Review

One year in review 2015: spondyloarthritis

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Received and accepted on December 4, 2015.

Clin Exp Rheumatol 2015; 33: 769-778.

Key words: spondyloarthritis, epidemiology pathogenesis, autoimmunity, DMARDs

Competing interests: none declared.

ABSTRACT

Spondyloarthritis represents a heterogeneous group of articular inflammatory diseases that share common genetic, clinical and radiological features. Recently, novel insights into the epidemiology, pathogenesis and treatment of these diseases have been provided. Herewith, we provide an overview of the most significant literature contributions published over the year.

Introduction

Spondyloarthritis (SpA) represents a heterogeneous group of articular inflammatory diseases involving spine, sacroiliac and, less frequently, peripheral joints (asymmetric mono-arthritis or oligo-arthritis). The main goal of the SpA management is to reduce disease activity and to control joint damage.

The aim of this review was to provide an overview of the most significant literature contributions published over the year. We performed a Medline search of English language articles published from 1st January 2014 to 31st March 2015 using the following key words: spondyloarthritis, pathogenesis, epidemiology and therapy. We reviewed all the articles and selected the most relevant works.

Epidemiology of spondyloarthritis

SpA is a heterogeneous group of chronic inflammatory arthropathies that share a genetic association with major histocompatibility complex (MHC) class I antigen (HLA-B27) and common clinical features. The SpA group includes axial SpA such as ankylosing spondylitis (AS) and peripheral SpA, the more frequent being psoriatic arthritis (PsA), reactive arthritis (ReA), SpA related to inflammatory bowel disease (IBD) and juvenile SpA. The classification of patients in the different SpA-related diseases relies on chronic inflammatory back pain (IBP) as well as articular (arthritis, enthesitis, dactylitis) and extra-articular (IBD, psoriasis, uveitis) features. Based on the specific clinical pattern, patients are classified as belonging to a specific subgroup. Moreover, a more recent contribution prompted a primary classification into axial and peripheral SpA.

Epidemiology is one of the most important factors in determining the impact of sickness in the population; in fact, prevalence data improve the understanding of the disease and its effect on healthcare costs and the health of the population.

IBP is the most common clinical manifestation that SpA share. A recent study conducted by Hamilton *et al*. considered the prevalence of IBP in a United Kingdom (UK) primary care population: the results showed that the prevalence of IBP varies according to the different classification criteria chosen. According to the ASAS criteria, the prevalence of IBP is 1.7%, while, according to the Calin criteria, the prevalence is 3%, and 3.4% when using the Berlin criteria (1).

According to the previous literature, the prevalence of AS is generally believed to be between 0.1% and 1.4% globally. The peak of incidence is recorded around the third decade of life and rarely after the age of 45. Ciurea *et al*. analysed a large cohort of 1199 patients with AS and found that the mean age at onset was 26.3 years in men and 29.3 in women (2). About 90% of patients with AS shows the HLA-B27 positivity even if with geographical differences in disease prevalence. Dean *et al*. carried out a systematic literature review to estimate AS prevalence worldwide and to calculate the expected number of cases. AS is more frequent within Europe (23.8 per 10000) and Asia (16.7 per 10000); the mean gender ratio is

3.4:1 (male:female) although there are some differences between geographic regions (3.8:1 in Europe and 2.3:1 in Asia) (3). On extra-articular manifestations (EAM) in AS, a recent study conduced by Stolwijk *et al*. reported an increased rate of 11.4% for acute anterior uveitis, 4.4% for psoriasis and 3.7% for IBD against the general healthy population (4).

Regarding PsA, there are no data on the prevalence and incidence of the disease over the last decade. Studies from across the world have reported that prevalence of PsA ranges from 0.1% to 0.42%. According to Henes *et al*., the proportion of psoriasis patients suffering from PsA has varied between 5.8% and 30% (5) with an average of 17%, also according to the new CASPAR criteria (6-7). PsA tends to appear earlier in patients with HLA-B27 positivity and these patients also show a shorter interval of time between the onset of cutaneous lesions and the onset of joint disease (8). PsA usually occurs in the 40–50 age range, although the disease may also occur in young children and in elderly patients.

SpA is the most frequent extra-intestinal manifestation in patients with IBD. In this regard, several studies have estimated the occurrence of SpA in IBD patients ranging between 17% and 39% (9). Musculoskeletal symptoms are usually diagnosed after the occurrence of IBD. Axial involvement is found in 2–16% of IBD patients, with a higher prevalence in patients with Crohn's disease (CD). The prevalence of symptomatic and asymptomatic sacroiliitis in IBD is between 12% and 20%; association with HLA-B27 ranges from 3.9% to 18.9%. Since the availability of x-ray and, moreover, magnetic resonance imaging (MRI), several studies have shown an increase in the prevalence of axial involvement (10).

