest [9]. In addition, or alternatively, they report waking at night (mostly in the second half of the night) due to back pain, which improves if they get up and move around [9, 10]. The recently published ASAS health index for AS covers the main complaints of patients suffering from axSpA [11].

According to the modified New York criteria [12], which are still widely used, the hallmark for a diagnosis of AS is the detection and grading of sacroiliitis using conventional radiographs [4]. The newer ASAS classification criteria have been designed to cover all patients with axSpA based on their predominant axial involvement, irrespective of the presence or absence of radiographic changes in the sacroiliac joints. Thus, MRI and *HLA-B27* have been included in the criteria, which, of course, still also include other classical clinical features of SpA such as enthesitis and extra-articular manifestations such as psoriasis [4].

Several referral systems have been proposed for patients with AS. The simplest, which was developed on a data-driven basis, concentrates on just three items: buttock pain, improvement with movement and psoriasis. Patients with chronic back pain that started before the age of 45 years, who also have two or three of these symptoms, can be directly referred to a rheumatologist. Patients with none or one of these symptoms but with a positive *HLA-B27* test are also recommended for referral to a rheumatologist [13]. This proposal is currently undergoing further evaluation.

There are several guidelines with recommendations for the management of patients with axSpA. The main set, from ASAS/EULAR, has been recently updated [14]. After physiotherapy, NSAIDs and biologic DMARDs such as the TNF inhibitors (TNFis) are frequently used in the treatment of AS, whereas conventional synthetic DMARDs are not efficacious for axial disease [14]. All TNFis are approved for AS, and all but infliximab are approved for nr-axSpA—for this indication, either elevated CRP or a positive MRI is required. The first biosimilars for infliximab, etanercept and adalimumab have now been approved by the European Medicines Agency and the US Food and Drug Administration. So far, the only non-TNFi approved for AS is the IL-17 A inhibitor secukinumab: secukinumab is not approved for nr-axSpA [15]. Whether this mechanism of action is any different from blocking TNF-α in its potency to inhibit progression in AS is not clear [16], but a head-to-head trial is ongoing. Apparently, TNFis appear to need $>$2 years until an

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effect on new bone formation can be documented [17]. However, the sensitivity to change of the modified Stokes AS spinal score scoring system is limited. Studies with other IL-17 inhibitors (such as ixekizumab) and specific IL-23 inhibitors (such as guselkumab or tildrakizumab) are planned or ongoing in patients with AS. As it stands now, IL-6 and IL-23 antagonists do not seem to work in AS [18]. The Janus kinase inhibitor tofacitinib has shown some efficacy in AS, but more studies are needed [19]. The recent trials on biologics and small molecules are well reviewed by Tahir in this supplement. As nicely highlighted by Noureldin and Barkham in this supplement, who also discuss unmet need aspects in the management of axSpA, there is strong evidence that NSAIDs have good efficacy in the treatment of patients with axSpA [14]: the effect is even used as a tool for diagnosis and classification [4]. There is little difference between the different agents, although celecoxib has some limited advantage over other NSAIDs in terms of gastrointestinal side effects [20]. The identification of risk groups is of utmost importance, particularly regarding cardiovascular safety [21].

There are conflicting results regarding the effect of NSAIDs on radiographic progression: whereas one study with a coxib showed a significant effect when continuous dosing was used [22], another with diclofenac did not report any difference *vs* an on-demand strategy [23]. Interestingly, in the diclofenac trial, only patients with elevated CRP levels showed the described benefit [23], which is unlikely (although it is possible) to be due to chance.

One of the major unmet needs in the management of axSpA is the lack of strategy studies—including studies related to the treat-to-target principle. This is elegantly discussed in the contribution of Helena Marzo-Ortega and colleagues in this supplement.

From the patients' perspective, the reduction of pain and stiffness and the preservation of function and mobility, along with employment and participation in society, are the most important aims [14]. This important topic is nicely discussed by Packham and colleagues in this supplement, who also stress that the impact of axSpA on patients' lives can be improved by different non-pharmaceutical interventions, including psychological counselling and coping strategies.

Since it may take many years for functional changes to occur as a result of new bone formation, reductions in disease activity and inflammation are the main targets in the first years of treatment of patients with axSpA. As it stands now, it does seem likely that we will be able to decelerate new bone formation through early interventions. Scientific research should put more focus on strategy trials that show that this is indeed the case.

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