

## One year in review 2018: axial spondyloarthritis

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### ABSTRACT

*Spondyloarthritis (SpA) is the umbrella term for a broad spectrum of inflammatory rheumatic diseases with typical but also rather different clinical manifestations, limited laboratory abnormalities and characteristic imaging features. For classification purposes, a so-called non-radiographic form (nr-axSpA) is differentiated from a radiographic one (r-axSpA) which is almost identical to the classical ankylosing spondylitis (AS) that is genetically strongly associated with the major histocompatibility complex class 1 antigen HLA-B27. In axSpA, the axial skeleton is affected by both inflammation and new bone formation, and joints might be affected. Rather typical musculoskeletal manifestations of SpA are enthesitis and dactylitis, the latter mainly in psoriatic arthritis (PsA). Extra-articular manifestations such as acute anterior uveitis (AAU), psoriasis (PsO) and inflammatory bowel disease (IBD) are also typical of SpA. In this paper we review the literature on axial SpA (axSpA) of 2018 (Medline search of articles published from 1<sup>st</sup> January 2018 to 31<sup>st</sup> January 2019).*

### Introduction

Spondyloarthritis (SpA) is the umbrella term for a broad spectrum of inflammatory rheumatic diseases with typical but also rather different clinical manifestations, limited laboratory abnormalities and characteristic imaging features. For classification purposes, a so-called non-radiographic form (nr-axSpA) is differentiated from a radiographic one (r-axSpA), which is almost identical to the classical ankylosing spondylitis (AS) that is genetically strongly associated with the major histocompatibility complex class 1 antigen HLA-B27. In axSpA, the axial skeleton is affected by both inflammation and new bone formation, and joints might be affected. Rather

typical musculoskeletal manifestations of SpA are enthesitis and dactylitis, the latter mainly in psoriatic arthritis (PsA). Extra-articular manifestations such as acute anterior uveitis (AAU), psoriasis (PsO) and inflammatory bowel disease (IBD) are also typical for SpA (in order of decreasing prevalence in AS) (1-3). In this paper we review the literature on axSpA of 2018.

### Methods

Following our regular annual reviews on different aspects of rheumatology (1, 2, 4-10) we will here provide a critical digest of the recent literature on axSpA of 2018 (Medline search of articles published from 1st January 2018 to 31st January 2019). In particular, we performed an on-line search on MESH database, using as key terms “chemistry”, “complications”, “diagnosis”, “drug therapy”, “epidemiology”, “genetics”, “imaging diagnosis”, “metabolism”, “microbiology”, “mortality”, “prevention and control”, “psychology”, “rehabilitation”, “surgery”, “therapy”.

### Axial spondyloarthritis

The term axSpA was introduced by the ASAS classification criteria of 2009 (11). This frequent inflammatory rheumatic condition primarily affects the axial skeleton, in early disease in particular the sacroiliac joints (SIj). While sacroiliitis (SI) without structural changes can only be detected by magnetic resonance imaging (MRI), erosions, sclerosis, joint space narrowing and ankylosis are detected by conventional radiography (12), with erosions and ankylosis being the most important. The basis for the classification as nr-axSpA or r-axSpA is the presence or absence of structural changes in the sacroiliac joints on x-rays. Since this is reportedly not very reliable, it has been proposed not to use the term nr-axSpA for diagnosis (13).

Competing interests: none declared.

## Epidemiology

The incidence and prevalence of axSpA, mainly including AS, have been investigated in many populations (14). The prevalence is probably around 1% of the population, and this is at least partly related to the prevalence of HLA B27.

Bohn *et al.* found a great variability for both, incidence and prevalence rates, in AS studies. Incidence rates per 100,000 person-years were between 4.0 (Iceland) and 15.0 (Canada), while the prevalence rates per 100,000 persons were 6.5 (Japan) and 540.0 (Turkey), respectively. The latter difference is due to the major difference in the HLA B27 prevalence which is only 0.4%. Another explanation could be the variation in the methodology used (*e.g.* screening method, study design, and classification criteria). More studies especially in so far under-reported populations (*e.g.* nr-axSpA; southern hemisphere countries) are needed. All studies should contain appropriate information on HLA B27 (15).

Inflammatory back pain (IBP), the key symptom of axSpA, is of limited value regarding selection of patients with axSpA in a chronic back pain population in primary care for referral to rheumatology. This was confirmed in a recent paper, in which it was reported that the net diagnostic gain for a diagnosis of axSpA was only 2.5–8.4% if the IBP criteria were fulfilled (16). The best criteria for referral of patients under suspicion of axSpA still need to be defined.

