

One year in review 2016: spondyloarthritis

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Received and accepted December 13, 2016.

Clin Exp Rheumatol 2017; 35: 3-17.

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EXPERIMENTAL RHEUMATOLOGY 2017.

Key words: spondyloarthritis,
pathogenesis, treatment, overview,
biological agents

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 present an overview of the most significant literature contributions published over the past year.

Introduction

Spondyloarthritis (SpA) is a heterogeneous group of articular chronic inflammatory diseases. These diseases comprise ankylosing spondylitis (AS), psoriatic arthritis (PsA), reactive arthritis (ReA), SpA related to inflammatory bowel disease (IBD-SpA), and undifferentiated spondyloarthritis (uSpA). More recently, a classification into axial and peripheral disease has been proposed by ASAS – Assessment of Spondyloarthritis International Society. Clinically, these diseases share several articular features (inflammatory back pain - IBP -, peripheral arthritis, enthesitis, dactylitis), and extra-articular features (uveitis, psoriasis, and inflammatory bowel diseases). Genetically, the diseases are associated with the major histocompatibility complex class 1 antigen, HLA-B27.

In this article we reviewed the literature of the past year (Medline search of articles published from 1st April 2015 to 29th February 2016) to identify the novelties in the epidemiology, etio-pathogenesis, and therapies of SpA.

Epidemiology

Data on the prevalence and incidence of the SpA have become particularly important in the last years to improve the management of available therapies and consequently of healthcare costs.

In the last year two studies were published about the epidemiology of the entire SpA group.

The first study, which was endorsed by EULAR, by Zlatkovic-Svenda *et al.*, estimated the prevalence of SpA in the Serbian population. The results showed that the prevalence of SpA was 0.32%, similar to that for rheumatoid arthritis (RA); with no differences between the sexes. In the EULAR survey, SpA prevalence in Serbia corresponded with the prevalence in France (0.30%), but it was lower than in Lithuania (0.83%) (1).

In the second one, Costantino *et al.* analysed the prevalence of SpA, in reference to HLA B27, in a cohort of French workers, the Gazel cohort.

The estimated prevalence of SpA, according to the ASAS classification criteria, was 0.43%. HLA B27 positivity rate was 6.9% in healthy controls and 75% in SpA patients with a 39-fold increased risk of developing the disease compared with B27 negative subjects (2).

Regarding comorbidities, an observational, cross-sectional, multicentric and international study was recently, published (22 participating countries from four continents), directed by the ASAS group.

The most frequent comorbidities were: osteoporosis (13.4%) and a history of gastroduodenal ulcer (10.7%), while the most frequent risk factors were: hypertension (34%), smoking (29%) and hypercholesterolaemia (27%). The study also revealed previously unknown risk factors such as elevated blood pressure (14%), underlining the not perfect monitoring of comorbidities (3).

On the epidemiology of AS, Exarchou *et al.* published a study based on the Swedish national patient register. They identified 11,030 cases of AS with a point prevalence of 0.18%. There was a different geographical distribution, with higher prevalence in the northern region, and a different distribution in relation to the level of education with

Competing interests: none declared.

higher prevalence in those with a lower level of education (≤ 9 years). The results unveiled furthermore differences between the sexes not only in prevalence but also regarding clinical manifestation and therapy. Indeed, men had a higher prevalence of the disease, had more often anterior uveitis and were more likely to receive tumour necrosis factor inhibitors than women. Women more frequently had peripheral arthritis, psoriasis and, regarding therapy, a prescription for oral corticosteroids (4). According to Sliwczynski *et al.*, the prevalence of AS in the Polish population was 7.48 for 10,000 persons of the general population (0.07%), lower than other countries, probably due to different methodologies in the studied populations and in the access to specialised rheumatological care. Interestingly, this study also calculated the costs for public healthcare generated by these patients, which were increased, most likely due to biological therapies (5).

In another study, Wright *et al.* found that age- and sex-adjusted incidence of AS in the population of Olmsted County, Minnesota, was 3.1 per 100,000. For the first time, an analysis was made of the risk for cardiovascular disease (CVD) compared with that predicted by the Framingham risk score (FRS). They found that risk of CVD in these patients was higher than expected and underestimated by the FRS, so it is clear that new tools for predicting CVD are needed (6).

Patients with AS had increased mortality compared with the general population for both sexes, as found by Exarchou *et al.* in a nationwide (Sweden) population-based study. CVD was the major cause of mortality. Lower level of education, male sex, higher age, presence of comorbidities (diabetes, infections, cardiovascular, chronic pulmonary and malignant diseases) and previous hip replacement surgery were identified as predictors of death (7).

Particularly in AS patients, the elevated risk for vascular mortality (cerebrovascular 60%, cardiovascular 35%) after adjustment for the following variables: CKD (chronic kidney disease), PVD (peripheral vascular disease), hypertension, IBD, diabetes mellitus, demen-

tia, and cancer remained only for men, probably because women had lower levels of inflammation and oestrogens played a protective role. The most common risk factors for vascular mortality were age; male sex; lower income; dementia; peripheral vascular disease; and, among patients aged 65 years or older, lack of exposure to non-steroidal anti-inflammatory drugs and statins (8). AS is characterised not only by axial and peripheral joint involvement but also extraarticular manifestations (EAMs). The most frequent are acute anterior uveitis (AAU), IBD and psoriasis. As Stolwijk *et al.* reported, the incidence rates of EAMs were 8.9/1000 person-years for AAU, 3.4/1000 person-years for psoriasis and 2.4/1000 person-years for IBD. The risk of developing these manifestations was remarkably increased in AS patients compared to controls. Particularly for psoriasis and IBD, it was higher in the first years after diagnosis, while for AAU, it increased also by ten years after the diagnosis of AS was made (9). As Roure *et al.* described, the most common types of psoriasis in SpA patients were plaque (66.7% of patients with psoriasis) and scalp psoriasis (65.5%). They also found that the differences between patients with *versus* without psoriasis were only older age at diagnosis and a lower proportion of radiological sacroiliitis (57.5% vs. 81.3%) (10).

The prevalence of PsA among patients with psoriasis ranges between 6% and 42%, but it is lower in Asian countries (1–9%).

However, in a study on Japanese patients with psoriasis, Ohara *et al.* found a mean prevalence of PsA of 14.3% (range 8.8–20.4%) similar to that in Western countries, probably due to the Westernisation of Japanese life style, characterised by an increase of psoriasis and PsA risk factors, and improved diagnostic tools (11).

According to the previous literature, Ranza *et al.* showed a prevalence of PsA, by CASPAR criteria, of 33% in a large cohort of Brazilian patients with psoriasis. Furthermore, about half of these patients were newly diagnosed. This underlines the need for close collaboration between dermatologists and

rheumatologists to identify and treat these subjects earlier (12).

SpA is a frequent extra intestinal manifestation in patients with IBD. The prevalence of SpA in Japanese IBD patients, as reported by Kamo *et al.*, was 33.6%, higher than other studies in Japan.

The results of this study unveiled that longer disease duration was a risk factor for development of SpA features (13).

Increased incidence of musculoskeletal manifestation was found also in patients with IBD on tumour necrosis factor (TNF)-inhibitor therapies without differences between Crohn's disease and ulcerative colitis (14).

Finally, in the last few years, more attention was given to non-radiographic axial SpA (nr-axSpA), particularly to its progression to AS. Wang *et al.* showed that only 26% of patients progressed to AS after a follow up of 15 years, interestingly patients in imaging arm of nr-axSpA were 3.5 times more likely to progress to AS than subjects in the clinical arm. Further studies are needed to evaluate clinical, laboratory and radiological features of nr-axSpA predictors of progression to AS (15).

