

One year in review 2017: spondyloarthritis

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ABSTRACT

The term spondyloarthritis (SpA) represents a condition characterised by a broad spectrum of clinical manifestations, laboratory abnormalities and imaging features; in particular, SpA is an inflammatory condition in which both peripheral and axial joints might be affected. The majority of people with this disease have either psoriatic arthritis or axial spondyloarthritis, which includes ankylosing spondylitis. Less common subgroups are enteropathic SpA, which is associated with inflammatory bowel diseases (Crohn's disease and ulcerative colitis), reactive arthritis, which can occur in people following gastrointestinal or genitourinary infections and undifferentiated SpA, that does not meet the diagnostic criteria of the other subgroups at onset, but that may evolve to do so later. Very interestingly, much of the emerging data show how SpA, during its course, tends to associate with the development of some comorbidities; in particular, with cardiovascular diseases, diabetes mellitus, osteoporosis and depressive disorders. Healthcare professionals in non-specialist settings do not always recognise the signs and symptoms of SpA, particularly spinal symptoms, which may be mistakenly attributed to other causes of low back pain, thus leading to significant delays in diagnosis and treatment of the disease itself and of its related comorbidities, with consequent disease progression and disability, compromising the health-related quality of life of patients. In this paper we reviewed the literature of the past year (Medline search of articles published from 1st March 2016 to 28th February 2017) with the aim of approaching the spectrum of SpA from some different points of view, to try to give the reader an insight into this clinically challenging group of rheumatic pathologies.

Introduction

The term spondyloarthritis (SpA) represents a condition characterised by a broad spectrum of clinical manifestations, laboratory abnormalities and imaging features, that genetically tend to be associated with the major histocompatibility complex class I antigen, HLA-B27. In particular, SpA is an inflammatory condition in which both peripheral and axial joints might be affected. Chronic back pain is the leading symptom of an axial involvement, with pronounced stiffness and improvement of pain and stiffness with exercise. Other musculoskeletal manifestations are arthritis, enthesitis and dactylitis. Extra-articular manifestations such as anterior uveitis, psoriasis and inflammatory bowel disease (IBD) (in order of decreasing prevalence) are also characteristic for SpA. The majority of people with this disease have either psoriatic arthritis (PsA) or axial spondyloarthritis (ax-SpA), which includes ankylosing spondylitis (AS). Ax-SpA primarily affects the spine, in particular the sacroiliac joint; based on the presence of a sacroiliitis (SI) detectable on x-ray, they are actually classified in AS or in non-radiographic ax-SpA (nr ax-SpA). PsA may manifest in a number of different patterns, with a major involvement of the small joints of the hands and feet, or predominant large joint involvement particularly in the knees or a combination of these. It may also involve the axial joints, and inflammation of the entheses and/or finger and toe joints. Skin and nail involvement may not be present at diagnosis and in its absence, a family history of psoriasis is required to meet the diagnostic criteria. Less common subgroups are enteropathic SpA, which is associated with IBD (Crohn's disease and ulcerative colitis), and reactive arthritis, which can occur in people following gastrointestinal or genitourinary infections. The final subgroup is

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people who have undifferentiated SpA (uSpA). These people generally have an asymmetrical oligoarticular (fewer than 5 involved joints) arthritis, often involving the knees. They do not meet the diagnostic criteria of the other subgroups at onset, but they may evolve to do so later (1).

Very interestingly, a great deal of emerging data show how SpA, during its course, tends to associate with the development of some comorbidity; in particular, with cardiovascular diseases (CVD), diabetes mellitus, osteoporosis (OP) and depressive disorders, but renal, neurologic and pulmonary disorders have also been reported (2).

Healthcare professionals in non-specialist settings do not always recognise the signs and symptoms of SpA, particularly spinal symptoms, which may be mistakenly attributed to other causes of low back pain. This can lead to substantial delays in diagnosis and treatment of the disease itself and of its related comorbidities, with consequent disease progression and disability, that seem to significantly compromise work ability, work quality and, more generically, the health-related quality of life (HRQoL) of this kind of patient (3).

Following the previous annual reviews of this publishing series (1, 4-16), we will here provide a critical digest of the recent literature on pathogenesis, clinical features and novel treatments of SpA. In this paper we reviewed the literature of the past year (Medline search of articles published from 1st March 2016 to 28th February 2017) with the aim of approaching the spectrum of SpA from some different points of view, to try to give to the reader an insight into this clinically challenging group of rheumatic pathologies.

Epidemiology

Over the past 12 months an alternative approach to the epidemiologic research, based on the codified extrapolation of data from administrative databases, has been proposed by Dubreuil *et al.* (17). The analysis of data included in electronic health record (HER) datasets allows for a more reliable approach to epidemiologic research, minimizing the risk of random error associated with

smaller studies and providing a better power to estimate effects and risk factors. The longitudinal design of large HER also allows long-term analysis, time-varying exposures and secular trends. However, the identification of specific disease features that might only be included as free-text within clinical notes can be challenging. The authors developed an algorithm that allowed to identify patients with AS within The Health Improvement Network (THIN), a large British primary care HER including health records for over 10 million of people in the UK. At least 2 AS diagnoses confirmed ≥ 7 days apart, or a diagnosis in combination with a DMARD or biologic drug prescription showed the highest positive predictive value in identifying the diagnosis. Among the identified cases, peripheral arthritis was common (41%), as was psoriasis (19.7%). Laboratory and radiographic features of SpA were also common (24.6-62.3%) (17).

Data from the ESPERANZA Study Group, a Spanish program developed for the early diagnosis of SpA, showed that familial cases of ax-SpA [presence of a first- or second-degree relative with ax-SpA or related-features as defined by the Assessment of SpondyloArthritis international Society (ASAS)] significantly differed from sporadic cases in terms of age at diagnosis (29.4 ± 9.2 vs. 31.5 ± 10 years), higher frequency of HLA-B27 positivity, lower BASMI and fewer signs of SI on magnetic resonance imaging (MRI) scans (18).

Significant differences in disease pattern and severity have been described between male and female patients with ax-SpA: male patients are younger despite a longer diagnostic delay, have a lower disease activity but a worse spinal mobility, secondary to more severe radiologic damage. Overall, they report a better quality of life (QoL) despite a higher permanent work disability. Conversely, dactylitis and enthesitis and higher swollen joint count are more frequent in women (19).

A retrospective study conducted from a dermatologic perspective on 278 patients with psoriasis identified a prevalence of psoriatic arthritis (PsA) of 30% (of whom only 8% had axial disease),

in line with previous reports and other recent publications (20, 21). On the other hand, 51% of patients with PsA had nail psoriasis. PsA patients were confirmed to be associated with higher rates of comorbidities, particularly risk factors for CVD, such as hypertension, diabetes and hypercholesterolaemia (22, 23).