After 20 years from the initial diagnosis of IBD (n=470), including 314 patients with ulcerative colitis (UC) and 156 with Crohn's disease (CD), 4.5% had developed AS, 7.7% axSpA and 11.5% IBP. A chronic IBD course (chronic intermittent or chronic continuous) was associated with axSpA (17). The prevalence of axSpA was similar in the UC and CD but somewhat higher than previously reported (5.1% in the South Limburg cohort (14), while the prevalence of IBP was higher than in the general population (about 6%) (18).

## Chemistry

Normal bone homeostasis, which is regulated by bone-resorbing osteoclasts and bone-forming osteoblasts, is

perturbed by inflammation. In chronic inflammatory diseases with disturbed bone remodelling, *e.g.* RA, patients show increased serum levels of the chemokine eotaxin-1 (CCL11). Sohn *et al.* found that the serum levels of CCL11 were significantly correlated with both, the modified Stoke ankylosing spondylitis spine score (mSASSS) and the number of syndesmophytes in AS patients; this correlation was maintained even after adjusting for confounding factors (19). Similar to MMP3 CCL11 may well serve as a new biomarker for bone formation in AS (19, 20).

Another molecule that seems to be relevant for new bone formation in AS is sclerostin, a secreted glycoprotein produced primarily by the osteocytes with anti-anabolic effects on bone formation. It was recently confirmed that serum sclerostin levels were higher in healthy controls than in AS patients (21). However, serum sclerostin levels and mSASSS did not correlate and they did not change after 4 months of anti-TNF therapy. Therefore, more studies are needed (22).

The atherogenic index of plasma (AIP), a logarithmic transformation of the plasma triglyceride (TG) level to the high-density lipoprotein level (HDL) ratio, may be a novel marker for the identification of atherosclerotic risk. Patients with AS have an increased risk of cardiovascular disease (CD). Cure *et al.* found that AIP may serve as a marker for subclinical atherosclerosis, highlighting that AIP values were higher in AS than in controls and that AIP values correlated with carotid artery intima-media thickness (cIMT). Interestingly, the regression analysis revealed an independent association between cIMT and AIP, whereas no independent correlations were found with other parameters – suggesting that AIP could represent a marker for the detection of subclinical atherosclerosis that is even better than the ratio total cholesterol (TC)/low-density lipoprotein (LDL) in AS (23).

## Genetics

AS is a highly heritable polygenic disease with some influence of environmental factors. Disease susceptibility is

mainly but clearly not only influenced by the MHC class I molecule HLA-B27. Several non HLA-B27 MHC and some non-MHC genes are also involved. Recent genome-wide association studies showed an association between AS and polymorphisms of non-MHC genes, in particular ERAP 1, ERAP 2 and NPEPPS (encoding for aminopeptidases influencing antigen presentation by HLA class I molecules), and IL23R (encoding the receptor for the pro-inflammatory cytokine IL-23) (24).

Feng *et al.* investigated the disease-causing mutations in a large AS family, consisting of 23 patients covering four generations exhibiting a mixed HLA-B27 (+) and (-) status. Linkage analysis with HLA+ and - patients and healthy subjects did not identify a mutation common to all patients, confirming genetic heterogeneity in this large pedigree. A linkage analysis restricted to only B27-positive patients located a 22-Mb region harbouring the HLA gene cluster in chromosome 6 and the subsequent exome analysis identified two non-synonymous mutations in the triggering receptor expressed on myeloid cells like 2 (TREM2) and inositol hexakisphosphate kinase 3 (IP6K3) genes. These genes were subsequently resequenced among 370 sporadic AS patients and 487 healthy individuals, founding a significantly higher mutation frequency of TREM2 in AS patients (1.51% vs. 0.21%), suggesting that TREM2 is a susceptibility gene promoting the onset of AS in HLA-B27+ individuals (25).

Involvement of long non-coding RNA taurine-upregulated gene 1 (lncRNA TUG1) in bone diseases other than osteosarcoma has not been studied to date. In a recent study by Lan *et al.* TUG1 expression was significantly downregulated in AS patients compared to healthy controls in both, serum and open SI joint biopsies. Furthermore, TUG1 expression significantly correlated with patients' smoking habits, disease activity and course of disease (26). The role of TUG1 expression in AS needs to be further studied.

Hub genes are highly interconnected genes; several methods assess interconnectedness. Using differential expres-

sion network (DEN) and pathway enrichment analysis, four hub genes were recently found to be potentially involved in a relatively small study with 15 AS patients: USP7, HDGF, EP300, and SHFM1 which had not been reported to be associated with AS to date. The authors suggest that EP300 and SHFM1 could play a role in the pathogenesis of AS (27).