Etiopathogenesis

The pathogenesis of SpA is multifactorial and not yet fully understood. Genetic factors (HLA-B27 and non-HLA-B27 related genes), inflammatory cytokines (*e.g.* TNF- α , IL-1, IL-6, IL-7, IL-17 and IL-23) and environmental triggers (infections, mechanical stress, abnormal intestinal microbiota) play an important role. These different factors and their complex interaction can lead to activation of autoinflammation and autoimmunity and to new bone formation.

Genetic factors

Despite the success of genome-wide association studies (GWAS) in AS, the identified genetic contribution only explains 25% of heritability.

O'Rielly *et al.* tried to discover rare and highly penetrant genetic variants in the pathogenesis of axial spondyloarthritis (AxSpA) investigating a well-characterised, multigenerational family through exome sequencing and HLA-B*27 genotyping. This analysis

revealed 9 base pairs in-frame deletion in SEC16A and 20 base pairs out-of-frame deletion in MAMDC4 which segregated with AxSpA. Both SEC16A and MAMDC4 deletions were detected together only in the AxSpA study family with a very strong linkage disequilibrium between these, but not in over 900 unrelated AxSpA cases or in 1150 unaffected controls. SEC16A acts as a scaffold protein with multiple central roles for coat protein complex II (COPII) vesicle formation and trafficking. The presence of rare syntenic SEC16A and MAMDC4 deletions increases susceptibility and modifies the disease course in the affected family members who carry the HLA-B*27 allele, particularly in those with an earlier age of symptom onset (16).

A possible association of specific killer cell immunoglobulin-like receptors (KIR) genes and haplotypes with susceptibility to AS was the object of the study by Díaz-Peña *et al.* carried out on a Spanish population. KIRs are regulators of cytotoxicity of natural killer cells and T cell subsets and may be relevant in binding to HLA-B27. The extensive polymorphism of KIR genes results in different signalling potentials towards NK and T cells. From this work it emerges that two activating genes, KIR2DS1 and KIR3DS1 seem to increase the risk of developing AS. Furthermore, also the inhibitory KIR2DL5 is associated with an increased risk of AS in patients presenting episodes of uveitis. However, the contribution of the KIR genes to AS susceptibility extends beyond the association with individual KIRs (17).

Vandelbosc *et al.* carried out the largest exploratory study involving a detailed analysis of the KIR genotype of Caucasian AS patients and healthy controls (both randomly selected and HLA-B27 positive) performed thus far. They analysed the relationship between the KIR genotype and important clinical parameters (age, sex, presence of HLA-B27, uveitis, use of TNF blocking therapy). This study revealed that KIR genes are not a major risk factor for susceptibility to AS, that a role of KIR3DL1 in AS is in disease severity rather than disease susceptibility, whereby KIR3DL1 has

a protective effect against the more severe manifestations of AS (18).

The first GWAS of AS revealed significant associations of the disease with several non-synonymous single-nucleotide polymorphisms (SNPs) situated in the gene for endoplasmic reticulum aminopeptidase 1 (ERAP-1). Among these the combination of rs17482078, rs10050860, and rs30187 results in the construction of 3 major haplotypes that are associated with SpA (the “protective” haplotype T/T/C, the “neutral” haplotype C/C/C, and the “susceptibility” haplotype C/C/T). Costantino *et al.* investigated whether such haplotypes might affect ERAP-1 mRNA expression, protein level, and/or enzymatic activity in antigen-presenting cells. The results demonstrated a strong correlation between SpA susceptibility conferred by the rs17482078/rs10050860/rs30187 haplotypes and ERAP1 expression levels, in terms of protein expression and partly of enzymatic activity, in these cells. Nevertheless, how increased production/activity of ERAP-1 may influence susceptibility to SpA remains to be determined (19).

Chen *et al.* studied the effects of ERAP1 silencing/inhibition/variations on HLAB27 β 2m-free heavy chains (FHC) expression and Th17 responses in AS to test the hypothesis that ERAP1 might contribute to the pathogenesis of AS through altered cell surface HLA-B27 FHC expression, known to be on the surface of peripheral blood mononuclear cells (PBMCs) from patients with SpA and HLA-B27-transgenic rats. The biological function of HLA-B27 FHCs is supported by its superior binding affinity to the immunoregulatory KIR3DL2 and leucocyte immunoglobulin-like receptor B2 (LILRB2). The results showed that ERAP1 inhibition of AS PBMCs reduces HLA class I FHC expression and Th17 expansion suggesting for the first time that ERAP1 inhibition may suppress Th17 response in AS (20). More recently, new associations between AS and 3 other aminopeptidases (ERAP2, LNPEPP, and NPEPPS) have been described. ER aminopeptidase 2 (ERAP2) has now also been shown to be associated with AS in HLA-B27-

positive or negative patients. Two variants in ERAP2 may affect its function. The most important one is rs2248374 which in homozygotes for the G allele causes a non expression of ERAP2 protein, having a protective effect for AS. The second functional variant, rs2549782, is almost never produced. Robinson *et al.* observed that rs2248374 variation does not have a significant effect on PBMC intracellular and cell surface HLA-class I expression and heavy chain formation, either on markers, ER stress or inflammatory cytokine production. This suggests that ERAP2 is more likely to influence AS risk through other mechanisms such as ligand alteration (21).

Bowes *et al.* attempted to validate novel SNPs associated with PsA susceptibility selecting them from their recent PsA Immunochip analysis collected from the UK, Ireland, Germany, Australia, Sweden and Italy. They found GWAS of rs2476601 to susceptibility of PsA mapping to PTPN22 and also confirmed association of PsA with a previously reported psoriasis locus, NOS2. The result is that the total number of confirmed, genome-wide significant, PsA loci is 10 including 4 that are PsA-specific (HLA-B, chromosome 5q31, PsA-specific variants within IL23R and now PTPN22). PTPN22 is a potent inhibitor of T cell activation. In addition, they also demonstrated that rs2476601 is differentially associated to PsA and not to psoriasis (22).

Role of Tregs (regulatory T cells) in AS

The role of regulatory T cells (Tregs) in AS was the object of study in Liao *et al.*'s work. They investigated the relationship between Tregs in PBMCs and disease activity in Taiwanese patients with AS and also the changes of Tregs in some of patients who received the anti-TNF. The percentages of Tregs in PMBCs were significantly higher in AS patients compared to normal individuals and positively correlated with the disease activity status. The increased Tregs during inflammation could be reversed by anti-TNF-therapy. These findings suggest that the percentage of Tregs in PMBCs might be a better predictor for

monitoring the clinical response after anti-TNF-treatment in AS patients (23).

Environmental factors

Several evidences suggest a close relationship between intestinal and joint inflammation in SpA. Cher *et al.* described, potential alterations in gut microbiota composition of patients with PsA and associated local inflammatory response, compared to subjects with psoriasis (Ps) and healthy controls and a decreased diversity in PsA and Ps gut microbiota, mainly due to lower relative abundance of several taxa. As a consequence, it is plausible an altered capacity of predisposed subjects to regulate intestinal immune responses leading to more widespread inflammation, either in the gut or in distal compartments, such as entheses or joints. The results showed a higher concentration of IgA in the gut lumen of PsA patients, reflecting an increased immune activation, and low levels of gut lumen RANKL (receptor activator of nuclear factor kappa-B ligand) compared to Ps subjects and controls. The latter has been found to be higher in the sera and synovium of PsA patients, and in the epidermis of psoriasis patients (24).

Baillet *et al.* undertook a study to compare the inflammatory responses to infection with *Chlamydia muridarum* in ZAP-70W163C-mutant BALB/c mice (SKG) susceptible to spondyloarthritis after systemic exposure to microbial β -glucan and BALB/c mice, to understand its immunologic basis. In response to the chlamydial antigen, production of interferon- γ (IFN γ) and interleukin-17 (IL-17) was impaired in T cells from SKG mice but tumour necrosis factor (TNF) responses were exaggerated, compared to the findings in T cells from BALB/c mice. The results demonstrated that Treg cells in SKG mice restrain TNF production, and in their absence, chlamydial infection triggers TNF-dependent inflammatory arthritis associated with a reduced rate of bacterial clearance (25).