Eder *et al.* prospectively followed patients with psoriasis for 8 years to investigate the incidence and risk factors for the development of PsA. The authors reported a higher incidence than expected from previous reports (2.7 cases per 100 psoriasis patients). Severe psoriasis, nail pitting, low level of education, and uveitis seemed to predict the development of PsA. Ax-SpA was diagnosed in 17.6% of patients, 44% of whom had nr ax-SpA with MRI evidence of SI, underlying the importance of identifying predictive factors able to help in the early diagnosis of SpA (24).

Faustini *et al.* explored the pre-clinical stage of PsA by performing an MRI scan on patients with psoriasis without a diagnosis of PsA. About half of the patients showed inflammatory lesions on MRI, 38% of whom had signs of synovitis, 11% osteitis, 4% tenosynovitis, 4% periarticular inflammation. The risk for developing overt PsA was 60% in patients with subclinical synovitis and arthralgias versus 13% in asymptomatic patients with normal MRI findings (25).

Aetiopathogenesis

An association between cartilage degradation serum markers (the procollagen IIA N-terminal peptide and a matrix metalloproteinase-generated type II collagen fragment) and disease activity in ax-SpA, particularly if untreated, has been confirmed together with an association with HLA-B27 positivity and smoking. Cartilage synthesis biomarkers were also found to be increased in PsA, without a strict correlation with disease activity (26). The IL9/IL9R axis has been demonstrated to play a relevant role in the pathogenesis of PsA, independently from IL23/IL23R, enhancing potentially new therapeutic options (27).

Genetics

An interesting genetic profiling analysis has been performed on patients with chronic back pain, aiming at finding a tool that would allow early identification of ax-SpA patients. Approximately 200.000 immune-mediated disease single nucleotide polymorphisms (SNPs) were analysed on 282 patients. The accuracy of genetic data was initially tested on 4.428 AS cases and over 9.000 healthy controls, showing excellent predictive value of the genetic test. Nevertheless, the authors did not demonstrate the superiority of the genetic risk scores over ASAS imaging criteria (28).

A novel genetic association has been identified through a family-based genome-wide analysis on 906 subjects from ax-SpA multiplex families. An association with a polymorphism near MAPK14, independent from HLA-B*27, has been demonstrated for the first time, together with a significant linkage with a new susceptibility locus: 13q13 (29, 30). Another novel association has been described with HLA-DP/DQ and STAT4 polymorphisms (31). The analysis of genetic associations between AS, Crohn's disease, psoriasis, primary sclerosing cholangitis and ulcerative colitis on more than 86.000 individuals permitted to identify 244 independent multi-disease signals, and 27 new genome-wide susceptibility loci, with 3 unreported shared risk loci. These results demonstrate the genetic overlap between these conditions, despite a clear demarcation of the genetic risk for the individual conditions (32). Moreover, some interesting observation suggest that an AS-related variant in the IL23R-IL12RB2 intergenic region, modulates the enhancer activity and regulates Th1-cell differentiation, leading to a higher production of IFN- γ -secreting Th1 cells (33). IL-4 and Pentraxin 3 gene polymorphisms have been described to be associated with AS susceptibility (34, 35).

Research has also been focused on the unresolved issue of predicting response to treatment and promoting a better patient-tailored approach to inflammatory arthritides. Fabris and colleagues identified the -308 TNF-alpha promoter

polymorphisms, known to confer a higher TNF-alpha expression, and the -174 IL-6 promoter polymorphisms as predictors of first-line TNF-alpha persistence on treatment in SpA patients (36).

Cubino *et al.* identified specific IL1B and IL6 polymorphisms associated with disease activity of PsA, particularly for peripheral involvement (37).

Axial involvement in PsA has been associated with the presence of peripheral joints erosions, extent of skin disease (PASI maximum), younger age at PsA onset and the presence of HLA-B*0801. A more symmetrical sacroiliac joints involvement, on the other hand, showed the peculiar characteristics of being more linked to female sex, osteolysis, and much less frequently HLA-B*2705 positivity. The authors concluded that the HLA profile can be helpful in identifying disease patterns, with HLA-B*27 positive patients resembling AS and HLA-B*0801 axial-PsA patients displaying more characteristic features of PsA such as asymmetrical or unilateral sacroiliac involvement. Moreover, the authors demonstrated that HLA-B*27 is not the predominant risk allele for the development of axial involvement in PsA, being identified in 23% of patients compared to 51% of axial-PsA patients testing positive for HLA-B*0801 (38). A role for other non-HLA genes - anthrax toxin receptor 2 (ANTXR2), IL2 receptor 2, caspase recruitment domain-containing protein 9 (CARD9), and small nuclear RNA-activating complex polypeptide 4 (SNAPC4) - has also recently emerged in the pathogenesis of ax-SpA (39) and PsA (40) and warrants further investigation for the potential clinical and therapeutic implications.

Clinical picture and comorbidities

Cardiovascular risk

AS is a chronic inflammatory disease that seems to be related to an increased risk of developing CVD. In particular, when studied throughout positron emission tomography, the carotid arterial wall of patients with AS showed higher rates of 18 F-fluorodeoxyglucose [18 F-FDG] uptake, if compared with age and gender-matched healthy controls; very interestingly, after a regimen of

three-month atorvastatin 40 mg daily, the carotid wall uptake of 18 F-FDG was significantly lower, demonstrating that a therapy with statin may decrease arterial wall inflammation in these patients, thus supporting the opportunity of revising CVD management in AS, with perhaps a role for early statin therapy (41). These data are enforced by an ultrasonographic study that shows a higher risk of carotid plaques formation in AS patients, even in those with a low or moderate cardiovascular (CV) risk [calculated according to the systematic coronary risk evaluation (SCORE), the Framingham Risk Score (FRS) and the Reynolds Risk Score (RRS)], being the presence of syndesmophytes a negative prognostic factor for atherosclerotic plaques formation (42).

Among patients with AS, those with kyphosis seem to represent a subgroup at higher risk for CV complications; in particular, they had a higher heart rate, a lower E/A ratio, longer mitral E-wave deceleration time and isovolumetric relaxation time (indicators of left ventricular diastolic dysfunction) and finally a higher incidence of left ventricular high voltage (43).

Lastly, in AS patients arterial stiffness tends to be higher than in age and gender-matched healthy controls and it seems to be related with disease activity and functional impairment (evaluated respectively with BASDAI and ASDAS and with BASFI) (44).

Since the association between psoriasis and CV morbidity has been well established, while the link between PsA and CV events was less clear, a meta-analysis of observational studies was performed to evaluate the magnitude of the risk of CVD diseases in patients with PsA compared with the general population. The authors found that people with PsA have a 43% increased risk of CVD (including myocardial infarction, cerebrovascular events and heart failure) and a 55% increased risk of developing incident CV events compared with the general population, with a magnitude of the elevated risk similar to that observed in patients with severe psoriasis. These data not only support the concept that PsA is an independent risk factor for CVD, but also stress the

notion that monitoring CV risk in PsA patients according to guidelines valid for the general population might consistently compromise the assessment of their CV morbidity (45).