Single nucleotide polymorphisms (SNPs) of genes involved in TNF- $\alpha$  signalling have been potentially associated with SpA. Considering the potential role of autoinflammation in SpA, other possible candidate genes such as the *MEFV* (Mediterranean fever) and *TNFRSF1A* (TNF receptor superfamily member 1A) genes, were studied by an Italian research group in 82 PsA and 55 AS patients, 98 of 137 on treatment with a TNF inhibitor. The TNFA haplotype -1031C/-308G seemed to have a protective role while TNFRSF1A and MEFV gene SNPs showed no increased risk of developing SpA. The TNFRSF1A c.625+10A>G gene may have an impact on the response to anti-TNF $\alpha$  therapy (28). This study was probably underpowered since mixing PsA and AS in one relatively small genetic analysis is difficult.

Komech *et al.* analysed the repertoire of TCR sequences in healthy donors and AS patients, to discover possible AS-linked TCR variants, since antigen presentation and cytokine signalling pathways are likely involved in the pathogenesis of AS. A particular antigen-specific subset of CD8<sup>+</sup> T cells with high similarity to clonotypes described in ReA, was detected in both, peripheral blood and synovial fluid samples in AS pathogenesis. This suggests common disease mechanisms (29).

Ruan *et al.* performed a prospective cohort study to investigate gene polymorphisms of IL-1 and IL-23 cytokine pathways by investigating 5 potential SNPs in genes encoding for IL-23R, IL-12B, TYK2, IL-6R, and IL-1R. The finding that the frequencies of IL-12B AA and IL-6R TT alleles were increased in AS compared with healthy controls and that IL-12B AA was correlated to higher BASDAI and BASFI values, while IL-6R T (rs4129267) seemed to

predict a worse ASAS-20 response as an independent factor by multivariate logistic regression analysis is questionable based on the inefficacy of anti-IL-1, anti-IL6 and anti-IL23 agents in AS (30).

#### Extra-articular manifestations and comorbidity

In addition to the frequent extra-articular manifestations of AS, such as IBD, PsO and AAU, there is increasing evidence that patients with AS are at a higher risk of developing cardiovascular (CV), psychiatric, musculoskeletal, pulmonary, renal and neurological complications compared with the general population.

Walsh *et al.* compared the prevalence and incidence of comorbidities between patients with AS and matched controls in the U.S. and found that a higher proportion of AS patients had asthma, CV disease, depression, dyslipidaemia, gastrointestinal ulcers, malignancies, multiple sclerosis, osteoporosis (OP), obstructive sleep apnea syndrome (OSAS), and spinal fractures than matched controls (31).

In a Swedish AS cohort study, higher age expectedly increased the probability of comorbidity. Male sex was associated with a 5-fold risk of OSAS and with a 3-fold increased risk of arrhythmia and/or valvular heart disease, while early onset and a longer disease duration of AS were associated with a higher prevalence of arrhythmia and/or valvular heart disease. Hypertension was the most frequent comorbidity affecting 45% of patients, and more than 10% had diabetes, malignancy, asthma, ischemic heart disease, urogenital disease, dyslipidaemia, or non-spinal fracture, respectively. Multiple comorbidities, including OP and hospitalisation due to infections, were frequent in AS patients with CVD. The prevalence of spinal or non-spinal fracture was expectedly related to OP, but also with chronic obstructive pulmonary disease (COPD), congestive heart disease, diabetes, and urogenital disease. AS patients with OSAS often had more diabetes, dyslipidaemia, hypertension, and features of the metabolic syndrome (32).

There is evidence for increased cardiovascular and cerebrovascular morbidity and mortality in AS (33, 34).

Inline with that, Park *et al.* found an adjusted hazard ratio for acute myocardial infarction (AMI) of 1.81 in patients with AS (35). Ischaemic heart disease (IHD) was more frequent among AS patients as compared to controls in a study that also reported a higher prevalence of hypertension, hyperlipidaemia, DM and smoking among AS patients. After adjustment for these risk factors no independent association of AS with IHD was found. This emphasises the need for stringent control of traditional risk factors in this disease (36).

Bengtsson *et al.* confirmed earlier data by Bergfeldt showing that patients with SpA are at increased risk of aortic regurgitation, cardiac rhythm disturbances and pacemaker implantation (37, 38). The presence of carotid plaques and the coronary artery calcification (CAC) score were found to be good predictors of CV events in intermediate risk groups of non-rheumatic individuals, and the presence of plaques or high CAC Score (CACS) values were considered indicators of very high CV risk (39). Rueda-Gotor *et al.* reported that carotid US is more sensitive than CACS for the detection of a high CV risk in axSpA patients (40).