Finally, given that MRI is more frequently used in the clinical practice today and that the ASAS group has proposed new classification criteria for SpA, a growing interest has turned to the pre-radiographic forms of spondyloarthritis. Since non-radiographic axSpA progresses to radiographic axSpA in a certain proportion of patients, differences in age and symptom duration are expected. Among non-radiographic axSpA patients. females constitute a 2:1 majority, HLA-B27 positivity seems to be less common and the frequency of EAM is the same in both groups. The epidemiology of non-radiographic axSpA in not yet well known, but data now available suggest that it is relatively common among patients with a diagnosis of IBP in general practice and affects from one-quarter to three-quarters of patients who satisfy the new ASAS criteria of ax-SpA (11).

Pathogenesis

The delay in diagnosis of Spa and lack of complete clinical response to treatment have raised interest in the pathogenetic mechanism involved in the genesis of this group of diseases. To date, despite the numerous studies made, the pathogenesis of SpA is not entirely clear. They are multifactorial diseases developing from a complex interaction of genetic risk factors (often HLA B27-related) and environmental triggers (infections, mechanical stress, abnormal intestinal microbiota), leading to activation of autoinflammation and autoimmunity.

Genetics of spondyloarthritis

Genome-wide association studies have shown the importance of autoimmune pathways including the IL17/IL23 pathway, control of NF-kB activation, aminoacid trimming of the MHC antigen presentation and other genes controlling CD8 and CD4 T cell subsets in the pathogenesis of these diseases.

HLA-B27-related genetics

HLA-B27 expression is correlated with the pathogenesis of Spa, especially of ankylosing spondylitis (AS), but the mechanisms underlying the striking association of SpA with the class I major histocompatibility complex molecule HLA-B27 remain poorly understood. Multiple theories have been proposed, including the presentation of arthritogenic peptides, cell surface HLA-B27 dimer recognition by NK receptors, and the propencity of HLA-B27 to misfold during its biosynthesis and trigger pro-inflammatory endoplasmatic reticulum stress. In the last year, one study has tried to determine whether HLA-B27 free heavy chains (FHC) contribute to the pathogenesis of SpA. FHC levels on $CD14^+$ PB cells were significantly higher in SpA patients than in controls, but were lower than the levels on the synovial fluid cells of SpA patients. HLA-B27-transfected U937 cells expressed higher FHC levels than either EGFP/HLA-A2- or EGFP-transfected cells. HLA class I FHC expression was significantly increased on monocytes of SpA patients and HLA-B27-transfected cells, implying that FHC, perhaps mostly derived from HLA-B27, plays an important role in SpA pathogenesis (12). Another study comparing AS and non-AS associated HLA-B27 subtypes transfected into HeLA cells, suggest that disease-associated alleles have more intracellular aggregates of misfolded MHC protein in the absence of an overt endoplasmatic reticulum stress. Bioluminescence resonance energy transfer (BRET) and Western blotting were used to monitor HLA-B oligomerisation in this study. At low expression levels, BRET signals were similarly elevated for all SpA-associated HLA-B27 alleles tested, but were lower for the non-associated B*2706. At higher expression levels, HLA-B27 signals remained steady while signals for HLA-B7 decreased sharply, reaching the level observed for B*2706. This was due at least in part to a decreased oligomer proportion without unfolded protein response outbreak. With increased expression, all HLA-B proteins accumulated to a high density in cytoplasmic vesicles with labile form and size. The extent of this phenomenon was closely correlated to the level of association with predisposition to SpA (13).

Non-HLA-B27-related genetics

The result of genome-wide association studies revealed that, in addition to HLA-B27, a few non-HLA genes are associated with susceptibility to SpA. Recently, some studies have identified common single nucleotide polymorphisms (SNPs) in non-HLA-B genes highly significant for association with SpA.

Several polymorphisms in the endoplasmic reticulum aminopeptidase 1 (ERAP1) are strongly associated with susceptibility to SpA. The combination of rs17482078, rs10050860 and rs30187 determines three major haplotypes with different levels of association with SpA. The mechanism by which ERAP 1 predisposes to SpA remains unknown. One hypothesis is that ERAP1 potentially contributes to the pathogenesis of AS, altering HLA-B27 peptide presentation. One study demonstrated that in both HLA-B27 and C1R-B27 cells, the proportion of 9-mer HLA-B27-bound peptides was decreased by ERAP1 silencing, whereas the percentages of longer peptides (11-13 mer) were increased. Surprisingly, following ERAP1 silencing, C-terminally extended peptides were readily identified and these were better able to bind to HLA-B27 (14). Another study aimed to characterise the alterations induced in the HLA-B27-bound peptidome expressed in live cells by the natural ERAP1 polymorphisms (R528K and N575D/Q725R) predisposing to AS. They found that the R528K polymorphism alters the expression levels of many HLA-B*27:05-bound peptides, depending on the susceptibility of their N-terminal residues to trimming and depending on the size of the amino acid side chains. The significant alterations in the B*27:05 peptidome and the structural features of the peptides determine their differential expression in distinct ERAP1 contexts (15). A recent study tried to determine whether such haplotypes might affect ERAP1 mRNA expression, protein level and/or enzymatic activity in antigen-presenting cells, a type of cell that is potentially relevant in disease pathogenesis. The authors found that in monocyte-derived dendritic cells (MD-DCs) there was a strong association between ERAP1 haplotypes and ERAP1 mRNA expression level, with higher levels in subjects harbouring the susceptibility haplotype. In B lymphoblastoid cell lines they observed a significant correlation between haplotype risk score and ERAP1 transcript or protein level. No difference was found in the enzymatic activity in MD-DCs and in B-LCLs (16).