Osteopenia

Although inflammation of the axial skeleton frequently leads to the formation of bony spurs, osteopenia is

detected in over 54% of AS patients. A recent study showed a high bone turnover-induced bone loss more severe with disease duration in HLA-B27 transgenic rats, highlighting an increased osteoclast-driven resorptive activity then osteoblastic bone formation. In these HLA-B27 transgenic rats the extracellular matrix of the bones lost some of its resistance to elastic and plastic deformation. Finally, their data suggest that IBD may only play a minor role in driving bone loss in HLA-B27 transgenic rats (26).

Ankylosis

Patients with juvenile-onset SpA may develop ankylosis of the midfoot resembling the spinal changes seen in the radiographic and magnetic resonance imaging (MRI) studies of patients with axial SpA (axSpA), particularly AS, and in patients with peripheral arthritis and enthesitis, specifically ankylosing tarsitis (AT). The objective of Pacheco-Tena *et al.*'s study was to describe the histopathologic characteristics of the midfoot in patients with tarsitis associated with SpA and in particular the expression of bone lineage commitment proteins within the ossifying tissues. They found only scarce mononuclear cell inflammatory infiltration, and mainly CD20⁺ and CD4⁺ cell subtypes, in the synovium of tendon sheaths and in the vascular structures adjacent to the enthesis. This suggests that osteoproliferation in the tarsal region might result from a predominantly mechanical rather than an inflammatory phenomenon. Because most patients developing AT have juvenile-onset disease, it is possible that bone growth factors might also play a role in this form of SpA (27).

Cortes *et al.*, for the first time, tested whether variants in genes involved in anabolic or catabolic bone pathways are associated with radiographic severity in AS. They observed experiment-wide significant association with the SNP rs8092336 in *RANK* (receptor activator of NF κ B) which encodes a TNF superfamily receptor involved in osteoclastogenesis, and in the interaction between T cells and dendritic cells. Association was also found with the SNP

rs1236913 in *PTGS1* (prostaglandin-endoperoxide synthase 1) also known as cyclooxygenase 1. Nothing association was observed between *HLA-B*27* and radiographic severity in this study, thus while *HLA-B*27* is clearly associated with AS susceptibility, it is not associated with the severity of ankylosis (28). Sakellariou *et al.* evaluated serum periostin levels in TNF inhibitor-naïve patients with axSpA and AS in comparison with healthy controls, their association with clinical, inflammatory and radiographic parameters and molecules involved in bone formation (total Dkk-1, sclerostin and VEGF) in addition to the association of serum periostin levels with syndesmophytes and structural progression, as well as with Dkk-1 and sclerostin serum levels. In these patients, AS patients had lower periostin serum levels compared with sex-, age- and BMI-matched apparently healthy individuals and among AS patients, periostin levels were higher in those with higher disease activity and higher systemic inflammation. On the other hand, periostin levels were negatively, but not independently, associated with BASRI (Bath AS Radiological Index). In contrast to sclerostin, there was no association of periostin levels with either Dkk-1 or VEGF levels in this study (29).

Inflammatory cytokines

Many different proinflammatory mediators may be involved in the pathways responsible for the immune pathophysiology of AS. PGE2 pathway enzymes are expressed in the inflamed synovium of RA, SpA and osteoarthritis (OA) patients and they are especially high in AS patients compared to early RA and unclassified arthritis (UA) patients. These results, stemming from the de Hair *et al.* study, suggested that pain sensation in these individuals cannot be clearly explained by altered synovial expression of PGE2 pathway enzymes and that other inflammatory mediators may be involved. Furthermore, PGE2 stimulation of new bone formation through the differentiation of osteoblasts may partly explain the difference in radiographic characteristics between RA and UA on the one

hand (joint space narrowing and bone erosions), compared to SpA on the other (new bone formation) (30).

Several lines of evidence suggest that IL-17A is involved in the pathogenesis of AS. In patients with long disease duration an increase in the number of IL-17-producing CD4⁺ T cells in the blood has been demonstrated. Diahann *et al.* tried to investigate whether IL-17-producing CD4⁺ T cells are involved in early active axSpA, including patients with axSpA and short disease duration without imaging abnormalities. Patients with axSpA showed an increased percentage of IL-17-producing CD4⁺ T cells similar in patients with and without MRI abnormalities, disease related and not HLA-B27 specific. The IL-17-producing CD4⁺ T cells expressed TCR α and CD161 and exhibited a memory phenotype. Furthermore, the authors found the expression of killer cell immunoglobulin-like receptor 3DL2 (KIR3DL2) by IL-17-producing CD4⁺ T cells in a small minority of cells, indicating that the interaction between KIR3DL2 and HLA-B27 is not required for induction and expansion of IL-17-producing CD4⁺ T cells in early disease, unlike long disease duration. Instead the higher frequency of KIR3DL2-positive CD4⁺ T cells in later stages of disease suggests that these KIR3DL2-positive CD4⁺ T cells expand as the disease becomes more chronic (31).

Another study tried to determine the role of IL-17A in epidermal hyperplasia and bone destruction associated with PsA through an *in vivo* gene transfer approach to overexpress IL-17A, thereby dissecting IL-17A from the IL-23/Th17 biology. Gene transfer of IL-17A induced serum TRAP (tartrate-resistant acid phosphatase) and bone destruction in the absence of synovial inflammation, in association with an expansion of an IL17R⁺CD11b⁺Gr1lowRANK⁺CSF-1R⁺ myeloid population (including osteoclast precursors), but with no increase in RANKL. Furthermore, they proposed a dual effect in inflammatory arthritis of IL-17A: to upregulate RANK on pre-osteoclasts making them hypersensitive to RANKL signal and to increase serum RANKL in the circulation. Bone and joint destruction in IL-

17A gene transfer coincided with skin pathology, thus is possible that IL-17A also induces the expansion of a second myeloid cell subset, associated with cutaneous pathology including epidermal hyperplasia, parakeratosis, and Munro's microabscess formation (32).

Przepiera-Bwdzak *et al.* assessed serum levels of IL-6 and IL-23 and their association with angiogenic cytokines and disease activity in AS, PsA and SAPHO patients. They found a serum IL-6, but not IL-23 correlated with ESR and CRP in SpA. However, SpA patients had significantly higher levels of IL-23 in comparison with the control group and AS patients had increased risk of elevated serum IL-23 levels compared to other SpA patients. These observations support a possible role of this cytokine in the pathogenesis of SpA acting locally in the joints and bones with no systemic effects. In conclusion they did not show correlation between serum IL-6 and IL-23 with VAS, BASDAI, and angiogenic cytokines (33).

Innate lymphoid cells (ILCs) populations are specialised cells involved in the regulation of innate immunity and inflammation through the secretion of polarised cytokines and chemokines. ILCs are classified into three groups based on the cytokine properties (ILC1-ILC2-ILC3 cells). Among these ILC3s there is an important source of 'type 17' cytokines, in response to IL-23, that express the retinoic acid-ROR- γ and are required for mediating immunity to extracellular bacterial infections. These ROR- γ ⁺ cells are involved in protective response by negatively regulating Th17 cells through the modulation of intestinal microflora. Specifically in the gut of patients with AS, ILC3 expressing the natural cytotoxicity receptor NKp44 are significantly expanded, produce IL-22 and induce mucins production and goblet cells hyperplasia. Ciccia *et al.* tried to better characterise the immunological origin and the behaviour of IL-23-responsive ILCs in the gut, synovial fluid (SF) and bone marrow (BM) of patients with AS. In addition, they also tried to study ILC1 and ILC2 in the gut of AS and finally to verify whether gut-derived ILCs may express

the α 4 β 7 integrin and recirculate in the peripheral blood (PB), inflamed BM and SF of patients with HLA-B27 AS. They observed that ILC3 defined as Lyn⁺IL-23R⁺NKp44⁺Tbet⁺ROR γ ^c cells were significantly and predominantly expanded in the gut, but also in the PB, SF and BM of patients with AS, produced high levels of IL-17 and IL-22 and expressed the homing integrin α 4 β 7. MADCAM1, the α 4 β 7 ligand, was found to be highly represented in the gut and in the inflamed BM of AS, suggesting that a re-circulation of ILC3 between the gut and the BM occurs. Finally, in the anti-TNF-treated patients, they observed a significant reduction of intestinal and circulating ILC3 and of the gut MADCAM1 expression. All together these results suggest a role for IL-23-sensitised gut-resident ILC3 migration in the development of AS. This study indicates that a gut-joint/spine axis exists in AS where ILC3 actively differentiate in the gut and migrate in extraintestinal sites where, through the production of IL-17 and IL-22, they may be responsible for the induction of inflammation (34).