A population-based study conducted in the UK confirmed that patients with PsA had an elevated prevalence of modifiable CV risk factors (hypertension, hyperlipidaemia, DM, and obesity) compared to healthy controls; on the contrary, in RA patients, only the adjusted prevalence of DM and obesity was significantly increased if compared to healthy controls. Both patients with PsA and with RA showed an increased incidence of a new diagnosis of CV risk factors. Interestingly, even if patients with inflammatory arthritides were at higher CV risk, their pharmacologic treatment for hypertension, hyperlipidaemia and DM resulted similar to that of the UK general population (46).

An age- and sex-matched case-control study conducted in a tertiary care institution showed that in PsA patients a polyarticular involvement and a previous diagnosis of DM could be independent risk factors for the development of CVD; data from another cohort study showed that hypertension, DM and the number of dactylitic digits were independent predictors of CVD, thus confirming the role of a combination between traditional CV risk factors and the level of disease activity in increasing CV risk in PsA patients (47, 23).

Finally, Gentile *et al.* found a relationship between the percentage of small dense low-density lipoproteins particles (sd-LDL), the mean size of LDL and the development of subclinical atherosclerosis (evaluated as carotid intima-media thickness) in patients with PsA (48).

Mood disorders

Subjective well-being (SWB), a concept of positive psychology that has gained increasing attention in medical science, refers to subjective and multidimensional evaluation of daily life and can be measured by the General Well-Being Schedule (GWBS). Compared with EQ-5D or SF-36, GWBS is a brief indicator of subjective feelings of psychological well-being and re-

flects mental health totally. Mengmeng *et al.* examined SWB in patients with AS and found that they had significantly impaired SWB on all scales of the GWBS except for the Control scale, if compared with age and gender-matched healthy controls. In particular, sleep quality, disease activity (evaluated with BASDAI index) and family function [evaluated with Adaptation, Partnership, Growth, Affection and Resolve (APGAR) index] have been found to affect SWB in AS. Moreover, a positive attitude towards therapy prospect seems to be associated with well-being of AS patients. In conclusion, better sleep, lower disease activity, more family care and a positive attitude towards therapy prospect predicted higher SWB; these results should influence current management strategies of AS patients, in order to improve the control of disease activity, sleep quality and family ties, paying attention to the relationship between rheumatologist and patient, mostly in sharing therapeutical decisions (49).

In *et al.* evaluated sleep quality and pattern in AS patients with sleep questionnaires and polysomnography examination and found that patients treated with TNF alpha inhibitors tended to have better outcomes than those treated with NSAIDs, thus confirming a relationship between an impaired sleep quality and a suboptimal control of disease activity (evaluated both with BASDAI and BASFI) (50).

A nationwide population-based retrospective cohort study performed by Shen *et al.* analysed the relationship between AS and the subsequent development of psychiatric disorders (schizophrenia, bipolar disorder, depressive disorders, anxiety disorders, and sleep disorders), highlighting that AS patients, during their disease, seemed to be at higher risk to develop depressive disorders, anxiety disorders, or sleep disorders than age- and gender-matched healthy controls. These observations highlight the opportunity for a psychiatric evaluation and potential intervention in patients with AS (51).

The results of Lewinson *et al.* confirmed the strong link between psychiatric field and SpA, in particular PsA in

this case. Indeed, they performed a 25 years follow up study of patients with psoriasis (identified using the Health Improvement Network, a primary care medical records database) and found that having a major depressive disorder was a significant risk factor for the future development of PsA, thus suggesting the opportunity to carefully manage psoriatic patients for psychiatric disorders (52).

Other comorbidities

Th2 and Th17 cells are known to be involved in the pathogenesis of AS. Some allergic disease share with AS part of their pathogenetic background; in particular, Th2 and Th17 are associated with asthma, whereas Th2 cells are associated with atopic dermatitis and allergic rhinitis. Starting from this issue, a population-based cohort database of Taiwan patients was examined to understand if AS patients were at higher risk of developing these allergic diseases, if compared with age- and gender-matched healthy controls. The authors found that AS patients presented a significant higher risk of both atopic dermatitis and allergic rhinitis, but not of asthma (53).

Hagiwara *et al.* arised a very interesting issue. Indeed, through a retrospective analysis of their cohort of patients with a diagnosis of PsA according to CASPAR criteria, they found that 20% of them had developed a malignant tumour; in particular, 16.5% had developed the neoplasia before PsA diagnosis, and 3.5% after. Nearly 96% of these cases were female patients and more than 45% of them had a breast cancer. These data should stress to pay attention to take into account the possibility of a paraneoplastic syndrome in patients with arthritis and/or enthesitis who apparently meet the CASPAR criteria, because careful screening and monitoring of malignant disease might significantly improve the quality of care of this kind of patients (54).

Uveitis is the most common extra-articular manifestation of AS. A retrospective study on AS patients who fulfilled the modified New York diagnostic criteria was performed by Li *et al.* to find out possible risk factors for the devel-

opment of this comorbidity. Their results highlighted that hip joint disease, the number of peripheral joints with arthritis, higher values of antistreptolysin O and of circulating immune complex, might predispose to the development of uveitis in AS, thus stimulating more careful eye assessment in subgroups of patients with these clinical characteristics (55).

DESIR is a prospective, multicentre, observational study in which Hmamouchi and colleagues analysed the presence of hypovitaminosis D in patients with early ax-SpA, trying to correlate it to indicators of disease activity and severity and with the development of comorbidities. Vitamin D deficiency was defined as <50 nmol/L and severe deficiency <25 nmol/L. Severe deficiency was significantly more frequent in the DESIR cohort than in the general French population (11.7% vs. 5%); after adjusting for season and ethnicity, vitamin D deficiency remained significantly associated with presence of radiological SI, higher ASDAS score and elevated BASDAI. These associations were confirmed during the two-year follow-up of the study. Moreover, vitamin D deficiency was significantly associated with the presence of baseline abdominal obesity, low HDL and presence of metabolic syndrome at baseline. These data give us important informations about vitamin D status in patients with early ax-SpA, suggesting the opportunity to perform longitudinal studies to regularly test and correct it during the assessment of patients, aiming at understanding possible improvement in the long-term outcomes of the disease (56).

Maas and colleagues analysed the prevalence of vertebral fractures in AS patients with active disease from the Groningen Leeuwarden AS (GLAS) cohort treated with TNF- α blocking therapy for 4 years and with available thoracic and lumbar radiographs at baseline and at 4 years. In 27 of 105 (26%) AS patients, radiographic vertebral fractures were observed at baseline. During 4 years of treatment, 21 (20%) patients developed at least one new fracture; significant risk factors for the development of new fractures were older age, smok-

ing, higher BASFI, low lumbar spine BMD (Z-score ≤ -2), presence of moderate (≥ 25 - $<40\%$) vertebral fractures, and use of anti-osteoporotic treatment at baseline. Most fractures were mild (≥ 20 - $<25\%$) and occurred in the thoracic spine. Patients with new fractures showed slighter improvements both in lateral spinal mobility and in lumbar spine BMD during treatment than the remaining patients. These data underline how the prevalence of radiographic vertebral fractures remains high in AS patients with active disease; indeed, although clinical assessments and BMD improved significantly, new vertebral fractures still developed during 4 years of TNF- α inhibitor therapy (57).