IL-23R is one of the genes that is associated with SpA, especially with AS and psoriatic arthritis (PsA) and with inflammatory bowel disease (IBD). In one study on the Iranian population affected by AS, the authors found that only rs1004819 had a significant association with AS, and that the remaining four SNP alleles they studied, were not associated with the disease. Moreover, there was no association between these five polymorphisms and BASDAI, BASFI, and BASMI indices. Two haplotypes, ACGAT and ACGAG, were found to be associated with the heritability of AS. In addition, two significant, protective diplotypes (D8, GCGAG/GTGGG; and D9, ACGAG/GCGAG) were discovered (17). Another study analyses the effect of SNPs previously linked to psoriasis (Ps) (IL12B rs6887695 and rs3212227, IL23Rrs2201841 and rs11209026, and IL23Ars2066808) in patients from a Northern Spanish population. Carriers of the IL23A rs2066808-A allele were significantly more frequent among PsA patients and an association between IL23R rs11209026-GG genotype with a more severe disease was found. Therefore, genetic variation at IL23R and IL23A has an influence not only on the risk for Ps but also on disease severity (18). Recently, these findings were confirmed also in Serbian patients: carriers of the G allele had a higher risk of developing PsA (19).

In the last year, many other studies have been performed on the predisposition of SNP to the development of AS. ANTXR2 variants have been associated with AS in two previous genome-wide association studies. These results were replicated in a recent study: five SNPs were nominally associated with AS, eight SNPs showed evidence of association, the strongest being with rs12504282, Seven of these SNPs showed evidence for association in the HLA-B27-positive subgroup, but none was associated with HLA-B27-negative AS. However, no statistically significant interaction was detected between HLA-B27 and ANTXR2 variants (20).

Another important SNP regards the tumour necrosis factor receptor II (TNFRII) gene. In a Chinese population the polymorphism at position nt587 of the TNF II gene was found to be associated with AS, and the TNFRII nt587 G allele may play an important role in AS susceptibility (21).

T-cell immunoglobulin- and mucin-domain-containing molecule 3 (TIM-3) has been established as a negative regulatory molecule that plays a critical role during the inflammation process. A recent study showed a positive association between TIM-3 -574T allele with AS; moreover, subjects carrying polymorphic -574GT genotype had significantly lower TIM-3 mRNA and protein levels in CD4(+) T cells, CD8(+) T cells, and monocytes. Therefore, polymorphisms in the TIM-3 gene is associated with increased susceptibility to AS possibly by downregulating gene expression (22).

Two SNP of caspase recruitment domain-containing protein 9 (CARD9) and small nuclear RNA-activating complex polypeptide 4 (SNAPC4) are associated with SA. During the last year it was confirmed that SNP rs11145835 that harbours CARD9 and SNAPC4 was associated with AS also in a Chinese Han population (23).

Human protein tyrosine phosphatase non-receptor 22 (PTPN22) and cytotoxic T-lymphocyte antigen-4 (CTLA-4) genes encode proteins that are actively involved in regulating T-cell activation. Some authors investigated the effects of genetic polymorphism on the genesis of SA and they demonstrated that PTPN22 -1123G/C and CTLA-4 +49A/G genetic polymorphisms had a combined effect on the development of AS (24).

A recent study investigated the methylation level of an inflammatory-related gene, SOCS-1, in serum samples of patients with SA. SOCS-1 methylation can only be found in serum samples from patients and the methylation of SOCS-1 was significantly associated with severity of patient's spondylopathy, sacroiliitis and acute phase reactant CRP. AS patients also exhibited higher serum IL-6 and TNF-α levels and they demonstrated a significantly higher SOCS-1 methylation (25).

The receptor activator of nuclear factor-kappaB ligand (RANKL) gene poly-

morphism is associated to AS. During the last year it was demonstrated that SNP rs2277438 of the RANKL gene was associated with the susceptibility of AS in a Chinese Han population and genotypes with G allele (GG and AG) were identified as the risk factors for the occurrence of AS (26).

The human major histocompatibility complex class I chain-related gene A (MICA) controls the immune process by balancing activities of natural killer cells, γδ T cells and αβ CD8 T cells, and immunosuppressive CD4 T cells. Recent genomewide association studies have shown that genes most strongly linked to AS susceptibility come from the region containing HLA-B and MICA. In particular, a recent study demonstrated that, independently of HLAB27, MICA*007:01 is a significant risk allele for AS in both Caucasian and Han Chinese populations, and that MICA*019 is a major risk allele in Chinese AS patients (27).