Emmerik *et al.* observed ILCs, essential to epithelial homeostasis and implicated in psoriasis pathogenesis, yet never been reported in PsA. Their study establishes that NKp441 group 3 ILCs also accumulate in the joints of patients with PsA. These patients had fewer CCR61 ILCs in PB. Reciprocally, CCR6 was up-regulated on SF ILCs from patients with PsA, which suggests that this chemokine receptor may contribute to the extravasation of ILCs into the joints of patients with PsA. ILCs from the SF of patients with PsA also expressed high levels of melanoma cell adhesion molecule (MCAM), an integrin linked to IL-17A-producing T cells and expressed in ILCs and high levels of CD56, which is associated with the effector phenotype of ILCs. The number of circulating NKp441, CCR61, and MCAM1 ILCs in blood was inversely correlated with PsA disease activity. They showed that IL-17A is produced by ILCs in the joints of patients with PsA and is produced by more than one ILC subset. Finally, they concluded that group 1 ILCs are predominant in

RA SF, whereas PsA SF is characterised by CCR6- and Nkp44-expressing group 3 ILCs with increased capacity to produce IL-17A. These findings underscore the critical role played by the IL-23/IL-17 pathway in PsA and ILCs as potential instigators of inflammation in the joints of patients with PsA (35). A recent work investigated the possible pathophysiological role of IL-27 and VEGF in AS detecting their levels and correlation with disease activity. IL-27 is an IL-12 family cytokine with an important role in immune regulation, VEGF is considered a pivotal factor in angiogenesis. The authors observed that IL-27 concentration was increased in AS patients and strongly correlated with disease activity as indicated by BASDAI irrespective of other markers of inflammation. In addition the serum levels of IL-27 were correlated with serum levels of VEGF. Both were found to be elevated in AS patients with peripheral arthritis and HLAB27 positive with higher levels in synovial fluid than serum in peripheral arthritis. By contrast, these were not increased in AS patients with hip and eye involvement. From these, they suppose that IL-27 may carry out its function in patients with peripheral arthritis by its interaction with VEGF (36).

In their study, Bleil *et al.* evaluated the role of IL-6 pro-inflammatory cytokine in AS through an *in situ* analysis of IL-6 expression at different sites of inflammation in zygapophyseal joints of patients with AS. Several previous observations suggest that IL-6 might be downstream of TNF-driven inflammatory processes in SpA and that TNF does not seem to play a role in the inflammatory process in AS. Thus the authors have collected further data confirming the view that IL-6 is not a key player in the pathogenesis of the axial inflammatory process in SpA with the limitation that the analysis was made on advanced disease articular material (37).

Yeremenenko *et al.* analysed the expression of Dkk-1 and its regulation by proinflammatory cytokines, to delineate its potential role in the structural phenotype of human arthritis, in the inflamed peripheral joints of patients

with SpA and RA. The results suggest that IL-6 levels in SF were similar in both types of arthritis. TNF and IL-1b levels, however, were significantly lower in SpA SF than in RA SF. In contrast with the previously reported differences in serum Dkk-1 levels and despite the marked differences in TNF levels in SF, they found similar levels of Dkk-1 in SpA and RA SF indicating that local Dkk-1 production is regulated by many other proinflammatory cytokines in addition to TNF, including gp130 signalling cytokines. Dkk-1 levels did not correlate with TNF and IL-1b levels in either SpA SF or RA SF. In contrast, Dkk-1 levels were significantly negatively correlated with IL-6 in both SpA and RA. *In vitro* experiments with fibroblast-like synoviocytes confirmed that Dkk-1 production was strongly induced by TNF but clearly suppressed by IL-6 (38).

IL-19 is a member of the IL-10 family of cytokines, primarily produced by epithelial cells and lipopolysaccharide (LPS)-stimulated monocytes in response to bacterial components and ligands from host cells (TLR-2 and TLR-4). Kragstrup *et al.* studied inducers of IL-19 production and the effect of IL-19 on the production of CCL2/MCP-1- chemokine (C-C motif) ligand 2/monocyte chemoattractant protein 1- essential for guiding monocytes to sites of inflammation, proinflammatory cytokines in peripheral blood mononuclear cells (PBMCs) from healthy controls (HCs) and in PBMCs and synovial fluid mononuclear cells (SFMCs) from SpA patients. IL-19 concentrations were decreased in synovial fluid compared with plasma and inversely associated with disease activity in SpA. SpA SFMCs produced less IL-19 in response to LPS compared with HC PBMCs. These findings indicate that IL-19 production is diminished in SpA. Thus, impaired IL-19 control of the innate immune system and thereby an inability to reduce inflammation might be involved in the pathogenesis of SpA activating pathways in the innate immune system seen in these diseases (39).

Suppressors of cytokine signaling (SOCS) proteins are intracellular inhibitors of cytokine signalling which ac-

tivate the cells through the JAK-STAT pathway (Janus kinase-signal transducers and activators of transcription). The SOCS family consists of eight SOCS proteins so far, SOCS1-7 and CIS-1 (cytokine-inducible SH2-domain-1), and are the negative-feedback regulator of the JAK-STAT pathway. The aim of Chen *et al.* in their study was to investigate the suppressors of SOCS1 and SOCS3 expression in PBMCs in AS, and their associations with clinical and laboratory manifestations. The authors observed a decreased SOCS1 and increased SOCS3 expression in AS PBMCs and T cells. The decreased cellular SOCS1 mRNA expression in the AS subgroup implies that the dysregulation of SOCS1 may be involved in the development of AS. The increased cellular SOCS3 mRNA expression in the AS patients and its correlation with acute phase reactants suggest that SOCS3 is up-regulated to negative feedback control of the disease inflammation. These data may reflect an inadequate regulation of active inflammation in the AS patients (40).

The monocytes recognise bacterial structures by Toll-like receptor (TLR) and nucleotide-binding oligomerisation domain (NOD)-like-receptors. Ligation of TLR or NOD receptors rapidly triggers the production of proinflammatory cytokines such as IL-1, IL-6, and TNF- α in monocytes. Conrad *et al.* characterised the phenotype and functional state of monocytes of patients with axSpA by performing a phenotypic analysis of them and determining their spontaneous and TLR and NOD ligand-induced cytokine production. They observed an elevated frequency of classic (*i.e.* CD14⁺⁺CD16⁻) monocytes and a reduction in non-classic (*i.e.* CD14⁺CD16⁺) monocytes in the peripheral blood of patients with axSpA. The enhanced cytokine production by monocytes of patients with axSpA in particular to suboptimal stimuli such as MDP (muramyl dipeptide) and FSL-1 (fibroblast-stimulating lipopeptid-1), which require co-activating signals such as ineffective doses of LPS or low levels of cytokines, suggests that the monocytes of patients with axSpA are pre-activated *in vivo*. In contrast to the

enhanced cytokine responses to MDP and FSL-1, cytokine production in response to LPS was, at least partially, reduced in patients with axSpA. This study reveals *in vivo* pre-activation of monocytes in axSpA patients indicated by enhanced spontaneous as well as MDP- and FSL-induced cytokine production by monocytes which correlates with BASDAI (41).

