AS and related SpAs are relatively common and highly heritable arthropathies, the pathogenesis of which is still poorly understood [1]. I should perhaps declare a personal, as well as a professional, interest in the field: I entered medical school 50 years ago, while suffering from AS that had gone undiagnosed for the previous 4 years. It took another 2 years (when I was first seen by an internist, a Professor of Medicine) for the disease to be finally diagnosed. I remember the dramatic efficacy of butazoldine, one of the early NSAIDs, which not only enabled me to finish my medical education, but also allowed me to join the Pakistan Army Medical Corps without revealing my illness, in my zeal to serve my country when it was attacked. But I may add that, during the 6 years before diagnosis, I had received many wrong treatments, including a year of treatment with streptomycin (which I self-injected), along with isoniazid (INH) and para-aminosalicylic acid (PAS), for a presumed diagnosis of tuberculosis. When this treatment did not make any difference to my symptoms, I was treated with i.v. infusions of honey, imported from West Germany. This also had no effect on my disease, but I think it took away any bitterness I may have had towards the Professor of Orthopedics for my delayed diagnosis and wrong treatment, and made me ever so sweet. I may also add that I underwent so many radiographs of my pelvis and back during the first 6 years that I must have glowed at night (I later did develop cancer of the kidney).

I am happy to say that thanks to many advances over the past 50 years, things have improved markedly for patients with AS and related SpA. I have previously highlighted some of the important advances of the first 40 years [2], so, in this editorial, I will briefly highlight some of the dramatic advances of the past decade, mainly in the fields of outcome assessment, early diagnosis and effective management, genetic predisposition and understanding the aetiopathogenesis of the diseases.

It is generally recognized that the Assessment of Spondyloarthritis International Society (ASAS; www.asas-group.org), founded by a handful of us in 1995 under the able leadership of Sjef van der Linden, has played a pivotal role in many of the recent advances. For example, ASAS established the basis for outcome assessment and developed assessment tools that dramatically expedited the research on TNF-antagonists in these diseases. Later, it expanded its mission to promote and support clinical and translational research. Its ultimate goal is to improve the well-being and outcome of patients with AS and related forms of SpA. The means to achieve this goal include increasing awareness of this group of diseases, facilitating early diagnosis, developing and validating assessment tools and evaluating treatment modalities. Some of the society’s recent achievements include the development of the new ASAS criteria for axial and peripheral SpA [3], the ASDAS [4], the ASAS handbook [5] and the ASAS slide deck.

The average diagnostic delay in AS—about 6 years—is attributable mainly to the late appearance of definite sacroilitis on radiographs [1, 3–6]. However, progress has been made in recent years towards earlier diagnosis by using MRI to visualize sacroilitis in patients with inflammatory back pain but normal radiographs [1, 3–6]. Both HLA-B27 and sacroilitis on MRI play a major role in the recently proposed diagnostic algorithm (which is meant to be applied in individual patients) [7], as well as in the new ASAS classification criteria for non-radiographic axial SpA in which sacroilitis on MRI has been given as much weight as sacroilitis on radiographs [3, 5]. The ASAS criteria for axial SpA will facilitate the studies and clinical trials in early axial SpA by helping identification of patients with early disease. (Although there are as yet no diagnostic criteria for SpA, clinicians should not be tempted to misuse these criteria as diagnostic criteria.) Most recently, the ASAS has developed new criteria for peripheral SpA that may better reflect the current view on peripheral SpA [8].

In terms of disease activity, the ASAS-endorsed ASDAS is a validated, highly discriminatory instrument for assessing disease activity in AS in comparison with the BASDAI. Its components include back pain, duration of morning stiffness, patient global assessment, peripheral joint complaints and CRP or ESR (CRP is preferred over ESR) [4, 9]. Cut-offs for defining a clinically important improvement and a major improvement have been defined. Also, definitions of various status scores have been selected.