Regarding PsA, it has been demonstrated that killer-cell immunoglobulin-like receptor gene polymorphisms KIR2DL2 and KIR2DS2 polymorphisms were significantly associated with the disease. The risk of PsA was higher when KIR2DS2 was present with the HLA-C ligands for the corresponding inhibitory KIRs, and was highest when KIR2DS2 was present in the absence of HLA-C ligands for homologous inhibitor KIRs, compared with when KIR2DS2 was absent. So the presence of HLA-C, HLA-B Bw4 and HLA-B Bw 4 alleles were associated with a higher PsA (28).

Another important gene in the pathogenesis of PsA is the tumour necrosis factor-α (TNF-α) gene. It was recently demonstrated that the SNP +489 variant allele A was significantly associated with PsA susceptibility and severity of clinical and laboratory parameters (29).

Autoimmunity

Spondyloarthritis is historically known as a non-autoimmune disease because it are characterised by the absence of autoantibodies in patients' sera.

In the last year, two groups reported the presence of circulating autoantibodies in SpA. Patients with axial SpA had a greater prevalence of autoantibodies against CD74, meaning that antibodies against CD74 could provide an important additional tool for the diagnosis of SpA (30). Recently, anti-CD74 antibodies with specificity to a class II-associated invariant chain peptide (anti-CLIP-ABs) were found in axial SpA patients (31). The pathogenetic role of these antibodies remains unknown. The presence of autoimmune mechanism is demonstrated also by the finding of anti-noggin and anti-sclerostin containing immune complexes in AS patients. Higher levels of IC probably contribute to neo-ossification in AS patients (32).

Enviromental triggers in spondyloarthritis

Recently some authors have analysed the role of microbiota and biomechanical stress in initiating and perpetuating inflammation. The role of the microbiota in the development of inflammatory joint diseases was investigated in the recent years. A bidirectional interaction exists between the bacteria constituting the intestinal microbiota and the immune system: on the one hand, the immune system regulates the quality and the quantity of microbiota; on the other hand, the role of microbiota is to educate the immune response. The important role of the microbiota in the development of joint diseases is confirmed by the fact that germ-free experimental models do not develop arthritis, but the transfer of the intestinal flora determined the development of the disease. The association of intestinal disease and joint disease is shown by the fact that 10–20% of patients with IBD develop sacroiliitis, by the discovery of microscopic inflammatory lesions in the biopsy from patients with AS but without intestinal symptoms, by the sharing of many genes and the development of arthritis after intestinal infections. Recently, a study on SKG mice demonstrated that the interaction between immunogenetic background and host microbiota leads to an IL-23-dependent loss of mucosal function, triggering ileitis in response to curdlan (33). In curdlan-treated SKG mice, another study demonstrated that arthritis, enthesitis, and ileitis were IL-23 dependent. In response to systemic β-1,3-glucan, IL-23 was induced in the ileum intestinal where causes local mucosal dysregulation and where the cytokines drive the SpA disease, including IL-17/IL-22-dependent enthesitis (34). In another study a single i.p. exposure to mannan from Saccharomyces cerevisiae induced an acute inflammation in inbred mouse strains resembling human Ps and PsA-like disease, whereas multiple injections induced a relapsing disease. They also noted the exacerbation of disease severity in mice deficient for generation of reactive oxygen species (ROS). The restoration of ROS production in fact ameliorated both skin and joint disease. They propose that mannan-induced activation of macrophages leads to TNF-α secretion and stimulation of local γδ T cells secreting IL-17A. The combined action of activated macrophages and IL-17A produced in situ drives neutrophil infiltration in the epidermis and dermis of the skin, leading to disease manifestations (35).

In last year, two studies analysed the role of S calprotectin in the pathogenesis of PsA and AS. S-calprotectin was significantly higher in patients with PsA, in particular, in polyarticular disease. The levels of S-calprotectin correlated with hs-CRP, swollen joint count and CXCL10 (36). Serum level of calprotectin was significantly higher also in patients with AS compared with healthy controls in another study, however, the calprotectin levels did not correlate with the measurements of disease activity, functional abilities, radiological damage, and the quality of life (37).

The role of the mechanical stress

Mechanical stress drives both entheseal inflammation and new bone formation in SpA. The mechanism by which the mechanical stress acting on inflammation and bone formation is still under investigation. In a recent study, TNF overexpred mice showed typical inflammatory features highly reminiscent of SpA. In these mice the authors suspended the hind limbs and the decreasing of weight on these limbs significally decreased the development of enthesitis and subsequent arthritis and osteoproliferation.