Clinimetrics

ASAS Health Index (ASAS HI) has been recently developed by Kiltz *et al.* to assess health in patients with AS according to the International Classification of Functioning, Disability and Health (ICF) categories. Before its creation, rheumatologists did not have any specific and freely available patient reported outcome (PRO) able to describe the overall picture of impairments, limitations and restrictions in activities or in social participation of patients with axial SpA (ax-SpA). Di Carlo *et al.* tested the Italian version of the ASAS HI in an Italian cohort of ax-SpA patients confirming its feasibility, reliability, and construct validity. Moreover, despite ASAS HI is a health index, they found that it could categorize patients into different subgroups of disease activity, if compared with both AS Disease Activity Score (ASDAS) and its simplified version (SASDAS); in particular, under the cut-off value of 4.0, patients could be defined to have inactive disease and this could represent a starting point easy to be assessed in routinary clinical practice (58).

The Psoriatic Arthritis Screening and Evaluation (PASE) questionnaire is a self-administered tool that can be used to screen for PsA among patients with psoriasis, mostly evaluated by a dermatologist or a general practitioner; it has proven to be able to distinguish between symptoms of PsA and osteoarthritis. Piaserico *et al.* tested the Ital-

ian version of this index in 10 Italian centres, establishing its capability to identify psoriasis patients with PsA, its usefulness to monitor the course of the disease and to evaluate the effects of the prescribed treatments. In particular, they found that the optimal cut-off value to discriminate between PsA and non-PsA patients was ≥ 48 (59).

The Disease Activity Index for Psoriatic Arthritis (DAPSA) is a disease-specific, validated and feasible tool for PsA assessment; it is based on the summation of tender and swollen joints (TJC68, SJC66), Patient Global Assessment (PGA), Patient Pain assessment (PP) on a 10 cm visual analogue scale and C-reactive Protein (CRP). Schoels *et al.* tried to derive criteria to define disease activity states and established response criteria for DAPSA, to allow its use both in trials and in clinical practice. According to their analyses, the states of remission (REM), low disease activity (LDA), moderate disease activity (MDA) and high disease activity (HDA) could be effectively distinguished by DAPSA cutpoints of 4, 14 and 28. The following cutpoints for the definition of DAPSA response were proposed: minor response, 50% change in DAPSA; moderate response, 75% change; major response, 85% change. Through these results, the authors enabled the definition of treatment targets, such as REM or LDA, to be used in a treat-to-target approach, as well as the definition of MDA and HDA, to be used as inclusion criteria in clinical trials; moreover, the response levels established in this paper, could be useful to assess treatment in many settings (60).

Serological biomarkers

A prospective study on patients with RA, AS and PsA treated with Adalimumab (ADA) from Hoxha *et al.* confirmed that the development of anti-ADA antibodies is related both with a significantly lower serum concentration of the drug and with a higher risk of having a loss of treatment efficacy. Moreover, they found that more than 90% of patients developing anti-ADA antibodies (up to 19% of the studied cohort), were positive for their detection after the first 4 weeks of therapy,

thus underlining how anti-ADA autoantibodies detection might be considered as an early indicator of a poor response to ADA therapy (61).

A new bone formation and a modest erosive osteopenia are a well known and typical feature of AS, but the cellular and molecular mechanisms of bone remodelling are not yet clear, thus limiting interventions aiming at improving the outcome of AS patients. Yuan *et al.* analysed bone metabolism in AS and found that serum heme oxygenase 1 (HO-1), a protein with a regulatory role in the osteoclastogenesis, and bone morphogenetic protein 7 (BMP-7) pathways, inducing osteoblastic differentiation and bone remodelling, might be involved in the development of the above mentioned AS specific bone modifications. In particular, they detected significantly higher serum levels of both HO-1 and BMP-7 than in age and gender-matched healthy controls. Moreover, together with Runt related-transcription factor 2 (Runx-2), a transcription factor considered a key regulator of osteoblasts differentiation, HO-1 and BMP-7 showed significant correlation with other bone markers, thus confirming their role in the pathogenic mechanisms of bone metabolism in AS (62).

Two studies have analysed the values of neutrophil to lymphocyte ratio (NLR), emerged as a marker of inflammation in neoplastic and CV disorders, in AS patients. The results showed that NLR in AS tends to be higher than in healthy controls; therefore, it might be considered as a marker of inflammation also in AS, even if it does not seem to correlate with disease activity (evaluated with BASDAI in both studies) (63, 64). A longitudinal observational study of consecutive patients with PsA was conducted in Israel, aiming at understanding if the levels of acute-phase reactants at diagnosis, before initiation of any treatment, can be used as predictors of a future need for a TNF alpha inhibitor to achieve control of the disease under real-life conditions. The authors found that CRP levels ≥ 0.9 mg/dl at the time of PsA diagnosis was an indicator of an inadequate response to treatment with conventional DMARDs and of a high probability to have the need of treat-

ing the patient with a TNF- α inhibitor. This data not only confirm the role of CRP as a marker of disease severity, but also have interesting clinical implications for the every-day management of PsA patients, suggesting that those with serum CRP levels ≥ 0.9 mg/dl at disease onset, are at a higher risk that conventional DMARDs will not be able to completely control their disease, thus leading to the need of starting anti-TNF alpha therapy (65).

Ozmen *et al.* performed an analysis of serum procalcitonin levels in a cohort of patients with a diagnosis of AS compared with healthy controls. They found that procalcitonin was normal both in AS and in control cohort and they did not find any significant correlation of its value with either disease activity or with therapy, thus suggesting that serum procalcitonin levels may be useful to diagnose a fungal or bacterial infection even in patients with AS (66). Since the role of angiogenesis has not been clearly established in patients with AS, Przepiera-Będzak *et al.* conducted a study aiming at analysing the serum levels of selected angiogenic cytokines (VEGF, EGF, bFGF, and aFGF) and their possible association with both disease activity and the development of extra-articular symptoms in patients with AS. As already found in other papers, serum VEGF levels were increased in patients with AS if compared with healthy controls, but no correlations were found between any serum angiogenic cytokines and disease activity or extra-articular involvement. Serum levels of EGF, aFGF, and bFGF did not seem to play a significant role in AS. Finally, increased serum VEGF levels were associated with a progression of the disease, as assessed by the BASMI index (67).