Therapy

NSAIDs

Non-steroidal anti-inflammatory drugs (NSAIDs) are regularly administered to patients with AS and recommended as first-line drug treatment together with physical therapy. In the 2015 Recommendations for the Treatment of Ankylosing Spondylitis and Non-radiographic Axial Spondyloarthritis, treatment with NSAIDs was strongly recommended in active AS and no significant differences were reported comparing continuous treatment compared to on-demand NSAID treatment. In the Recommendations, no particular NSAID was recommended. In patients with stable AS, NSAIDs are conditionally recommended (42).

However, few studies have analysed the relative effectiveness of NSAIDs in AS. Eleven NSAIDs are currently approved in Europe for the treatment of AS and five in USA. A recent systematic review and meta-analysis of randomised controlled trials (RCTs) has been performed by Wang *et al.* in order to assess the efficacy and safety of 20 NSAIDs in the short-term treatment of patients with AS (43).

NSAID effects on pain, morning stiffness and NSAID-related adverse events (EAs) have been evaluated. Comparing NSAIDs on morning stiffness, 13 NSAIDs have shown efficacy in reducing morning stiffness, however, this reduction was not statistically significant when compared to placebo. A similar result was found comparing EAs. The review included 25 RCTs in the evaluation of pain and all NSAIDs demonstrated greater efficacy if compared to placebo. However, only 15 demonstrated an efficacy statistically superior to placebo and the etorocoxib was more effective than celecoxib, ke-

toprofen and tenoxicam. The same result seems to be confirmed by a recent open label, multicentric, randomised, prospective, non-controlled study conducted in order to evaluate the efficacy of etorocoxib in patients refractory to traditional NSAIDs and eligible for anti-TNF- α . Out of the 57 axial AS patients enrolled, 46% achieved a good response after 4 weeks and 33% after 24 weeks. In addition a decrease in CRP serum levels, although not significant, was observed after 4 weeks (44). In a recent RCT review, traditional NSAIDs showed high quality evidence in pain relief and improved function and also COX-2 NSAIDs were more efficacy than placebo at 6 weeks. However, no differences in benefits and damage were reported between the different NSAID classes. Some studies indicated a retard in radiographic progression using NSAIDs but this result has to be confirmed (45).

In the report by Varkas *et al.*, the effect of full-dose of NSAIDs on the extent and intensity of sacroiliac bone marrow oedema on MRI was evaluated. In this study, 117 patients with a clinical suspicion of SpA and a positive MRI of the sacroiliac joints were enrolled. Comparing BASDAI and BASFI between baseline and week 6, they improved significantly; a decrease in intensity of the bone marrow oedema (BME) lesions was also observed from baseline to week 6. However, the study reported a high level of dropouts among patients receiving full-dose NSAIDs.

DMARDs

Patients with persistent active disease, despite NSAID treatment, should be treated with TNF- α inhibitors. In fact, conventional non-biological disease-modifying anti-rheumatic drugs (cDMARDs) are recommended only for patients with active axial spondyloarthritis despite treatment with NSAIDs and with contraindication to the use of TNF inhibitors (42).

cDMARD use in AS presents a very low or moderate level of evidence of efficacy. cDMARDs are often administered in patients with peripheral arthritis. The recent review by Simone *et al.* confirmed that sulfasalazine (SSZ)

was better in peripheral joint diseases compared to axial involvement, methotrexate (MTX) has limited evidence in AS. In addition, combination therapy with cDMARDs had more evidence in peripheral involvement. On the contrary, cDMARDs are considered effective in peripheral PsA and cyclosporine (CSA) showed benefits in PsA similar or greater than SSZ (46).

In addition, another recent paper reported the effectiveness of CSA in patients with PsA to control both peripheral articular and skin involvement (47).

The recent paper by Gossec *et al.* reviewed the management recommendations for the treatment of PsA. The overall trend of published recommendation in PsA therapy is to start, as stated, with NSAIDs, followed by intra-articular injection. Conventional synthetic DMARDs are often used as second-line treatment and, based on the available literature, this review reported MTX as the first choice, even though few studies have been made on this drug (48).

Biological agents

• Anti-TNF α

TNF- α inhibitors are typically used in SpA when the disease has not responded adequately to conventional therapy. From the RCTs reviewed, there is evidence that the treatment with anti-TNF- α agents is very effective and leads to an immediate reduction of disease activity (BASDAI, ASAS), improvement in function and spinal mobility (BASFI), reduction in pain intensity, signs of inflammation on MRI, acute phase reactants and peripheral arthritis and enthesitis (49).

A meta-analysis investigated the efficacy of TNF- α -blockers *versus* placebo for the treatment of AS and nr-axSpA. 20 double-blind, placebo-controlled RCTs with data from 3096 patients were included in the analysis: 15 studies with AS patients, 4 with nr-axSpA patients and one with both. The evidence showed that TNF- α blockers, if compared to placebo, improved disease activity and functional capacity for both AS and nr-axSpA patients; in nr-axSpA patients the differences between anti-TNF- α and placebo were smaller (50).

The results of clinical studies on anti-TNF- α treatment also have demonstrated efficacy on signs and symptoms of other PsA manifestations, such as enthesitis, dactylitis and skin psoriasis (51).

A study by Haddad *et al.* investigated the disease characteristics of patients with PsA who achieved minimal disease activity (MDA) and tried to identify the predictors of MDA and to identify and describe patients who discontinued or reduced the dose of TNF- α inhibitors and continued to be in an MDA state. MDA is achieved in 64% of patients treated with TNF- α blockers and male sex and normal ESR are predictors for MDA. On withdrawal or reduction in treatment, 11.6% of patients maintained the MDA state (52).

Regarding the effect of TNF- α inhibitors on MRI inflammation, a study compared BME in MRI before and after treatment in order to verify the efficacy of anti-TNF- α and DMARDs, alone or in combination, as treatment for sacroiliitis. Fifty-six Chinese patients with axSpA and BASDAI score ≥ 4 were recruited and divided into 3 groups: anti-TNF- α alone vs. DMARDs alone vs. combined anti-TNF- α and DMARDs. MRI examinations were performed before and after treatment. After treatment, the ASDAS (AS disease activity), SPARCC score (Spondyloarthritis Research Consortium Canada score), ESR and CRP were significantly improved in the anti-TNF- α monotherapy and combination groups; no statistically significant differences in clinical disease activity and radiological inflammation of sacroiliac joints (SIJ) in patients in the DMARDs alone group; significant changes were seen after only 3 months of treatment. Anti-TNF- α treatment resulted in an effective reduction of disease activity and BME of SIJ after 3 months of therapy; in addition, it became evident from this study that the SPARCC score can be used to assess severity of disease prior to treatment (53).

The 2015 Recommendations for the Treatment of Ankylosing Spondylitis and Non-radiographic Axial Spondyloarthritis strongly recommended TNF- α inhibitors in patients with active AS

and, in the case of active disease, despite treatment with TNF- α inhibitors, recommended trying another TNF- α inhibitor and not to start therapy with DMARDs. Patients with stable AS treated with TNF- α inhibitors and NSAIDs or DMARDs should continue using a TNF inhibitor and stop NSAID or DMARD therapy (42).

Considering the association therapy of anti-TNF- α and NSAIDs, a study by Moltó *et al.* evaluated the NSAID sparing effect of TNF- α inhibitors in patients with early axSpA, by comparing the percentage of patients reaching several endpoints and by modelling NSAID intake using mixed models. The study population is the DESIR cohort, an observational, prospective, multi-centre cohort study involving patients with recent onset of inflammatory back pain suggestive of axSpA. This study compared NSAID intake in a matched population of patients receiving either TNF- α inhibitor or usual care, without a protocolled treatment algorithm. The percentage of patients who received NSAID treatment decreased in both groups over time, but this decrease was significantly greater in the group of patients receiving TNF- α inhibitors. Treatment with TNF- α inhibitors was thus associated with a decrease in the proportion of patients taking NSAIDs and with a rapid and sustained decrease in NSAID intake (54).