Importantly, enthesitis occurred equally in the presence or absence of mature T and B cells, underscoring the importance of stromal cells. They also demonstrated that Erk1/2 signalling plays a crucial role in mechanotransduction-associated inflammation (38). Another study investigated the histopathologic characteristics of the midfoot in patients with tarsitis associated with SpA. Slight oedema and hyalinisation were found in some tendon sheaths, and a few inflammatory cells were detected in the entheses. In bones, they found some changes suggesting osteoproliferation, including endochondral and intramembranous ossification, but no inflammatory cells. In entheses showing bone proliferation, they detected osteocalcin and osteopontin in cells with a fibroblast-mesenchymal phenotype, suggesting that ossification may be in part explained by the differentiation of mesenchymal entheseal cells toward the osteoblastic lineage induction of entheseal cells toward an osteoblast phenotype. These results demonstrate that the midfoot involvement in patients with SpA characterised by osteoproliferation and abnormal expression of bone lineage proteins, but no inflammatory infiltrates. In this sense, tarsitis resembles the involvement of the spine in patients with AS (39).

Ankylosis

The ankylosis that occurs in joints and enthesis in course of spondyloarthritis is primarily an endochondral ossification. This mechanism is regulated positively by BMPs and Wnt through the activation of osteoblasts and receives inhibitory signals by factors such as NOGGIN, sclerostin and DKKI. Noggin and sclerostin have recently been associated with the disease process in mice and human studies. Last year, for the first time, IgG autoantibodies to noggin and sclerostin were found in AS sera showing that higher levels of IC probably contribute to neo-ossification in AS patients. Another study recently tried to identify biomarkers for bone metabolism in patients with AS and explain the relationship between these biomarkers and disease activity, back mobility, osteoproliferation, and bone mineral density. They found higher serum levels of Wnt-3a, lower levels of sclerostin and sRANKL in AS patients. Serum levels of Wnt-3a are associated with increased BASMI and mSASSS, indicating that Wnt-3a could be a biomarker for the osteoproliferative process (40).

Spondyloarthritis and DMARDs

Although several reviews and meta-analyses have shown lack of evidence of efficacy of traditional disease-modifying anti-rheumatic drugs (DMARD) in spondyloarthritis, recently, some studies were conducted to evaluate their efficacy and tolerability. In 2014 Fagerli *et al*. (41) enrolled 181 patients starting sulphasalazine (SSZ) as their first DMARD and 543 patients starting a tumour necrosis factor-alpha inhibitor (TNFi) as their first DMARD and they observed a trend toward better 3-month responses to SSZ in patients with peripheral joint swelling. The authors support current EULAR/ASAS recommendations (42) of SSZ as an optional treatment in SpA patients with peripheral disease, although overall responses were modest. Initial treatment with SSZ does not seem to impair later TNFi response.

Two studies were published about the use of methotrexate (MTX) in patients affected by psoriatic arthritis (PsA). The first (43) investigate the effect of concomitant MTX on responses and drug survival in patients with PsA starting their first TNFi. The authors included 440 patients, 170 receiving TNFi as monotherapy and 270 receiving concomitant MTX. Responses were similar in the two groups in both analyses. Drug survival analyses revealed a borderline significant difference in favour of patients receiving co-medication (p=0.07), and this was most prominent for patients receiving infliximab (IFX) (p=0.01). The second one (44) analysed the tolerability of MTX in 193 PsA patients: MTX had been stopped in 71 patients most commonly due to gastrointestinal intolerability after a mean period of 18.6 months.

In PsA patients, also the efficacy and safety of leflunomide, alone or in association with MTX, was assessed (45); 85 patients were identified: 43 were on leflunomide alone and 42 were on combined leflunomide and MTX therapy. 30 patients discontinued leflunomide mainly due to toxicity. Of the 55 patients who continued the drug, 38%, 48% and 56% achieved a >40% reduction of actively inflammed joint count at 3,6 and 12 months respectively. PASI50 was achieved by 27%, 28% and 38% at 3, 6 and 12 months, whereas PASI75 was obtained by 19% at 3 and 6 months and 32% at 12 months. Thus, leflunomide is effective for the treatment of PsA and psoriasis and is reasonably well tolerated over 1 year of treatment in clinical practice.

Furthermore, last year the efficacy and safety of cyclosporine A (CsA) were evaluated in a particular subset of PsA patients with HCV, HBV, HSV-1 and -2, HHV-6, EBV, or parvovirus infection comorbity (46). At baseline, 126 out of 225 evaluable patients had 2 or more seropositivities indicative of former infections, and 31 patients presented seropositivity for HCV, HBV, HSV-1 and -2, HHV-6, EBV, or parvovirus infection; one of them, positive for HBAg, was treated with lamivudine, while the remaining 30 received no specific treatment. None of the 31 patients developed virus reactivation. A reduction (p<0.001) of PASI, BASDAI, and VAS scores was observed at 6 and 12 months. The authors concluded that the treatment of PsA with CsA as monotherapy or in combination was safe and effective.