It is well known that anti citrullinated peptides autoantibodies (ACPA) are associated with bone erosions in RA; in particular, they seem to directly mediate bone destruction. Although ACPA are specific for RA, up to 17.5% of PsA patients have been reported to be ACPA seropositive. To deeply analyse the relationship between ACPA and bone remodelling, an observational study was conducted on a cohort of 1996 patients

with PsA, founding that the subgroup of ACPA seropositive patients (5.3% of the cohort) had significantly higher swollen joint counts, 28-joint DAS values and significantly higher rates of erosive changes and dactylitis than ACPA seronegative ones. Multiple logistic regression analysis confirmed the association of ACPA seropositivity and the risk of erosive disease, thus suggesting that the osteocatabolic effect of ACPA is not confined to RA but is also detectable in other nosological entities as PsA, that are characterised by a distinct pathogenetic background (68).

Clinical picture of SpA

Data from the Outcome in AS International Study (OASIS) were analysed to investigate gender-attributable differences regarding clinical outcome (disease activity, physical function and quality of life) and radiographic damage in patients with AS over time. Disease activity was assessed by the BASDAI, ASDAS and CRP; physical function by BASFI; quality of life (QoL) by the Short Form36, Ankylosing Spondylitis Quality of Life (ASQoL) score and the European Quality Of Life scale; radiographic damage was evaluated with the modified Stoke AS Spine Score (mSASSS). The authors found that men had a better QoL than females, but a worse radiographic damage both at baseline and over time. On the contrary, no gender-attributable differences in the remaining studied clinical outcomes were found (69).

Data from the OASIS were also analysed to understand whether extra-articular manifestations could influence the outcomes of AS. The outcomes evaluated were functioning (assessed with BASFI and the physical components of the SF-36), QoL (assessed with ASQoL and EuroQoL) and radiographic damage (assessed with mSASSS). Univarably, IBD was associated with worse BASFI over time, but not in a multivariable model; in a multivariable model, IBD was associated with EuroQoL over time. Univarably, psoriasis was associated with radiographic damage and ASQoL over time, but not in a multivariable model. AAU was not associated with any outcome over time (70).

A study from China, based on Magnetic Resonance Imaging (MRI), analysed the characteristics of AS patients with an early hip involvement (pointed out only from MRI and not yet from conventional radiography). Indeed, in patients with hip pain or limited hip function but lacking definitive evidence of hip involvement on radiography, MRI is able to diagnose hip involvement in its earlier phases, thus allowing to carry out therapeutical strategies before advanced stage had took place. Interestingly, the early-stage hip involvement resulted significantly associated to a younger age at onset, a worse BASMI score, and a more active inflammation in the sacroiliac joints (71).

Lee *et al.* studied with MRI the kind of inflammatory lesions of both vertebral bodies and facet joints in a cohort of AS patients, taking into account also the distribution of the lesions across 23 discvertebral units (from C2 to S1). They found that bone marrow oedema of the facet joints was uniformly distributed across the spinal column, while bone marrow oedema of the vertebral bodies was significantly more expressed in the thoracic column. These results may help researchers to have an insight into the pathogenetic mechanisms of AS, contributing to better understand its clinical outcomes (72).

A study by Zabotti *et al.* has confirmed the important role that US may have in the diagnosis of early PsA (ePsA), differentiating it from early RA (eRA). In particular, the authors found that US examination of the hands showed significant more sites of synovitis in eRA than ePsA, while a peritendon extensor digitorum tendon inflammation at the metacarpophalangeal joint was more frequent in ePsA than in eRA. Moreover, a finger soft tissue oedema was found almost exclusively in ePsA and a central slip enthesitis at the proximal interphalangeal joint was detected only in cases of ePsA (73).

A cohort of PsA patients was studied to deeply analyse the possible association between nail psoriasis and distal interphalangeal joint (DIP) involvement. A total of 450 fingers from 45 PsA patients were analysed; the authors found that DIP arthritic changes were sig-

nificantly more frequent in fingers with psoriatic nail disease. In particular, they found that DIP arthritis development was more commonly associated with two specific subtypes of psoriatic nail lesions, that were crumbling and onicolysis (74).

As already anticipated in the section on Genetics, Haroon *et al.* investigated the genetic and clinical associations of radiographic SI among an ethnically homogenous consecutive cohort of patients with a diagnosis of PsA (according to CASPAR criteria), trying to correlate the different radiographic patterns with clinical and genetic characteristics. They defined SI as \geq grade 2 radiographic changes (according to New York criteria), unilateral or bilateral; they used the term “asymmetrical” if grades were different between the 2 SI joints, and the term “unilateral” if the opposite SI joint was completely uninvolved. The authors found that 25% of PsA patients developed SI on long-term follow up. Significant clinical and genetic associations were found with SI and respectively a PsA developed at younger age, a severe skin psoriasis, peripheral joint erosions, and HLA-B*0801. In particular, SI diagnosis was only marginally associated with HLA-B*2705, as already observed in other studies; moreover, HLA-B*0801 tended to be associated with asymmetrical SI, whereas HLA-B*2705 with symmetrical SI. Therefore, these two different patterns of HLA antigens seem to explain two clinically different subtypes of radiographic SI; the meaning of this concept is that the genes involved in PsA susceptibility could also specify distinct clinical phenotypes (38).

Quality of care

A recent paper by Marchesoni *et al.* presented an overview on the clinical approach to patients with PsA in a group of Italian rheumatologists. This study showed some very interesting aspects of real-life management of PsA. In particular, the most important results of the survey were that diagnosis of PsA should be made using both the CASPAR criteria and clinical judgment, that all of the features of the psoriatic disease are relevant in the assessment and

therapy of PsA, that treatment recommendations are taken into account, that all of the available biological agents may be used in bio-naïve patients, that anti-drug antibody testing is still not used in daily practice, that both switching or swapping are useful options in the case of bio-failure because of lack or loss of efficacy, and that swapping is considered the best choice in the case of bio-failure due to adverse events. In conclusions, this data show that assuring the best care to PsA patients means to widely assess the patient during the clinical evaluation and to choice therapy taking into account patient clinical features together with the evidence of drug efficacy and safety (75).

Working disability in SpA

Considering the worldwide economic crisis, work participation of patients with chronic diseases has received renewed attention. It is well known that, occurring in young adults at the pick of their productive lifespan, SpA are usually associated to restrictions in activities of the daily living, to a reduction of health-related quality of life (HR-QoL), to a reduction in work productivity and to a higher risk of unemployment.

Castillo-Ortiz *et al.* compared the incidence and prevalence of work disability (WD) in the OASIS cohort of AS patients to those of the general population, and tried to identify both disease- and system-related factors contributing to an adverse work outcome (AWO); they analysed data from the cohort for a total of 12 years, to better understand the trend of WD and the development of AWOs during time. For analyses, WD was defined as withdrawal from work due to official WD and AWO as a new condition or an increase in the level of WD, or as a decrease in working hours during followup. They found that patients with a longstanding AS still had a chance to become work disabled over time 3-fold higher than the general population. Presence of uveitis, age, inflammatory bowel diseases and worse scores on the Bath Ankylosing Spondylitis Functional Index or Bath Ankylosing Spondylitis Disease Activity Index were the more relevant clinical predictors of AWO; in addition, the

socioeconomic context of the country of residence seemed to play an important role for work outcomes in AS patients. These data represent an insight into the main disease-specific as well as system-related contextual factors that contribute to AWO in patients with AS, therefore could be useful both for clinicians and decision makers to promote not only prevention, but also job retention strategies (76).