To move from diagnosis to aetiology and pathogenesis, the use of powerful genome-wide association studies has uncovered a number of candidate genes and genetic regions that are associated with AS, although it is not yet
clear how they actually induce this disease [10]. HLA-B27—located in the MHC—is the main disease predisposing gene; it is distributed worldwide with variable prevalence and represents a family of closely related proteins encoded by an ever-increasing number of described alleles [11]: 75 alleles of HLA-B27 are known thus far, based on nucleotide sequence difference; at the translated protein level, there are 62 known subtypes of HLA-B27 [11]. Not all subtypes are associated with disease, and the existence of a possible hierarchical ranking among some of the subtypes for disease association has been observed [11]. Although the precise biological explanation for the remarkable association between AS and HLA-B27 has remained elusive since the link was first described in 1973, slow and steady progress is now being made in unravelling this unsolved puzzle [9–12].

A significant positive association of AS with endoplasmic reticulum aminopeptidase 1 (ERAP1) has been observed in European populations [10], and its crystal structure has been solved at high resolution. This association with AS is seen only in patients who possess HLA-B27, but not in those who lack it [9, 10]. This suggests a gene-to-gene interaction of ERAP1 with HLA-B27, and also suggests that ERAP1 may be playing a pathogenic role in AS by facilitating the trimming of small peptides to optimal length for binding to HLA-B27 for antigen presentation [9, 10].

Associations of AS with the IL-23 and IL-1 cytokine signalling pathways have also been reported; these findings have stimulated much new research into the disease and have led to therapeutic trials [9, 10]. Additional genes associated with AS susceptibility include IL1R2, ANTXR2 and gene deserts at 2p15 and 21q22 [10]. The associations with the gene deserts suggest a possible involvement of non-coding RNA in AS pathogenesis. A very recent study of a large cohort of Korean patients with AS has confirmed the association of ERAP1 and gene desert at 2p15 [13].

Subclinical gut inflammation has been demonstrated in patients with AS and related SpA, although there is no obvious anatomical link to explain this intriguing association between joint and gut inflammation [9, 14, 16]. Human genome studies combined with animal model research provide new means to understand this gut–joint axis. Both innate and adaptive immune responses seem to be involved. The IL-23 pathway, through the control of Th17 cells (which are highly pro-inflammatory and induce severe autoimmunity), plays a fundamental role in the intestinal immune response. Paneth cells play a role in regulating mucosal immunity by being the pivotal source of IL-23, a master regulator of gut mucosal immunity [9, 14]. The Th1, Th17 and regulatory T cells (Treg) must be continually fine-tuned to balance the immune tolerance of microbes in the gut lumen with the need to protect the body from pathogens. Over-expression of Paneth cell-derived anti-microbial peptides in the ileum of AS patients with subclinical gut inflammation has been reported, and this probably represents an important early alteration of the mucosal innate immune component and intestinal host defense in AS [9]. A recent study of tissue and circulating Treg cells, and quantitative gene expression analysis of ileal biopsies of 18 AS and 15 active Crohn’s disease patients as well as 15 healthy subjects, has provided the first evidence that an active Treg cell response, mainly dominated by IL-10 production, occurs in the gut of AS patients [14]. This is probably responsible for the absence of a clear Th17 polarization observed in the ileum of AS patients. The ongoing genetic studies have provided increasing evidence for a strong genetic overlap between AS, Crohn’s disease and psoriasis, although there are also major differences in the genes involved in these three diseases [9, 10, 16, 17].

For patients with active AS, medical therapy with TNF-blockers (without concomitant DMARDs) is dramatically effective and increasingly considered the standard of care when patients fail to respond adequately to conventional treatment with NSAIDs and physical exercises [1, 18]. The most recent data show that anti-TNF therapy in AS is clinically efficacious, not only in the short- but also in the long-term, and that serious adverse events have remained rare or can largely be prevented by appropriate screening [9, 18]. However, a definite influence on radiographic progression after long-term continuous treatment compared with conventional therapy has not been proven so far during 5 years of treatment and follow-up [18].

In conclusion, it is pleasing to see the rapid progress highlighted above, but much more is needed and expected. Some of the challenges for the future include: achieving very early diagnosis; developing diagnostic criteria; starting early treatment; preventing new bone formation and spinal fusion; identifying new targets for treatment, developing new, more effective and safer and cheaper therapies; achieving disease remission; achieving treatment-free disease remission; disease prevention; and understanding aetiology and the interaction between genes that predispose to disease and influence disease progression and severity.

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