In a population-based cross-sectional study COPD was more frequently found in AS patients than in controls, and multivariate logistic regression confirmed an independent association between these conditions. There are many arguments favouring smoking cessation in AS patients (41).

Vitamin D deficiency has been associated with several inflammatory conditions (*i.e.* connective tissue diseases, RA). In a study by Fernandes *et al.* a higher prevalence of hypovitaminosis D was confirmed in SpA (enrolled from the ASAS-COMOSPA study initiative, an international cross-sectional study of patients with SpA). The finding that Vitamin D deficiency was associated with active SI needs to be confirmed (42).

Whether the kidneys are directly involved in pathologic processes in AS can be discussed. Mainly, amyloidosis

and IgA nephropathy have been described. Renal involvement has been defined by microscopic proteinuria (24h urine protein >0.2g), and/or microscopic haematuria (urine erythrocytes > 25/ $\mu$ l) and/or eGFR decrease (lower than 60mL/min/1.73m<sup>2</sup>) (43), but these are rather common kidney pathologies and not very specific. Of course, long-term use of non-steroidal anti-inflammatory drugs (NSAIDs) can be relevant for the development of renal insufficiency. Recent data obtained in a cohort of 925 AS patients, 201 of which had any renal problem, suggested that an increase in uric acid or immunoglobulin A, or a decrease of serum albumin may indicate kidney disease (44).

A study from Korea investigated the prevalence of Herpes Zoster (HZ) in patients with AS. The adjusted hazard ratio of HZ infections was significantly higher in cDMARD and TNF- $\alpha$  inhibitor (TNFi) users than in DMARD non-users. In particular, current treatment with TNFi increased the risk of HZ significantly in both, female patients and in patients aged >50 years, suggesting that HZ vaccination may be useful in these subgroups (45).

AAU is a characteristic extra-articular manifestation of AS that can occur at any time during the disease course. Recent studies have confirmed that AAU is more frequent in male AS patients, HLA-B27 positives and those who had previous episodes of AAU. Evidence-based guidelines for the management of AAU in AS are currently not yet available (46).

Yang et al. investigated whether the HLA-B27 status had an influence on AAU in AS patients. HLA-B27+ AS patients were more frequently males, had more bilateral ocular involvement, a higher frequency of fibrinous exudates, synechiae and secondary glaucoma as compared with HLA-B27+ patients with no evidence of AS. Moreover, visual outcome was poorer, possibly due to the higher prevalence of complicated cataract in HLA-B27+ AS patients. Interestingly, this analysis showed that retinal involvement was not rare in HLA-B27+ AAU, but for the development of this complication, the presence of AS was not a risk factor (47).

### Imaging

Different imaging techniques are useful tools for diagnosis, prognosis, and monitoring of the response to therapy in SpA. They detect both, inflammation and structural damage. The sensitivity and specificity of the different techniques and scoring systems, also including subclinical spondylitis, synovitis and enthesitis, is critical for the understanding of their performance.

#### Ultrasound (US)

Yurdakul *et al.* reported that the difference of the distance between T11-T12 and L4-L5 between the flexed and erect position, as measured by US, was reduced. They also found that a difference <0.79 cm between T11-T12 may identify a significant decrease in lumbar sagittal mobility<sup>48</sup>. It is unclear whether this is any better than a standardised physical examination.

#### Positron emission tomography (PET)

PET/MRI has been used to detect osteoblastic activity in different kinds of lesions identified by MRI. Sawicki *et al.* studied 13 patients with active AS who underwent 18F-Fluoride PET/MRI of the SIJ. They reported that inflammatory rather than chronic AS lesions were associated with regional hyperaemia and osteoblastic activity (49).

Bruijnen *et al.* confirmed that PET-CT cannot only identify bone formation in AS, but can also detect bony changes during anti-TNF therapy (50).

#### MRI

Currently, a novel MRI technique, iterative decomposition of water and fat with echo asymmetry and least square estimation (IDEAL), is increasingly used to evaluate lipid metabolism; it is a robust method for the quantitative evaluation of fat content and provides information on the fat spatial distribution. Guo *et al.* reported that IDEAL may be useful as a quantitative and objective method for evaluating the fat infiltration in the periarticular bone marrow of SIJs in patients with AS. They also found that the sensitivity of IDEAL was better than that of routine sequences in detecting micro-fat infiltration of SIJs and can be used to quantitatively

assess the fat content of tissue and to potentially detect changes after treatment (51). This technique needs further study.