Other papers investigated the co-medication therapy with methotrexate (MTX). For RA it has consistently been shown that co-medication with MTX increases the clinical efficacy of TNF inhibitors and reduces joint damage, while in PsA no RCTs have addressed whether co-medication with DMARDs increases the efficacy of TNF- α inhibitors. Most RCTs found no differences in efficacy for peripheral arthritis between PsA patients treated with and without MTX. Some data have suggested that the concomitant use of MTX may reduce the progression of structural damage; no significant differences in other outcomes have been reported. The use of concomitant MTX appears to prolong the drug survival of TNF- α inhibitors (55).

This topic is also assessed in another

study, evaluating the effect of co-medication with conventional synthetic DMARDs on retention to TNF- α inhibitors in patients with AS and uSpA. In this study, it was evidenced that in patients using DMARDs co-medication there was a superior drug survival among patients with AS and uSpA (56). Regarding PsA, a study conducted in a Japanese population with active disease found no significant differences in the mean reduction in clinical measurements between the group treated with TNF- α inhibitors plus MTX and the group treated with MTX alone (57).

Finally, the study by Janta *et al.* evaluated the possibility of tapering the TNF inhibitors dosage in patients with PsA that have achieved disease remission, similarly to what is recommended for RA. One hundred and two patients with PsA treated with TNF- α inhibitors were included in the study; in patients with a maintained remission or MDA a dosage tapering was made: an increase of the interval between doses for subcutaneous TNF- α inhibitor or a reduction in the dosage for intravenous TNF- α inhibitor (72.5% of patients received a full dosage, 27.5% of patients received a tapered dosage). All the patients underwent a dermatologic assessment, with PASI evaluation, and a rheumatologic assessment, with tender and swollen joint count, MASES, evaluation on dactylitis, disease activity and pain VAS, DAS28, BASDAI, BASFI, HAQ. Moreover, all the patients were evaluated with US examination. The results showed no significant differences between clinical and US findings in patients on full and tapered dosages of TNF- α inhibitors; in particular, patients with a tapered dosage of biologic therapy did not present a higher level of US inflammation. In addition, the duration with biologic therapy and with current biologic therapy was significantly higher in patients with tapered dosages of TNF- α inhibitors (58).

Etanercept

Recently, etanercept (ETN) has been approved by the European Medicines Agency for the treatment of nr-axSpA with objective signs of inflammation on MRI and/or elevated CRP. The lat-

est data on ETN has suggested clinical efficacy, with significant improvement in signs and symptoms in patient-reported outcomes (PROs), as well as a reduction of MRI inflammation, and a good safety profile in patients with nr-axSpA who do not respond to the first-line therapy with NSAIDs (59).

The 48 results of the phase III, double-blind EMBARK study showed the long-term maintenance of these achievements (60).

Moreover, a study by Dougados *et al.* suggests that ETN in patients with nr-axSpA non-responders to NSAIDs provided significant improvement in PRO measures for disease-specific, functional and productivity domains, nocturnal and average back pain compared with placebo (61).

Infliximab

Elalouf *et al.* published a review article on safety and efficacy of infliximab (IFX), which shows that IFX has proved to be an efficient therapy for the treatment of the different aspects of active AS, including axial, articular and extra-articular manifestations. The inhibition of the immune system mildly increases the risk for general infections and opportunistic agents; other serious adverse effects, such as malignancy, autoimmunity and congestive heart failure exacerbation, have been described, but there are no specific guidelines about these issues (62).

These data on effectiveness and safety have been confirmed by a 5-year retrospective study, also with the purpose of identifying predictors of disease outcome. Seventy patients with AS and inadequate response to NSAIDs were enrolled and treated with iv IFX administered at 0, 2, 6 weeks and every 4 weeks for a 5-year period. These data confirm that IFX therapy is safe, tolerable and effective in AS patients, causing a rapid and persistent improvements in BASDAI 50 and ASDAS scores. The female gender, the use of steroids and high inflammatory levels seems to be a negative predictor of drug response and disease outcome. Moreover, the improvement noted in disease activity, mobility and function was maintained over the 5-year study period (63).

If we consider the early non-radiographic phase of AS, since its identification as a distinct entity, many studies have been made comparing it to the radiographic phase; the data have confirmed that these patients have comparable disease burden and so both need treatment. Not all the nr-axSpA patients will progress to AS if left untreated and many of them will not develop any structural changes in the spine, so systemic treatment with biologics may not be justified. Soliman *et al.* published the first study evaluating the effectiveness of local IFX injection into the sacroiliac joints (SIJs) of 7 nr-axial SpA patients with active sacroiliitis, non-responders to NSAIDs. Follow-up MRI was done at 24 weeks post-injection. This study showed that there was a significant decrease in back pain, stiffness, and BASDAI indices; all patients achieved ASAS20 and five (71.4%) achieved ASAS40. These results highlighted that SIJ injection of IFX could be a therapeutic option in early nr-axial SpA who failed to respond to NSAIDs, with comparable efficacy to systemic anti-TNF- α (64).

Adalimumab

In 2015, the ABILITY-2 trial was conducted to evaluate the efficacy and safety of adalimumab (ADA) in SpA. Patients with peripheral SpA with active disease, a score of at least 40 mm on a 0–100 mm VAS pain and VAS disease activity and an inadequate response or intolerance to NSAIDs, were randomised 1:1 to receive ADA 40 mg every other week or placebo for 12 weeks, and then ADA for 144 week. The primary endpoint of the study was a novel composite efficacy outcome measure: the proportion of patients achieving the Peripheral SpA Response Criteria (PSpARC40) at week 12. The PSpARC40 was defined as $\geq 40\%$ improvement from baseline in the VAS scores for patient's global assessments of disease activity and patient's global assessment of pain, and $\geq 40\%$ improvement from baseline in at least one of the following features: swollen joint count, tender joint count, total enthesitis count, dactylitis count. The results of the study showed that a significantly greater percentage of pa-

tients with peripheral SpA treated with ADA achieved a PSpARC40 response at week 12 compared to patients treated with placebo, with a significant difference observed as early as week 2. The only predictor of response to ADA was the baseline CRP level. The overall incidence of AE was similar in the two groups (65).

Two other studies published in the past year investigated the long-term effectiveness of ADA. In the first study ADA was administered to patients with active nr-axSpA. ADA seemed to be effective on clinical and radiological outcomes at 2 years and the use of this drug in early phases may prevent radiographic damage and be associated with low disease activity or remission. The study also confirmed its good safety and tolerability profile (66).

In another study they investigated the long-term maintenance of spinal mobility, physical function and quality of life in patients with AS after 5 years of treatment with ADA in the ATLAS trial, an RCT demonstrating the short-term (12–24 weeks) improvements in physical function, disease activity, general health and ASQoL in patients treated with ADA compared with placebo. The current study provided an assessment of the long-term improvement in spinal mobility using the linear BASMI (BASMI_{lin}), through 5 years of ADA treatment. BASDAI, BASFI, SF36, AS quality of life (ASQoL), total back pain and CRP were also assessed. Improvements in BASMI_{lin} were sustained through 5 years, with a mean change of -0.6 from baseline. Improvements in disease activity (BASDAI), total back pain and function (BASFI), ASQoL and CRP showed the same pattern. BASMI_{lin} was significantly correlated with all evaluated clinical outcomes ($p < 0.001$); the highest correlation was with BASFI at 12 weeks and at 5 years. Treatment with ADA for up to 5 years demonstrated sustained benefits in spinal mobility, disease activity, physical function and quality of life in patients with active AS (67).