A lot of data show how an impaired work productivity influences significantly the indirect costs of SpA, calculated as absenteeism (the total amount of sick leave expressed as days in a year or hours per week) and presenteeism (corresponding to a patient-reported reduced productivity at work), using tools such as the Work Productivity and Activity Impairment Questionnaire. Ramonda *et al.* reported the results about work disability and working life derived from an Italian survey on SpA patients called Atlantis. They highlighted how patients with SpA experience major disadvantages in their working life, with one half of the respondents claiming they were disabled, and one half reporting that SpA interfered significantly with their work commitments; besides, the study showed that SpA was the main source of absenteeism and presenteeism of the interviewed patients. Absenteeism resulted associated with disease activity and depression, whereas presenteeism with older age, disease activity, anxiety, and depression. Moreover, the survey was able to identify some issues never investigated before, in particular a restriction in work prospects and career (experienced by one half of the cases), the need to change or leave the job or even the loss of the job (reported in up to 21% of the cases) and the experience of a discrimination at the workplace (reported in up to 14% of the cases). Finally, the authors found that the employment rate was slightly lower than in the general population, being 53% instead of the expected rate of 58%, according to the official employment statistics in the general population in Italy in 2013. Unemployment resulted associated with older age, social deprivation, longer disease duration, functional impairment, and

depression. The confirmed relation between the level of disease activity and work disability suggest that an earlier diagnose and a better control of disease activity might represent central factors to improve work productivity in SpA patients and to improve their working life (77).

Imaging

During the past 12 months a large number of studies on imaging techniques in SpA were published, focusing the attention both on axial and peripheral disease. Imaging is nowadays a central tool for SpA diagnosis and, in the last period, a numbers of study focused the attention on MRI diagnostic potential. Other studies have confirmed the importance of imaging technique to assess pharmacological response or disease progression. This chapter will review the latest studies on imaging in SpA divided by methodic.

Magnetic resonance imaging (MRI)

MRI represent the diagnostic cornerstone of non-radiographic axial SpA and it's one of the main imaging technique used to assess persistent low back pain (LBP). A study of 1037 patients aged 18–40, with LBP showed that at MRI spinal SpA-related findings were rare, on the contrary, at sacroiliac joints (SIJ) level 28% of the studied population had at least one MRI finding typical for SpA (78). SI on MRI according to the ASAS definition was the most common alteration, present in 21% of patients, with a 10% fulfilling the ASAS criteria for SpA. These data suggest the high prevalence of SpA among young adult with persistent LBP. The other side of the coin showed that bone marrow oedema (BME) at SIJ is not exclusively diagnostic for axial-SpA. The authors suggest that the relatively high prevalence of SI findings in the study sample may have other causes not associated with SpA and other MRI features could increase the specificity for the diagnosis of the disease. Interestingly among patients with BME at the SIJ, a significantly higher prevalence of erosions were present in patients fulfilling the ASAS criteria for SpA (41%) compared to those who did not (20%)

(79). To better understand the diagnostic value of the chronic SIJ alterations seen at MRI in SpA patients other studies focused the attention on non-BME findings. Interestingly a new MRI sign, the “backfill sign” showed a high specificity for axial-SpA diagnosis (80, 81). The “backfill sign” was defined in T1-weighted turbo spin-echo (T1SE) images as complete loss of iliac or sacral cortical bone at its anticipated location and increased signal that is clearly demarcated from adjacent normal marrow by irregular dark signal reflecting sclerosis at the border of the eroded bone (81). The sign could be longitudinal or punctiform and it could represent a fat metaplastic tissue refilling excavated subchondral bone (however no histopathological analysis of this lesion had been performed). The MRI presence of “backfill sign”, fluid signal and ankylosis had a specificity of 95.8%, 95.3% and 99.5 % for SpA (80). Another group found that backfill sign had a specificity of 98% and a sensitivity of 59% for ax-SpA (81). To better clarify the diagnosis of ax-SpA using MRI De Hooge *et al.* investigated the diagnostic performance of MRI lesions in SIJ and spine in patients with suspected ax-SpA and they showed that patients with at least five fatty lesions on MRI-spine assured a specificity of ax-SpA diagnosis higher than 95% (82). Interestingly, another group assessed the utility of replacement the radiographic sacroiliitis (according to modified New York criteria) by structural alterations on MRI. Using chronic MRI alterations more than 80% of patients did not change their previous diagnosis according to modified New York criteria. The authors concluded that structural MRI findings can be used as an additional tool or a substitute for radiographic changes defined by the modified New York criteria (83). Despite these new MRI findings the latest update of the ASAS MRI working group stressed the importance to not change the actual definition of “active sacroiliitis”: the clear presence of BME is still considered the cornerstone of the imaging criterion ‘active sacroiliitis on MRI’ according to the ASAS classification criteria for ax-SpA. However, the working group suggests that SIJ MRI

structural features could enhance confidence in the classification of ax-SpA but that there is no consistent beneficial effect of adding spine MRI alterations to the current classification (84).

In the last 12 months new studies have evaluated the links between MRI findings and disease activity parameters of SpA (85, 86). Active inflammatory lesions of facet vertebral joints seen on spine MRI in SpA patients were closely associated with erythrocyte sediment rate (ESR) and C-reactive protein (CRP) (85). Moreover the DESIR cohort study showed that in male patients, but not in female, clinical disease activity parameters, particularly the ASDAS score, are longitudinally associated with inflammatory lesion in SIJ on MRI (86). Interestingly the presence of BME in SIJ of SpA patients, and the severity of the lesions, seem to strictly correlate with other systemic complications typical of chronic inflammatory states: Kim *et al.* demonstrated that BME, and the severity of the findings, are associated with low bone mineral density (BMD) in the femoral neck of SpA patients. A multivariate analysis identified the presence of BME as one of the main and independent risk of low BMD in SpA patients (87). These data confirm that active inflammation on MRI may represent a pivotal tool to assess disease course and activity and not just be useful for classification purpose.

Finally other studies underlined the importance of MRI for assessing peripheral joint inflammation in SpA patients (88-90).

Conventional radiology

In the last 12 months few studies have evaluated conventional x-ray imaging in SpA patients. Maas *et al.* assessed the presence of vertebral fractures in a group of patients with active AS using thoracic and lumbar spine radiographs at baseline and after 4 years of anti-TNF therapy. In 27 of 105 patients (26%) vertebral fractures were present at baseline and new ones still developed during biological therapies, thus confirming that a low BMD could represent one of the main complications of active SpA (57). Another interesting study on

GESPIC cohort of patients shed light on the links between disease activity and radiographic spinal progression but it will be discussed below in the Treat to Target (T2T) chapter (91).