#### Computed tomography (CT)

CT is the most appropriate method for assessing new bone formation, but its radiation exposure has limited its use in follow-up studies to date. However, with the development of new hardware and software, most notably the multi-slice scanners, iterative reconstructions and progress in imaging protocols, low-dose CT (ldCT) is likely to be a viable alternative for spinal radiographs.

De Bruin *et al.* developed a scoring method for the assessment of syndesmophytes in the spine of patients with AS, the CT Syndesmophyte Score (CTSS). The authors demonstrate that new bone formation in the spine can be reliably assessed. They confirmed earlier data that most progression during the follow up period was seen in the thoracic spine (52, 53).

From the same cohort of patients de Koning *et al.* compared the CTSS for low-dose CT with the mSASSS for CR, observing that, covering the whole spine, ldCT detects 50% more progression compared with CR that is limited to the cervical and lumbar spine. Thus the authors demonstrate a superiority of ldCT in assessing new bone formation in the spine of AS patients (54).

### Disease activity, quality of life and working ability

AS can cause employment obstacles and can result in a serious socio-economic load.

A study conducted by Boonen and colleagues showed the presence of contextual factors (the quality of contact with colleagues, the possibility of postponing work, the presence of more than 50 workers in the company and the degree of manual profession) able to influence work outcomes over time, that should not be ignored when aiming at improving work outcomes in patients with AS (55).

It is well known that AS usually develops when people are more likely to be working and receiving an income, but little is known about the effects of in-

terventions reducing pain and improving the economic circumstances of patients out of the labour force due to AS. Schofield *et al.* observed an additional 131 people aged 19–64 with AS (111 males, 20 females) would be in the labour force after using adalimumab (ADA) for 24 weeks. National benefits consisted of an increase in annual earnings of AU\$7.4 million for patients, due to increased labour force participation, savings of \$2 million in annual welfare payments, and an increase of \$1.3 million in income tax revenue (after 24 weeks), thus showing substantial economic benefits in addition to health benefits for individuals, and savings for government (56).

Sağ *et al.* confirmed how AS significantly influences working conditions and work productivity. In particular, they found the impairment in the work productivity resulted associated with BASDAI and depression, difficulty in time-off activities was correlated with BASFI, anxiety and depression were correlated with BASDAI. Considering the items of SF-36, the impairment in work productivity was correlated with the subparameter vitality, whereas difficulty in time off activities was correlated with general health status, social functions, vitality and mental health<sup>57</sup>. Analysing the theme of participation in society of persons with chronic diseases, a Dutch cross-sectional study showed that AS patients were significantly more frequently dissatisfied with life than controls (17.9% vs. 8.6%). In particular, less physical difficulty and higher satisfaction with interpersonal relations and leisure were associated with higher satisfaction with life and satisfaction with work was independently associated with satisfaction with life, thus suggesting it would be important to support persons with AS, trying to improve their social role participation, particularly in those areas that tend to be ignored in the clinical assessment of AS patients, as close relationships and leisure activities (58).

A study from Taiwan showed that biological disease-modifying anti-rheumatic drugs (bDMARDs) might assure a better quality of life (evaluated through-out short-form 36 and Global Quality of

Life scale) and a lower risk of relapse (defined as defined as the QoL becoming worse than that before bDMARD treatment) in AS patients (59).

Esen *et al.* aimed at defining anxiety and depression rates in RA and AS patients (under treatment) with similar age and gender; their data confirmed how chronic pain-related diseases are often associated with mental disorders, especially depression and anxiety; therefore, a multidisciplinary approach including psychiatric support should be taken into account when planning treatment for patients with AS (60).

A Turkish study highlighted a role of AS in compromising sleep quality (SQ), in particular in those patients with a scarce control of disease activity; anti-TNF alpha therapy improved SQ parameters, but not polysomnography, thus suggesting that in patients with AS, its determinants might be more associated with disease pathogenesis rather than disease activity (61).

Another study on SQ in axSpA was conducted by Wadeley and colleagues. About 20% of the analysed patients were classified as poor sleepers; they had higher values of disease activity and fatigue scores and more night-time back pain than good sleepers. Moreover, a poor SQ appeared associated with poor mood, female gender, greater fatigue, greater disease activity (specifically, spinal pain and stiffness) and compromised mobility; however, the authors were not able to determine the direction of causality between poor sleep and markers of active disease (62).