Golimumab

Golimumab (GLN) has been shown to be efficacious in AS and nr-axSpA

with similar efficacy and safety profile as other anti-TNF- α . Many reviews published in the last year addressed this topic, demonstrating that GLN can reduce signs and symptoms of active SpA, improve physical function and quality of life, and reduce MRI inflammation, with a good tolerability (68, 69).

The novelty of GLM is perhaps its dosing regimen, *i.e.* subcutaneous self-administration once monthly, which allows for the least disturbance in the life of patients (70).

The publication of the 5-year results of the GO-RAISE study, in addition, showed that all the improvements achieved were sustained with up to 5 years of GLM treatment of patients with AS. In addition, long-term safety is consistent with that of other TNF-antagonists (71).

GLM was also investigated in a phase III, double-blind, randomised, placebo-controlled trial (GO-AHEAD) that evaluated sc GLM 50 mg vs. placebo in active nr-axSpA with high disease activity and inadequate response to or intolerance of NSAIDs. Patients treated with GLM showed significantly greater improvement in symptoms compared to that treated with placebo, with achievement of ASAS20 at week 16; also the secondary endpoints (ASAS40, BASDAI 50, ASAS partial remission etc) and functional, spinal mobility and quality of life assessments (BASFI, BASMI and MASES) have similar differences between the two treatment arms. GLM was also well tolerated and with a favourable risk/benefit profile (72).

The effectiveness GLM was compared with that of pamidronate (PAM) in a 48-week, randomised open-label trial, evaluating efficacy and tolerability and the effects on MRI inflammation, serum markers of inflammation and bone resorption. Patients with active SpA despite NSAIDs use were randomised 2:1 to receive sc GLM 50 mg or iv PAM 60 mg monthly for 48 weeks in an open label manner. GLM and PAM have similar effect on clinical response and improvement in PROs (BASDAI, spinal pain and health-related QoL). However, only GLM was effective in reducing levels of inflammatory mark-

ers (ESR and CRP), BASDAI, BASFI, ASDAS and MRI inflammation of the spine and the SIJ (73).

Certolizumab

Regarding certolizumab pegol (CZP), in the last year we had some news from the RAPID study; in this study a total of 325 patients with active axSpA were randomised 1:1:1 to receive placebo, CZP 200 mg every 2 weeks or CZP 400 mg every 4 weeks. For axSpA a study was published assessing the effects of CZP on patient-reported outcomes (PROs) during the 24-week, double blind phase of the RAPID axSpA. Patients treated with both dosages of CZP reported significant improvements in PROs: nocturnal back pain, ASQOL, total back pain, fatigue, SF-36, physical component summary (PCS), mental component summary (MCS) (74).

Another study investigated the incidence of uveitis flares in axSpA patients. During the 24-week double blind phase the rate of uveitis flares was lower in CZP than in placebo and this difference was maintained when considering only those patients with a prior history of uveitis. The incidence of uveitis flares remained low to week 96 and was comparable to rates reported for AS patients receiving other anti-TNFs (75).

For PsA a study reported the efficacy and safety of CZP over the 96-week open label period of RAPID-PsA. CZP efficacy in treating signs and symptoms of PsA was maintained over 96 weeks with both dose regimens and regardless prior anti-TNF exposure. The maintenance of improvements was observed across a broad range of disease manifestations including dactylitis, enthesitis, cutaneous manifestations and peripheral arthritis. No clinically relevant progression of structural damage over the long term was demonstrated in patients treated with CZP (76).

Novel biological agents

Anti-IL17

Interleukin-17A seems to have a role in the pathogenesis of PsA; in fact an increased number of cells producing this IL have been found in circulation, joints and psoriatic skin plaques. *Secukinumab* is a human monoclonal

antibody that targets and neutralises IL-17A. A recent double-blind, phase 3 study, enrolling 606 patients with PsA confirmed the efficacy of secukinumab confirming that IL-17A may be a therapeutic target. In this study patients fulfilling the Classification Criteria for Psoriatic Arthritis (CASPAR) and with an active disease despite previous therapy with NSAID, DMARD or TNF inhibitor (with a washout period of 4 to 10 weeks), were enrolled. A concomitant therapy with stable dose of MTX or glucocorticoids was allowed. The primary outcome was the ACR20 at week 24, the second outcome was the improvement of PASI75, PASI90, DAS28-CRP, SF36, ACR50 response and radiographic progression. 202 patients received intravenous (iv) Secukinumab at dose of 150 mg every 4 week, 202 patients received iv Secukinumab at 75 mg every 4 weeks and 202 patients received placebo. These last patients were switched to subcutaneous Secukinumab at dose of 150 mg or 75 mg at week 16 or 24, in accordance to clinical response. The proportion of patients with an ACR20 response was significant higher in the two groups treated with secukinumab than in the placebo group. The same result was found for the ACR50 response at week 24. Patients treated with Secukinumab showed a significant improvement of all the secondary outcomes and a less radiographic progression at week 24. During the 16-week placebo controlled study, adverse events (AEs) were found in 64.9%, 60.4% and 58.4% of patients treated with secukinumab 150 mg, secukinumab 75 mg and placebo respectively. Out of the serious AEs, 4 patients had a stroke (all receiving secukinumab 75 mg) and 2 patients (one treated with 150 mg and the other receiving 75 mg of secukinumab) had myocardial infarction. No cases of active tuberculosis or serious opportunistic infections were observed, except for candidiasis reported in 6 patients (4 patients oral candidiasis, 1 skin candidiasis and 1 oesophageal candidiasis), all receiving secukinumab. Malignant or unspecified tumours were found in 0.3% of patients treated with secukinumab 150 mg, 1% of subjects receiv-

ing secukinumab 75 mg and 0.5% of patients treated with placebo (77).

The phase 3, double-blind, placebo-controlled study enrolling 397 patients, subcutaneous secukinumab was administered at the dose of 300, 150 and 75 mg and the fourth group of patients received placebo (1:1:1:1). The patients in this last group were randomly assigned to receive 300 or 175 mg of secukinumab at week 16. The proportion of patients reaching the ACR20 response was significantly greater in patients treated with the three doses of secukinumab. PASI75, PASI90 responses rates and the change in DAS28-CRP and SF36-PCS were significantly greater in patients treated with 300 mg and 150 mg of secukinumab. The type and the incidence of AEs during the first 16 weeks were similar in the four groups. No deaths, no reports of suicide or suicidal ideation were reported during the study. Also in this study, candida infection was more frequent in patients treated with secukinumab than in those treated with placebo (78). The paper by Baeten *et al.* reported data from the primary analysis of MEASURE 1 and MEASURE 2. Eligible patients presented ankylosing spondylitis fulfilling the modified New York criteria, a BASDAI ≥ 4 and a score for spinal pain of 4 cm, despite NSAID therapy were enrolled. Previous treatment with DMARDs and TNF inhibitors were allowed, but with a washout period. In MEASURE 1, the patients were divided into two groups: in one patients were treated with iv Secukinumab (10 mg/kg) at baseline and weeks 2 and 4 and after with subcutaneous secukinumab (150 mg or 75 mg) every 4 weeks starting at week 8. In the other group placebo was administered with the same schedule and at week 16 the patients were randomly reassigned. The proportion of patients achieving ASAS20 was the first outcome measure and was met in both secukinumab groups (150–75 mg) compared to placebo; also all the secondary outcomes were met in both groups. In MEASURE 2, patients were treated with subcutaneous secukinumab (150 or 75 mg) or placebo at baseline and weeks 1, 2 and 3 and every 4 weeks from week 4.