Anti-TNF-alpha

Since the beginning of 2000, anti-TNF-α agents are increasingly being used for the treatment of SpAs.

According to the 2010 update of the Assessment of SpA International Society (ASAS) recommendation, all patients should have tried a minimum of two non-steroidal anti-inflammatory drugs (NSAIDs) for a minimum of 4 weeks in total, before starting anti-TNF-α agents (47). Even in the last years, some studies have confirmed the general efficacy of anti-TNF-α agents in SpAs and PsA with peripherical involvement. Particularly, TNFi have showed their ability to induce resolu-

tion of erosion in the sacroiliac joints of patients with axial SpAs through MRI (48) and their wide use in clinical practice to successfully treat patients with early axial SpA (49). The efficacy of TNFi was described even in PsA by Eder *et al*. who demonstrated that in a clinic setting, patients with erosive PsA receiving TNF-α blockers had a better radiographic outcome compared to those treated with MTX (50).

Furthermore, the effects of TNFi on working life and physical activity were described in an Australian cohort of AS patients. Treatment with anti-TNF-α therapy lead to a significant improvement in working life (employment, sick leave and productivity) and physical activity (participation rate, hours/week, and physical intensity) (51). The efficacy of TNFi in patients affected by non-radiographic SpAs was evaluated in two consecutive studies in 2014. In the first one none of the 19 patients enrolled showed radiographic progression in the spine or sacroiliac joints after 2 years of treatment with anti-TNF, unlike other non-radiological spondylitis cohorts without biological therapy (52). The second study included 112 patients with non-radiographic SpA and high disease activity treated in clinical practice in Southern Sweden. After 6 month of TNFi treatment, the patients showed a reduction in Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) and Bath Ankylosing Spondylitis Functional Index (BASFI) score (53).

In 2014, Gulyas *et al*. (54) conducted a study to evaluate the efficacy, reasons for switching, and drug survival of TNF when they are used as first- and second-line drugs in AS. 175 patients were on TNFi and 77 of them received at least two TNFi. The decrease of the BASDAI was similar among non-switchers and switchers using either the first or second TNFi, but the response rates to the first and second TNFi were worse in switchers than in non-switchers. Following the failure of the first TNFi, the retention on therapy was unfavourable, especially in patients on infliximab (INF) after 1 year of treatment, mainly due to drug's inefficacy. The frequency of side effects that led to switching was higher in the INF group than in patients treated with other agents. A similar analysis was performed by Jani *et al*. (55) who administered a regional survey in the north-west of England to 548 of PsA patients who started biologic therapy between August 2007 and June 2012. At 12-week assessment, 74% of patients had an adequate response to TNFi and 17% switched between biologics. According to the previous study, the main reason for cessation of initial biologic and sequential use was secondary inefficacy followed by lack of efficacy over time.

Recently, some studies were conducted to investigate the frequency of infections in patients with SpAs treated with TNFi and to identify factors predisposing to infection. In 2014, Germano *et al*. (56) reported the infection rates in Rheumatoid Arthritis (RA) and SpAs patients under DMARDs, corticosteroids (CS) and TNFi, alone or combined, in a single-centre retrospective observational cohort study. Three hundred and thirty-one infections (318 non-serious and 13 serious) have been registered among 176 of the 341 patients. The Incidence Rate/100 patient-years of all infections was 36.3 ranging from 12.4 (DMARDs + CS) to 62.7 (anti-TNF-α + CS). The most frequent infection site was respiratory tract, and bacteria were responsible for three quarters of all infections. So the authors concluded for a major risk of infections when using anti-TNF-α and CS therapy together, whereas DMARDs alone were relatively safe. Controversial results were reported by Wallis *et al*. (57) who analysed 440 patients diagnosed with SpA attending the Toronto Western Hospital AS clinic. A total of 259 infections, of which 23 were serious, were recorded in 185 patients. Eighty per cent of infections were bacterial and 15% viral. The most common site of infection was the lung, followed by skin, genitourinary tract, upper respiratory tract, sinus and gastrointestinal tract. There was no significant difference in the rate of any infection or serious infection in patients on TNFis compared with patients never on biologic agents.

Concerning the risk of infection with Mycobacterium tuberculosis, in the last years two studies were conducted to validate the safety of resuming TNFi therapy following Tubercolosis (TB) developed as a complication of previous TNFi. Of 683 patients observed, 13 patients developed an active TB infection during TNFi treatment (4 on etanercept, 4 on adalimumab and 5 on infliximab). TNFi treatment was reinitiated in six patients: four within 2 months after TB treatment and two after completion of TB treatment. Four patients reinitiated with the same TNFi, whereas two patients started with another TNFi. During a mean follow-up of 30.6 months, all six patients successfully completed TB treatment with no TB infection relapses (58). Similar results were presented by Suh *et al*. (59) who used data of 1,012 patients with RA or ankylosing spondylitis (AS) treated with TNFi at Seoul St. Mary's Hospital between January 2003 and July 2013 to identify patients who developed active TB.