Inline with that, Nie and colleagues showed that patients with extra-spinal manifestation, depression and anxiety, longer duration of diagnostic delay, higher disease activity, worse functional status and global well-being, high level of pain and fatigue, had poorer SQ. They suggested to improve SQ in AS patients keeping regular exercise, strengthening the management of pain, relieving anxiety and preventing/treating extra-spinal manifestation (63).

Another recent study investigated the prevalence of psychological disorders, sleep disturbance, and stressful life events in a cohort of AS Chinese patients. They confirmed more severe

anxiety, depression, sleep disturbances and stressful life events in AS than controls; moreover, their results also underlined that pain, functional limitation, sleep disturbance and education were major contributors to psychological disorders in AS patients (64).

Madsen performed a study aimed at examining the natural variation of the patient-reported outcome (PRO) evaluating fatigue, pain, patient global assessment (PaGI) and the Bath Ankylosing Spondylitis Functional Index (BASFI) in patients with ax-SpA defined “stable” on the basis of the BASDAI (a change in BASDAI <20 between two consecutive visits). Very interestingly, they found that in axSpA patients in a “steady state” on the basis of BASDAI, a natural variation of PRO measures seemed substantial and unpredictable; therefore, the authors suggest to interpret with caution clinical changes observed in the daily routinary assessment of patients (65).

Another study on patients with AS and nr-axSpA in a phase of inactive disease (defined as values of ASDAS CRP <1.3) was performed in Italy from Monti *et al.* They found that concomitant fibromyalgia, decreased spinal mobility and concomitant therapy with NSAIDs had an influence on the prevalence of inactive disease in axSpA patients (66).

Van Tubergen *et al.*, starting from the concept that patients’ experience of overall health is often assessed through a single-item global question, evaluated if single-item questions on the constructs health, well-being and QoL were interchangeable, comparing patients with AS and population controls. They confirmed that patients and controls identified content-related dissimilarities among the three analysed constructs; however, this was not reflected in different scores of the globals, thus indicating the possible need of a more specific evaluation of health-related themes in AS patients (67).

Meghnathi *et al.* observed that Extreme PRO, defined as a score  $\geq 8$  on at least three of first five BASDAI items, were present in less than 15% of patients with early axSpA. Patients with extreme PRO were older, more frequently females, had higher BASDAI, reported

more frequently history of depression and use of anti-depressive drugs. As expected, they were more likely to receive anti-TNF alpha; however, they were less likely to maintain the treatment at 2 years (68).

## Therapy

### *TNF-alpha inhibitors*

Zardi *et al.* studied the prevalence of atherosclerosis in patients with AS treated with TNF inhibitors (TNFi), compared with age- and sex-matched healthy controls. Patients with AS had significantly lower values of intima media thickness (IMT) at the common carotid artery and the carotid bulb and also less carotid plaques than the healthy controls. However, no differences were found in IMT values at the level of internal carotid between the groups. Whether these results are related to the reduction of inflammation, remains unclear at present (69).

A head to head comparison regarding the treatment of AS patients with NSAIDs or TNFi in therapy naïve patients has not been performed to date. Whether NSAID use concomitant to biologics has additional efficacy is not really known. A Dutch study group, analysing consecutive patients from the Groningen Leeuwarden AS cohort, reported that NSAID use decreased significantly after starting TNFi, while, on the contrary, it remained stable during conventional treatment. In general, NSAID use changed frequently at an individual patient level and was significantly associated with disease activity. Some AS patients may be able to completely stop NSAIDs during TNFi therapy (70).

Lian *et al.* retrospectively analysed the efficacy of different discontinuation strategies of etanercept (ETN) in a cohort of 258 Chinese patients with axSpA in stable remission or low disease activity. Their data show that it may be feasible to slowly increase the dosing interval, thus trying to reach the lowest effective dose. In particular, tapering by 25% of the ETN starting dose every 3 months, seemed to be a good and cost-effective choice (71).

A retrospective analysis of data collected from 122 Dutch AS patients treated

with ETN, infliximab (IFX) and ADA, aimed to find gender differences in relation to TNFi drug survival and occurrence of adverse events in daily practice. Female patients had significantly shorter treatment periods compared to males and more switches of TNFi. Patients on ETN showed the highest number of switches within the first 20 months, and the most common switch was to ADA. Moreover, being positive for HLA-B27 and the use of co-medication were predictors for switching. Interestingly, both female sex and age were associated with a higher infection risk (72).

A study from the South Korea showed that the mSASSS, C reactive protein (CRP) and the body mass index at baseline, being a current smoker, and a delayed start of TNFi use were all associated with radiographic progression, while the presence of peripheral arthritis and the TNFi index (defined as the ratio of the period of TNFi use to the entire period of disease) seemed to protect against its development, thus underlying how an early and long-term use of TNFi may reduce or decelerate radiographic damage in patients with AS (73).