The patients in the placebo group were reassigned at week 16. The first end point was the same than in MEASURE 1 and was met at week 16 in patients in which secukinumab was administered at the dose of 150 mg together with the secondary outcomes except for ASAS. The incidence of infections was higher in patients treated with secukinumab than placebo (MEASURE1). Between the EAs, neutropenia and candida infections were reported; in the MEASURE 1 increased levels of cholesterol and triglyceride were observed in patients treated with secukinumab, but this trend was not confirmed in MEASURE 2. In total, in the two studies, 2 myocardial infarctions (one resulted in death) and one stroke were observed in the secukinumab patients. One suicide in one patient receiving placebo was reported (79). The study by Baraliakos *et al.* reported data on patients with an active AS with baseline BASDAI ≥ 4 and a pain score (VAS) ≥ 4 treated with secukinumab. All the patients underwent an MRI at baseline and after 2 years and the study indicated reduced inflammatory activity after 2 years for the patients treated with secukinumab according to the Berlin score and VLevel findings (80). The recent report by Boyd *et al.* confirmed the fact that therapy targeting IL-17A can be an alternative treatment to TNF inhibitor in PsA, not only for skin involvement but also for peripheral arthritis. An ongoing trial (SPIRIT-P1) with *Ixekizumab*, a humanised monoclonal antibody targeting IL-17A, in active psoriasis had the primary aim to evaluate ACR20 response at week 24 (clinicaltrials.gov - NCT02349295) and preliminary results indicated that the outcome was met (81).

A recent review reported that *Brodalumab*, a human anti-IL17A receptor, may have good efficacy in psoriasis and in small studies a moderate-to-good effect on PsA has been indicated. However, more studies are needed to confirm these data and to better investigate the safety profile (82).

Anti-IL12 and Anti IL-23

Different studies have suggested a role of IL-12 and IL-23 in the pathophysiol-

ogy of PsA leading to the development of new therapeutic targets. *Ustekinumab* is a fully human monoclonal antibody that targets the subunit p40, shared by IL-12 and IL-23. It inhibits the activity of both cytokines. The recent report by Torres *et al.* indicated that ustekinumab improved signs and symptoms led to PsA and it may be a therapeutic option in patients that presented skin and articular involvement. It also presents a good safety profile (83).

Anti-IL6

• *Sarilumab*

The efficacy and safety of sarilumab in AS was investigated in the ALIGN study, a phase II, randomised, multicentre, double-blind, parallel-group, placebo-controlled study; AS patients with an inadequate response to NSAIDs or intolerant of NSAIDs were randomised to receive either SC placebo or one of five SC dose-regimens of Sarilumab (100, 150 or 200 mg every other week, or 100 or 150 mg every week) for 12 weeks. The primary efficacy end point was ASAS20 response criteria at week 12. The ALIGN study showed that SC-administered sarilumab was well tolerated but did not demonstrate a statistically or clinically significant effect compared to placebo. Sarilumab at high doses significantly reduced CRP values compared to placebo; this demonstrated that a biological effect of IL-6 blockade was achieved. However, lack of clinical or imaging improvement suggests that IL-6 may not play a major role in the inflammatory process underlying. Sarilumab showed a safety profile similar to reports with other IL-6 inhibitors: infections and laboratory abnormalities, including neutropenia, elevated transaminases and hyperlipidaemia were the most commonly observed safety findings (84).

Other treatments

Apremilast

Apremilast represents the first oral therapy specifically developed for PsA. It's a small molecule that targets PDE4, modulating intracellular signalling. Apremilast has been approved for the treatment of active PsA and psoriasis, based on clinical efficacy and a favour-

able safety profile. This is important in the treatment of this severe joint disease, since the role of conventional DMARDs in PsA is limited compared to RA. MTX appears to be efficacious only in a subset of PsA patients, but has no effect on enthesitis and dactylitis. Moreover, other conventional DMARDs have not been widely used in PsA because their benefits have not been promising (85).

Apremilast demonstrated to be effective for treatment of active psoriatic arthritis in the PALACE 1 trial, improving signs and symptoms; it seems to be very helpful in cases of enthesitis and dactylitis and in cutaneous psoriasis and it showed improvement in physical function and quality of life (85, 86).

Also, the high level of safety makes apremilast an attractive therapeutic option before treatment with biological therapy, including the fact that routine laboratory monitoring is not necessary (85, 87).

A substudy of the PALACE 1 trial also evaluated the pharmacodynamic effects of apremilast on plasma biomarkers associated with inflammation. In patients with active psoriatic arthritis apremilast reduced circulating levels of Th1 and Th17 proinflammatory mediators: IL-8, TNF- α , IL-6, MIP-1 β , MCP-1 and ferritin at week 24 and IL-17, IL-23, IL-6 and ferritin at week 40 were significantly decreased in the Apremilast arm. It also increased anti-inflammatory mediators like IL-10 and IL-1 receptor antagonists (88).

Physical therapy

Physical therapies seem to play an important role in the management of SpA, in particular to avoid stiffening in a flexed position and to improve functional capacity and life quality. In the 2015 Recommendations for the Treatment of Ankylosing Spondylitis and Non-radiographic Axial Spondyloarthritis, physical therapy is strongly recommended both in patients with active and stable AS. Active interventions are preferred to passive ones and the latter should be a supplement for the active (43). Recent RCTs have shown the importance of physical therapy on pain and function in SpA suggesting

starting this therapy at the beginning of the disease. However, although it is not clear what kind of protocol could be used and that there is a gap between physical therapy performed in RCTs and in daily practice, it is widely accepted that patient education, physical treatment and regular exercises may improve pain, physical function, mobility and help to prevent deformities. However, the data from the DESIR cohort showed no functional benefit for patients with early SpA treated by physiotherapy in the early stage of the disease. In this prospective study, 708 patients naïve of TNF blockers were enrolled and subjected to at least 8 supervised session of physical treatment at the beginning of the disease. The first aim was to evaluate the improvement of at least 20% in BASFI at six months; also secondary outcomes were evaluated (improvement in BASFI at 1 and 2 years and the ASAS20 response criteria at 6 months). Physiotherapy did not show any benefit both either on the primary or on the secondary outcomes (89).

A recent randomised single blind study on physical therapy reported that SpA patients might benefit from physical exercise and relaxation. In this study two groups were compared: the experimental group that underwent aquatic exercises and a relaxation programme and a control group that did not participate in any supervised exercise. Statistical analysis showed significant differences in the quality of life in the first group (90). As stated, among the different protocols of physical treatments, there is no standardised physical therapy approved for patients with low back pain. However, the McKenzie protocol, composed of repeated movements and sustained postures, is actually recognised as a standard approach for the assessment and the treatment of mechanical lower back pain. The study by Rosu *et al.* (91) aimed to demonstrate the efficacy of specific exercises derived from the McKenzie method by enrolling 52 patients with AS (according to the 1984 modified New York criteria, with early stage axial AS and without spinal, cardio-vascular and respiratory involvement). The patients

were divided into two groups: 28 in the McKenzie training group and 24 in a classical kinetic programme. A significant improvement in pain, metrolgy, disease activity and function was observed in the McKenzie group after both 12 and 24 weeks suggesting the inclusion of exercises derived from this programme in the standard-care of AS.

Local injection therapy

Steroid injection of sacroiliac is common used in the management of patients with SpA. In active AS and isolated active sacroiliitis, despite NSAIDs treatment, locally glucocorticoids are conditionally recommended in the 2015 Recommendations. Also in active enthesitis and in peripheral arthritis locally glucocorticoids are conditionally recommended. On the other hand, peritendon injections of Achilles, patellar and quadriceps tendons should be avoided (43). A recent study investigated the role of local therapy in patients with SpA and in particular tried to identify factors that may determine its efficacy. Twenty-nine patients with back pain and sacroiliitis confirmed by a contrast-enhancement MRI were enrolled and underwent a CT-guided glucocorticoid injection (40 mg of triamcinolone per joint in bilateral treatment and 60 mg in unilateral treatment). After treatment, the CT images were evaluated: 23 patients underwent a true intra-articular injection while in the other patients the needle tip reached the retro-articular space. All the patients presented an improvement of pain the day, the week and months after treatment. However, only the group that had the articular injection achieved sufficient pain reduction after 6 months. For this reason the authors concluded with the suggestion that this treatment should be carried out under appropriate image guidance (92).

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