Fifteen patients, 10 of whom with AS, developed active TB. All patients discontinued TNF-α inhibitors with starting the treatment of TB. Eight patients were re-administered TNF-α inhibitors due to disease flares and promptly improved without recurrence of TB. So, both studies suggest that re-administration of TNFi could be safe and should be considered to control RA or AS flares for patients with anti-TNF-α therapy-associated TB.

Data on the safety of TNFi in patients with PsA and concomitant hepatitis C virus (HCV) infection have recently been published (60). A total of 15 PsA patients with concomitant HCV infection were included in the study. At baseline, 13 patients had low viral load, and liver enzyme tests were within the normal range and they remained stable, during the observation period. On the other hand, a patient, at baseline, presented a high viral load with slightly increased values of AST and ALT that decreased after six and twelve months. Another patient, at baseline, had low viral load, but with slightly increased AST and ALT values that normalised during the follow-up. The data suggest that anti-TNF-α agents are effective and safe in PsA patients with concomitant HCV.

Concerning the safety profile of TNFi, two studies were designed to investigate the possible association between these agents and malignancy in patients affected by SpAs. The first is a large single-centre study conducted in Belgium to report the incidence of malignancy in patients with SpAs treated with one or more anti-TNF therapies and to compare the results with the incidence of malignancy in the Belgian population (61). A total of 231 patients started treatment with one or more anti-TNF therapies and they were included in the study. 6 out of 231 patients developed a malignancy after the start of anti-TNF treatment. The overall incidence rate of malignancy in our study population is 500.1 per 100000 patient years, indicating a higher incidence compared to the Belgian population. In conclusions, the authors observed a tendency towards a higher incidence of malignancy in SpA patients treated with anti-TNF therapy. However, it is not clear whether this increased risk is disease-related or treatment-related. A consecutive study on the influence of TNFi in the development of malignant lymphoma in patients with AS and PsA observed conflicting results (62). Through the Swedish National Patient Register, the authors assembled data from 1908 patients with AS exposed to TNFi and 2065 patients with PsA before lymphoma diagnosis. The incidence of lymphoma in AS or PsA patients treated with TNFi was not substantially different from those of TNFi-naive AS and PsA patients. These findings indicate that TNFi does not affect the risk of lymphoma in AS or in PsA.

Infliximab

In the last two years, only two studies were published on the therapy with infliximab (IFX) in patients affected by PsA and SpAs. The first one described dose regimens, dose escalation and clinical outcomes in TNFi naive patients with PsA treated with IFX in routine rheumatology care (63). The authors conducted an observational cohort study based on the nationwide Danish Rheumatologic Database (DANBIO) and Center for Rheumatology Research (ICEBIO) registries. Stratified by country, characteristics of patients treated with ≤3mg infliximab/kg body weight, 3–5 mg/kg or ≥5 mg/kg every 8 weeks were described. Outcomes were evaluated by ACR 20%, 50% and 70% responses and European League Against Rheumatism good response after 6 months and disease activity after 12 months. 376 Danish and 86 Icelandic patients with PsA were treated with IFX in routine care and the majority of these received continuous treatment with doses below the 5 mg/kg recommended in international guidelines. The starting infliximab dose did not affect the time until dose increase, drug effectiveness or drug survival. The Icelandic patients received lower doses than the Danish patients but had similar response rates and longer drug survival. The other study (64) aimed to assess whether combination therapy with IFX plus NSAIDs is superior to NSAID monotherapy for reaching ASAS partial remission in patients with early, active SpA who were naïve to NSAIDs or received a submaximal dose of NSAIDs. 158 patients were randomised to receive naproxen (NPX) 1000 mg daily plus either IFX 5 mg/kg or placebo at weeks 0, 2, 6, 12, 18 and 24. A greater percentage of patients achieved ASAS partial remission in the IFX+NPX group than in the placebo+NPX group at week 28 and at all other visits. Also, other disease activity, such as BASFI and BASDAI, were evaluated and showed greater improvement in the group treated with IFX. Patients with early, active axial SpA who received IFX+NPX combination treatment were twice as likely to achieve clinical remission as patients who received NPX alone.

Etanercept

Low doses of etanercept (ENT) were evaluated in a prospective open-label study in 38 patients affected by AS (65). Patients, who were in clinical partial remission with ETN 25 mg twice weekly at week 12 and 16, changed to a weekly regimen without changing the dose. If clinical remission persists at week 24 and 28, despite the reduction of the dose, patients changed to an every-other-week regimen, continuing with this administration schedule for the entire duration of the study if at week 36 and 46 clinical remission was maintained. At the end of the study, 18 patients were still in remission, 4 with a weekly regimen, and 14 with an every-other-weekly regimen. This study indicates that a consistent percentage of subjects with AS, maintains the partial remission with low doses of ETN leading to an economic benefit and a better safety of the drug.