Other techniques

A study of computed tomography (CT) showed that CT of the abdomen in patients with inflammatory bowel diseases and inflammatory back pain found bony structural lesions of spine and/or SIJ in almost half of the patients. The Authors conclude that these findings should guide the radiologists to further clinical evaluations (79). As suggested in the previous years 18F-fluoride PET/CT identify patients with active AS showing a good correlation with the BASDAI and ASDAS (93). 18F-fluoride PET/CT seemed able to quantify peripheral joints inflammation also in PsA patients (94). In the last 12 months two studies assessed the capability of new imaging techniques to really quantify the inflammatory response in affected joints of SpA patients. Dynamic Contrast-Enhanced Magnetic Resonance Imaging (DCE-MRI) is a MRI with contrast agent that gives quantitative informations about the microvascularisation of pathological tissue, like inflamed synovia. DCE-MRI was able to quantify synovial inflammation in subjects with chronic arthritis, SpA patients included (95). The authors concluded that this new technique could be useful for clinical purposes but also for translational research agenda. On the same topic, quantitative imaging by pixel-based contrast enhanced ultrasound (CEUS) quantify the vascularisation of a tissue evaluating automatically the perfusion data after subadministration of contrast agent. CEUS data showed a linear relationship between the degree of synovial vascular perfusion and presence of pathogenic Th-17 cells in PsA joints (96).

Therapy

Non-steroidal anti-inflammatory drugs (NSAIDs)

NSAID treatment is the first-line drug therapy in patients with AS and PsA, performing good efficacy on pain and stiffness (97). Moreover, there is some

evidence about NSAIDs effectiveness in the prevention of new bone formation in AS due to their capabilities to impair the production of prostaglandin E2 (PGE2). However, it is not clear if this effect is greater in continuous instead of on demand therapy (98). In a randomised multicentre trial, Sieper *et al.* aimed to confirm the inhibitory effect of NSAID on radiographic progression in patients with AS. They enrolled 167 patients with AS and randomised them for treatment with either continuous or on demand diclofenac for two years. Their results are in contrast to other published reports on the effects of NSAIDs on osteoproliferation, indeed they found a numerically greater reduction of new bone formation in the on demand group, even adjusting results for patients with syndesmophytes at baseline, or elevated CRP only, or smoking status only (99).

In the 2016 update of the ASAS-EULAR management recommendations for ax-SpA, the task force suggested the continuous use of NSAIDs if symptoms recur after stopping or reducing the dose of NSAID therapy. According to this update the decision of a continuous use of NSAIDs is based on the symptoms of the patient instead of a possible protective effect on structural damage progression (100).

Furthermore, it seems that there is no difference in efficacy of different NSAIDs in AS (indomethacin, celecoxib, diclofenac, ketoprofen). Choice of NSAID should be based on the patient's past history of NSAID use, risk factors for adverse effects, and comorbidities (101).

Disease-modifying anti-rheumatic drugs (DMARDs)

According to the EULAR recommendations, patients with peripheral PsA who still have an active disease despite previous NSAID therapy, should be treated with conventional synthetic DMARDs (csDMARDs), with the recommendation of methotrexate (MTX) as first choice; whereas, according to EULAR/ASAS criteria, Sulfasalazine is a treatment option in patients with peripheral arthritis in AS (102, 2).

It is well known that csDMARDs are

not useful for treating axial involvement. In fact, biological DMARDs (bDMARDs) should be considered in patients with ax-SpA, both radiographic and non radiographic SI with elevated CRP and/or inflammation on MRI, or patients with PsA with persistently high disease activity despite conventional therapy (non-pharmacological treatments, NSAIDs, csDMARDs). TNF alpha inhibitors [in alphabetical order: adalimumab (ADA), certolizumab pegol, etanercept, golimumab and infliximab] are recommended for patients with active disease refractory to csDMARDs (2).

Shiber and Moland performed a longitudinal observational study to determine if high CRP levels at diagnosis of PsA could be a predictor of the need to treat the disease with anti-TNF alpha molecules. They conclude that a CRP value ≥ 0.9 mg/dl at diagnosis significantly predicts an inadequate response to treatment with csDMARDs and the need for treatment with TNFalpha inhibitor (79).

The association therapy between TNF alpha inhibitors and MTX is not well established for PsA. In a recent study Behrens *et al.* examined data from an observational study on ADA, to evaluate the added value on PsA outcomes of a concomitant treatment with MTX in patients already taking ADA. They concluded that in these patients concomitant MTX did not influence joint or skin outcomes, independently from axial involvement (103).

Biosimilar drugs are highly similar to their reference product (RP) in physicochemical and biological terms. Due to lower costs of biosimilar *versus* RP, there is interest in determining if naïve patients can be effectively and safely treated with biosimilar, and whether those already on RP treatment can be safely switched to its biosimilar. Working on Program evaluating the Auto-immune disease iNvestigational drug cT-p13 in rA patientS (PLANETAS) extension study, Park *et al.* investigated the efficacy and safety of switching from infliximab RP to its biosimilar (CT-P13) in patients with AS. After an observation period of 102 weeks, they concluded that CT-P13 seemed to

have comparable efficacy and safety as the RP treatment. Moreover, also switching from the infliximab RP to its biosimilar after one year of infliximab RP treatment, showed comparable efficacy, immunogenicity and safety than maintaining CT-P13 treatment during the second year of treatment (104).

Although the use of anti-TNF alpha is the mainstay therapy of ax-SpA, a significant portion of patients do not have an appropriate response; moreover, switching to an alternative anti-TNF alpha appears to be associated to a lower response. In a recent observational study was explored the effectiveness of switching anti-TNF alpha therapy in a cohort of patients with a diagnosis of SpA. The results of this study showed that patients with ax-SpA, after switching to a second anti-TNF alpha, had impaired drug retention rate and treatment response; these parameters were more compromised at first in those who have discontinued the first line therapy owing to a lack of effectiveness and secondly in those who have discontinued the first line therapy owing to the onset of adverse events (105).

In case of failure or toxicity of an anti-TNF alpha therapy, it is possible to choose some other class of bDMARDs; in particular, during the last year, new biological targets have been studied.

Actually, Interleukin-17A is postulated to play a role in the pathogenesis of PsA and its inhibition showed good results both in PsA and in AS patients (106, 107)

The FUTURE1 study, a two-year, phase III trial, aimed at evaluating the effect of secukinumab (an anti IL-17) on patient-reported outcomes (PROs) of subjects with active PsA. Data showed that secukinumab therapy was associated to clinically meaningful and sustained improvements in the PROs of the enrolled subjects (108).