Thomas *et al.* analysed the long-term survival on golimumab (GOL) of patients with RA, PsA and AS showing that AS patients remained significantly longer on therapy than those with RA and PsA. There was no difference between biologic-naïve and -experienced patients, nor between non-biologic concomitant therapy or GOL monotherapy treated patients. Finally, a good safety profile of GOL was confirmed in real life (74).

Ruwaard *et al.* reported differences in retention rates and clinical outcomes in biological-naïve AS patients treated with ADA or ETN. The latter seemed to have longer drug survival in their cohort (owing to inefficacy, adverse events, loss to follow-up, planning a pregnancy, or uveitis). However, no difference was noted in the mean reduction of disease activity (mean ASDAS-CRP value and percentage of patients in moderate disease activity, defined as ASDAS-CRP <2.1) between the two groups (75).

Martínez-Feito *et al.* performed an

observational prospective study to investigate the association between serum GOL trough levels, clinical disease activity and treatment response during the first year of therapy in patients with axSpA. Both, in univariable and in multivariable analyses, serum GOL trough levels were inversely associated with disease activity. Moreover, the authors found that a concentration range of 0.7–1.4 mg/L seemed to be useful to achieve a good clinical response (76).

A recent study on the Swiss Clinical Quality Management cohort investigated the impact of TNFi on spinal radiographic progression in AS (defined as an increase in  $\geq 2$  mSASSS units in 2 years). Prior use of TNFi reduced the odds of progression by 50% in the multivariable analysis; while no direct effect of TNFi on progression was present in an analysis including time-varying ASDAS, the indirect effect, via a reduction in ASDAS, was statistically significant, thus confirming a role of TNFi in reducing the accrual of spinal damage in AS patients, reasonably thanks to their capability to inhibit disease activity (77).

Bornstein and colleagues confirmed that immunogenicity may compromise the efficacy of TNFi, especially ADA and IFX) in patients with axSpA. The authors favour a strategy that includes the measurement of anti-drug antibodies and drug levels to have a more tailored treatment of patients (78).

The Spanish Register of Biological Therapy in Spondyloarthritis registers patients with axSpA on biologic treatment since 2013, including both, patients starting biologics (incident patients) and those already on biologics (prevalent patients). Moreno *et al.* studied whether disease activity and function at treatment initiation has changed after publication of the ASAS classification criteria, highlighting that biologic therapy is administered earlier than previously and in a higher proportion also of patients with nr-axSpA (79).

The ABILITY-3, a multicentre, two-period study, explored the ability to withdraw ADA in patients with nr-axSpA who achieved sustained clinical remission after open-label treatment. Patients who achieved sustained remission were

randomly assigned to double-blind treatment; 70% of patients continuing ADA versus 47% of those receiving placebo did not experience a flare up to and including week 68, thus showing a significant protective role of continuous treatment with ADA in maintaining disease remission (80). However, almost half of the patients did not experience a flare after discontinuation.

#### *Interleukin-17A inhibition*

An extension of the phase 3 MEASURE 1 trial evaluated the efficacy and safety of the human anti-IL 17A monoclonal antibody secukinumab in AS over 3 years. In agreement with previous reports, it confirmed a sustained efficacy of secukinumab to control signs and symptoms of the disease and in maintaining physical function in AS patients over 3 years, with a favourable safety profile. The exposure-adjusted incidence rates for serious infections including *Candida*, CD, UC, malignant/unspecified tumours and adjudicated major adverse cardiac events per 100 subject-years were low (81).

Similarly, Braun and colleagues, presented data of the open-label 3 year extension of MEASURE 1, highlighting the sustained efficacy of secukinumab on signs, symptoms and MRI outcomes, in association with low rates of both, radiographic progression and adverse events, confirming the overall consistent safety profile (82). Analysing pooled data from MEASURE 1 and MEASURE 2, Braun *et al.* reported that the rapid and sustained efficacy of secukinumab 150 mg in patients with AS was largely irrespective of baseline CRP values with, however, a greater magnitude of response in patients with an elevated CRP at baseline (83).

#### *Small molecules*

Maksymowych *et al.* used the definition of Minimally Important Changes (MICs) for SpondyloArthritis Research Consortium of Canada (SPARCC) MRI scores ( $\geq 2.5$  for SIj and  $\geq 5$  for spine) in biologic-naïve patients with AS treated with tofacitinib or placebo. The MIC for SIj and spinal MRI scores were achieved by more patients treated with tofacitinib. About a third of tofacitinib-

treated AS patients experienced a significant reduction in spinal MRI scores at week 12 (84).