The effects of ETN on NSAID intake and conventional clinical outcomes in axial SpA patients were evaluated in the multicenter, randomised, double-blind, placebo-controlled SPARSE study (66). Patients with active axial SpA despite optimal NSAID intake were randomised to receive ETN 50 mg or placebo once weekly for 8 weeks. All patients were advised to taper/discontinue their NSAID intake during the treatment period. NSAID intake was self-reported by diary and ASAS-NSAID scores calculated based on ASAS recommendations. This trial showed that more patients in the ETN group were able to reduce their NSAID intake and to achieve BASDAI50 and ASAS40 at week 8.

More recently, in 2015, the ESTHER trial was conducted to determine the degree of fluctuation of osteitis on MRI during long-term treatment with ETN in patients with early axial SpA with active inflammation on whole-body MRI in the spine and/or the sacroiliac joints at baseline (67). The authors analysed MRI data from 328 sacroiliac joints and 943 spine vertebral units in terms of osteitis in the pooled data set of 41 patients who were treated with ETN for 3 consecutive years. The results of the study clearly show that there was a consistently small amount of osteitis on MRI of the sacroiliac joints and spine in patients with early axial SpA compared with baseline values and only a very low rate of new-onset osteitis during 3 years of continuous treatment with ETN. Although osteitis persisted in 17–20% of sites, the amount of inflammation decreased in these sites, as shown by mean MRI score.

The efficacy and safety of ETN were also assessed in a randomised con-

trolled trial of patients with active non-radiographic axial SpA who had not responded sufficiently to NSAIDs (68). Patients who met the ASAS classification criteria for axial SpA but not the modified New York radiographic criteria for AS and who had a symptom duration of >3 months but <5 years, a score of >4 on the BASDAI and had been treated unsuccessfully with >2 NSAIDs were enrolled. 106 patients were randomised to the ETN group (50 mg/week) and 109 to the placebo group and all continued background NSAID treatment for 12 weeks; during the subsequent open-label period, all patients received ETN 50 mg/week. At 12 weeks, the number of patients with improvement according to the ASAS40 was significantly higher in the ETN group than in the placebo group. Patients who received ETN also showed a greater reduction in MRI-based scores for sacroiliac joint inflammation and spinal inflammation compared with placebo at week 12. At week 24, patients in the placebo group who had switched to ETN at 12 weeks exhibited similar improvement to those treated with ETN for 24 weeks. Therefore, ETN resulted effective in improving symptomatic disease activity, function, systemic and skeletal inflammation over 12 weeks in patients with non-radiographic axial SpA, and these changes were sustained over 24 weeks.

Finally, also data confirming the safety and tolerability of ETN in patients with AS have recently been published. The data were extracted from five randomised controlled trials and four open-label studies evaluating ETN, analysing1323 subjects. Rate ratios of serious infections and inflammatory bowel disease (IBD) events for ETN *versus* placebo/sulfasalazine during the double-blind studies were 2.19 and 1.09, respectively. There were no reports of opportunistic infections. Using the Surveillance, Epidemiology and End Results database, the standardised incidence ratio for malignancies was 1.47. These data suggest that ETN is well tolerated in subjects with AS.

Adalimumab

In 2014 the first study aimed to evaluate the efficacy and safety of adalimumab in Chinese patients with AS was published (69). Chinese adults with active AS who had an inadequate response or were intolerant to ≥1 NSAIDs were randomised to adalimumab 40 mg (n=229) or matching placebo (n=115) subcutaneously every other week for 12 weeks, followed by a 12-week open-label adalimumab every other week 40 mg phase. The results of this study show that adalimumab reduces the signs and symptoms of active AS in adult Chinese patients and provides additional evidence that adalimumab is effective in patients with AS. Efficacy of adalimumab was demonstrated through multiple measures of disease activity, spinal mobility, physical function, quality of life, and work productivity. Adalimumab was also associated with a rapid onset of action, with significant results seen after 2 weeks of treatment. Further, adalimumab was safe and generally well tolerated for up to 24 weeks of therapy in this patient population.

In the same year, another study analysising the relationship between clinical response, adalimumab levels and anti-drug antibodies (ADAb) in AS was carried out (70). 115 consecutive AS patients treated with adalimumab in the Netherlands and Taiwan were monitored for 24 weeks. Adalimumab levels and ADAb titres were determined, response to adalimumab treatment was defined as a BASDAI response and disease activity was measured using the Ankylosing Spondylitis Disease Activity Score using C-reactive protein (CRP) (ASDAS). The results showed that adalimumab levels vary widely among patients, and ADAb were detected in 27% of AS patients. Adalimumab levels were significantly lower for patients with ADAb compared with patients without ADAb. A significant association was demonstrated between adalimumab levels and ASDAS. Eleven patients had no detectable adalimumab levels and high detectable ADAb titres. In these patients, CRP and erythrocyte sedimentation rate remained elevated during treatment. Adalimumab levels resulted related to clinical response in AS patients measured with ASDAS and a influenced by ADAb.

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