Tofacitinib is an oral Janus kinase inhibitor that has been investigated for the treatment of both psoriasis and PsA. In a recent phase III study, Asahina *et al.* demonstrated short-term efficacy of tofacitinib and maintenance of efficacy for 52 weeks in Japanese patients with moderate to severe plaque psoriasis and/or active PsA. All 12 patients with

psoriatic arthritis achieved an ACR20 response by week 16th with both 5 and 10 mg b.i.d. doses of tofacitinib; rates were maintained with tofacitinib treatment to week 52, although interpretation of the response is limited by the low number of patients (109).

Apremilast is an oral small molecule approved for the treatment of adults with active psoriasis and PsA. It specifically inhibits the activity of phosphodiesterase-4 (PDE4). For its safety profile, apremilast may offer a treatment option in patients with active PsA presenting contraindications to treatment with cs-DMARDs or biologic DMARDs, or in patients unresponsive to both cs-DMARDs and biological agents (110).

Management of biologics

The 2016 update of the ASAS-EULAR recommendations for the management of ax-SpA reports "If a patient is in sustained remission, tapering of a bDMARD can be considered"; therefore it is considered appropriate to slowly taper bDMARDs in patients who are in sustained remission for at least 6 months. Increasing the interval spacing between subsequent drug administrations could be the most practical approach (2).

Concerning this topic, Almirall *et al.* studied patients with ax-SpA under a biologic tapering strategy, aiming at evaluating anti-TNF alpha serum levels, the development of anti-drug antibodies and the onset of an active SI on MRI during the reduction of the dose of the drug. They enrolled 20 patients who remained in low disease activity more than one year after dose tapering of anti-TNF alpha, without NSAIDs consumption. Among the enrolled patients (16 undergoing ADA 40 mg every 3 weeks and 4 undergoing Infliximab 3mg/kg every 8 weeks), 18 had therapeutic drug levels, none developed immunogenicity and none developed active SI detectable on MRI (111).

Infusion reactions can occur during and after intravenous administration of Infliximab. A recent retrospective study analysed the incidence of infusion reactions in patients with RA (37), PsA (17), AS (51) who were treated with

infliximab infusions. Experimenters enrolled patients receiving only one premedication protocol over time and clustered them based on the type of premedication: no premedication (group 1), paracetamol, esomeprazole, hydrocortisone and chlorpheniramine maleate (group 2), paracetamol, hydroxyzine, ranitidine and 6-methylprednisolone (group 3). They observed that infusion reactions were observed in 23/51 patients of group 1, in 7/35 patients of group 2 and none of 19 patients of group 3, suggesting that premedication protocol of group 3 could prevent infusion reactions more efficaciously than the others (112).

Local injection therapy

Despite growing progress in the treatment of articular chronic inflammatory disorders, refractory mono-oligo-arthritis is still a common clinical finding and injections with glucocorticoids (GC) may be a good therapeutic option.

A recent study analysed the efficacy and the US changes in SpA patients with symptomatic Achilles enthesitis refractory to a 6 weeks regimen of full-dose NSAIDs, after US-guided local GC treatment. It was confirmed that US-guided GC injection is an effective and safe treatment for refractory Achilles enthesitis in patients with SpA; interestingly, it was noted that pain reduction at the injected sites was not clearly correlated with the improvement in sonographic features (such as tendon thickness) (113).

In recent years several studies were published about the use of intra-articular TNF alpha blockers to treat refractory monoarthritis, with conflicting results. Carubbi *et al.* assessed the safety and efficacy of US-guided intra-articular injections of anti-TNF alpha agents compared to GC in patients with RA or PsA. Patients received three intra-articular injections monthly and were evaluated with both visual analogic scales for involved joint pain (Jvas), US and MRI (the last one was performed only for RA patients with metacarpophalangeal joint or wrist monoarthritis). The authors discovered a significant reduction of jVAS in both RA and PsA patients treated with TNF alpha inhibitors,

achieving a 20% difference in efficacy versus GC injection strategy, regardless the type of anti TNF alpha molecule used. Moreover, a significant reduction of synovial membrane thickening, joint effusion and PDUS scores detected at US examination was achieved in both RA and PsA patients treated with intra-articular anti-TNF alpha compared with patients treated with GC injections (114).

Physical therapy

In ax-SpA patients should be encouraged to exercise. In AS, physical exercise is not only a support of the pharmacological therapy but is itself an important slice of the overall therapy.

Physiotherapy is beneficial for people with AS, in particular regarding spine mobility, pain and physical function. In addition, rehabilitation seems to have favorable effect on AS patients with balance impairment (115).

Stasinopoulos *et al.* compared the effectiveness of combined low-level laser therapy (LLLT) and passive stretching (group A) with combined placebo LLLT and the same passive stretching exercise (group B). They found that group A had a significant improvement after 8 weeks of treatment in VAS, BASFI and BASDAI scales and in Schober test, cervical rotation, Lumbar side flexion and intramalleolar distance. After 8 weeks of follow-up, the improvement remained significant only for the pain (116).

Another recent study showed that in patients with AS a continuous ultrasound treatment increases the effect of exercise in terms of pain, stiffness, lumbar mobility, and quality of life. Nevertheless, at 6 weeks it was not found any significant benefit on night pain, morning stiffness, BASFI, BASMI and function scales in patients treated with ultrasounds when compared to placebo group (117).

Treat to target strategy in SpA

The treat-to-target (T2T) strategy has become an important concept in the clinical management of patients with SpA. Firstly described for patients with rheumatoid arthritis, the T2T strategy could be briefly defined as a precise

treatment scheme aiming at allowing patients to reach the target of their therapy, that is disease remission (or a condition of low disease activity). This concept may be translated to SpA management, with the core targets of obtaining clinical disease remission and of avoiding radiographic progression. In the last 12 months a study focused the attention among the links between SpA disease activity and radiographic progression. One hundred and seventy-eight patients with a definite ax-SpA were assessed, at baseline and after 2 years, for the presence of syndesmophytes. The results of the study showed a strong relationship among disease activity according to ASDAS and radiographic spinal progression, underlining that persistent high disease activity is associated with accelerated radiological axial progression in subjects with early SpA (91). Interestingly, as previously seen, male patients with ax-SpA showed a longitudinal correlation between ASDAS values and inflammatory lesions in SIJ at MRI (86). Moreover, the presence of syndesmophytes (42) and of a clinical disease activity (118) are associated with extra-articular frequent complications of the disease, as CV comorbidities of SpA patients. These evidences may suggest that an optimal control of disease activity could represent the key to manage SpA radiological progression and, eventually, extra-articular complications. Furthermore, clinical outcomes of early active non-radiographic SpA improved simultaneously MRI axial features after Etanercept treatment (119). The T2T strategy is important also in PsA patients. Among the several scores used to assess PsA patients, a new scoring system, the Disease Activity index for Psoriatic Arthritis (DAPSA), was recently developed and validated (60). DAPSA score is also a valuable tool to predict structural alterations in PsA patients, because higher DAPSA scores were significantly and independently associated with bony alterations in PsA patients (120). Interestingly, DAPSA strictly correlate with US findings, underlining the clinical relevance that this score could represent in the routinary assessment of PsA (121).

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