#### *NSAIDs*

Yan *et al.* studied the ability of NSAIDs to control AS activity by regulating the level of proinflammatory cytokines. In particular, the erythrocyte sedimentation rate, CRP and IgA levels were lower after NSAIDs therapy than before treatment. Moreover, after treatment, the levels of IL-6, IL-17, and TNF- $\alpha$  were markedly reduced. In patients with a very good response to NSAIDs, IL-10 levels increased, while IL-12 levels decreased (85). The significance of this finding is not clear.

The novel NSAID  $\beta$ -d-mannuronic acid (M2000), a strong inhibitor of COX-1/COX-2 enzymes, specifically suppresses the gene expression of COX-2. Fattahi and colleagues reported that the administration of M2000 in AS patients leads to a down-regulation of Th17 and Th17-related cytokines that may correct the Th17/Treg imbalance, with possible improvement of disease activity (86).

#### *Bisphosphonates*

Li *et al.* retrospectively analysed 86 patients with AS treated with alendronate, observing that alendronate did not show a higher efficacy either to treat bone loss, or to enhance the quality of life, disease activity, and functional status in this kind of patients (87).

#### *Physical exercise*

The decline of spinal mobility is a hallmark of AS, in the earlier stages due to inflammatory pain, during the course of the disease due to ankylosis. However, spinal mobility does physiologically also decrease with age. A Swedish group tried to assess predictors of spinal immobility in AS patients. They found exercise habits may have an impact in preventing the development of spinal immobility in AS independently of disease duration and inflammation, thus confirming exercise should be considered a significant part of the non-pharmacological treatment and self-care for patients with AS (88).

Similarly, Coksevim *et al.* studied a global postural re-education exercise

programme which seemed to increase the improvement of pain, function, and mobility in patients with active AS (89). Another study on physical exercise, performed by a Turkish group, showed that balance and stability exercises could increase the duration of maintaining balance and could improve the benefits of physiotherapy in patients with AS (90).

#### *Surgery*

Britto and colleagues analysed the clinical and laboratorial characteristics of AS patients who underwent spinal surgery at their institution, observing 50% cases of aseptic spondylodiscitis, 37.5% cases of spinal fractures and 12.5% cases of cervical kyphotic deformity. These clinical findings tend to be discrepant with the literature, with a higher incidence of spondylodiscitis and a lower incidence of vertebral fractures, maybe due to regional characteristics or to the fact that the analysed population included only those patients who underwent spinal surgery (91).

A study group from China evaluated the main determinants of satisfaction after a total hip arthroplasty in patients with AS. They found that the improvements in joint function and self-care ability after total hip arthroplasty seemed to be the most important factors in determining patient satisfaction, in particular in AS patients with hip fusion (92).

#### *Therapy for comorbidities*

Navarro-Millán *et al.* analysed patients from the Reasons for Geographic and Racial Differences in Stroke (REGARDS) study to understand if patients with inflammatory arthritis (IA) (PsA, AS and RA) were sufficiently treated for dyslipidaemia, considering that hyperlipidaemia guidelines do not currently identify IA as a CVD risk factor. The fully adjusted odds of treatment were similar between participants with and without IA, hypertension, or diabetes. On the contrary, patients with diabetes and no IA and patients with hypertension and no IA were twice as likely to be treated for hyperlipidaemia as those without IA, diabetes, or hypertension. These data confirm the need to update hyperlipidaemia guidelines for

patients with IA, that should be considered as an independent risk factor for CVD, to optimise the treatment and the clinical assessment in this kind of patient (93).

### Conclusion

There are five studies that deserve to be highlighted. First, we like to stress that the new technique of low dose CT (52, 54) is a major step forward in our ability to assess new bone formation in AS. This implies that the old well evaluated technique of CR scored by mSASSS did have limited sensitivity to change which does explain some of the data published in the last decade. Nevertheless, even with that limitation it seems now clear that using TNFi in AS is associated with less radiographic progression over time, and this depends also on effects on CRP (77). CRP was confirmed to be a good indicator of treatment response also for anti IL-17 therapy but it was also shown that patients with normal CRP show significant response rates (83). It is not entirely clear whether this is similar for TNFi. An important study with patients classified as nr-axSpA (80) showed that discontinuation of adalimumab was possible after treatment success, since almost 50% of patients remained flare-free for several months, but continuation of anti-TNF therapy had higher success rates, which this leaves room for different treatment strategies. Taken together, we found evidence of definite progress in the field.

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