Review

One year in review 2018: psoriatic arthritis

E. Calabresi[1], S. Monti[2,3], G. Governato[1], L. Carli[4]

[1]*Rheumatology Unit, Department of Clinical and Experimental Medicine, University of Pisa;*
[2]*Department of Rheumatology, University of Pavia, IRCCS Policlinico S. Matteo Foundation, Pavia;*
[3]*PhD in Experimental Medicine, University of Pavia;*
[4]*Rheumatology Unit, AOUP, Pisa, Italy.*

Emanuele Calabresi, MD
Sara Monti, MD
Gianmaria Governato MD
Linda Carli MD, PhD

Please address correspondence to:
Dr Linda Carli,
Rheumatology Unit, AOUP,
Via Roma 67,
56126 Pisa, Italy.
E-mail: 81clinda@gmail.com

Received on March 4, 2019; accepted in revised form on March 12, 2019.

Clin Exp Rheumatol 2019; 37: 167-178.

Key words: psoriatic arthritis, ankylosing spondylitis, imaging, comorbidities, quality of life

Competing interests: none declared.

ABSTRACT

Spondyloarthritis (SpA) is an inflammatory 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 1 antigen, HLA-B27, and in which both peripheral and axial joints might be affected. In addition to arthritis, the typical musculoskeletal manifestations are enthesitis and dactylitis. Extra-articular manifestations such as acute anterior uveitis (AAU), psoriasis (PsO) and inflammatory bowel disease (IBD) are also typical of SpA. In this article we have reviewed the literature of the past year on one of the most important variants of SpA, i.e. psoriatic arthritis (PsA) (Medline search of articles published from 1st January 2018 to 31st January 2019).

Introduction

The term spondyloarthritis (SpA) represents a condition characterised by a broad spectrum of clinical manifestations, laboratory abnormalities and imaging features that genetically tends to be associated with the major histocompatibility complex class 1 antigen, HLA-B27, in which both peripheral and axial joints might be affected. In addition to arthritis, the typical musculoskeletal manifestations are enthesitis and dactylitis. Extra-articular manifestations such as acute anterior uveitis (AAU), psoriasis (PsO) and inflammatory bowel disease (IBD) (in order of decreasing prevalence) are also characteristic of SpA (1, 2).

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 (SIj); 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 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 (2).

At present, we could say that SpA represents one of the most intriguing issues of modern rheumatology. Indeed, not only does it tend to present in a very pleomorphic way, but also, during its progression, it tends to associate with a very wide spectrum of comorbidities [in particular with cardiovascular diseases (CVD), diabetes mellitus, osteoporosis (OP), psychiatric disorders, but renal, neurologic and pulmonary disorders have also been reported] and with a reduction of the ability to work and the quality of work of subjects, thus seriously compromising the health-related quality of life (HRQoL) of patients (3).

Following the previous annual reviews of this series (1, 2, 4-9), we will here provide a critical digest of the recent literature on one aspect of SpA, *i.e.* psoriatic arthritis (PsA). 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"; articles were published from 1st January 2018 to 31th January 2019.

Current recommendations on PsA

identify up to six PsA disease domains: peripheral arthritis, enthesitis, dactylitis, spondylitis, and skin and nail PsO. The development of comorbidities might further contribute to disease heterogeneity. Recent new advances in the knowledge of the immunological mechanisms at the basis of PsA allowed an improvement in therapeutical strategies that, together with the advances in imaging techniques and the recognition of different patterns of clinical manifestations of the disease itself, might assure a progressive improvement in the routinary assessment of PsA patients, aiming at reaching a better quality of care (10).

Epidemiology

The incidence of PsA has been reported for an inland area of central Italy (CAMPO-RHE study) reporting that, of 1003 adult patients referred by a general practitioner to the rheumatologic clinic of Campobasso, there were 19 new diagnoses of PsA, accounting for an incident case rate of 22.59/100,000/year on the population at risk (11).

Chemistry

Over the past 12 months there has been an increasing interest in the predictors for the development of PsA, and in the imaging or clinical features useful to allow making an early diagnosis of the disease. The identification of potential circulating biomarkers able to identify cases of undiagnosed PsA amongst those with cutaneous PsO has shown promising results in a cohort of 100 PsA patients, 100 PsO, and 100 healthy controls. CD5-like protein, integrin ß5, Mac-2-binding protein, myeloperoxidase, metalloproteinase 3 were candidate biomarkers for PsA, performing better than C-reactive protein (CRP) (12).

Genetics

The delay in diagnosis, the lack of specific diagnostic and prognostic biomarkers and of complete clinical response even after therapy with tumour necrosis factor (TNF) α inhibitors, such as etanercept (ETN), infliximab (IFX), adalimumab (ADA) and golimumab (GOL), have raised the interest in the pathogenetic mechanism involved in SpA diseases, with the aim also of identifying biochemical and genetic biomarkers that might help the diagnostic work up and the evaluation of treatment effectiveness. Single nucleotide polymorphisms (SNPs) in genes involved in TNF-α signalling, such as those in the promoter region of the *TNFA* gene, in *TNFSF15* (TNF ligand superfamily, member 15), *TNFR-1* (TNF receptor 1) and *TRADD* (TNF receptor type 1-associated death domain protein), have been identified as potentially associated with SpA. This is of great interest not only because TNF-α is involved in the propagation and perpetuation of inflammation in SpA, but also because of the clinical efficacy of treatments based on drugs targeting the TNF-α pathway. Taking into consideration the potential role of autoinflammation in disease pathogenesis, other potential candidates are the *MEFV* (Mediterranean fever) and *TNFRSF1A* (TNF receptor superfamily member 1A) genes, involved in the pathogenesis of the autoinflammatory disorders familial Mediterranean fever (FMF) and tumour necrosis factor receptor-associated periodic syndrome (TRAPS), respectively. The latter gene encodes the TNFR-1 and genetic variations might underlie functional alterations of the TNF-α signalling, while variations in *MEFV* gene were shown to be very common among FMF Turkish patients with AS as a sole clinical manifestation. Starting from these data, an Italian research group, investigated whether, in addition to the established *HLA-B27* genetic predisposing factor, biomarkers of inflammation, SNPs in the promoter region of *TNFA*, or variants of the autoinflammatory *TNFRSF1A* and *MEFV* genes, might be of help in SpA diagnosis and/or in predicting the response to anti-TNFα treatment. They enrolled 137 SpA patients (82 with PsA and 55 with AS; 98/137 under TNF-α inhibitor therapy) and 373 controls coming from the north-east of Italy. TNFA polymorphisms (-1031T>C;-857C>T;-376G>A;-308G>A;-238G>A) and HLA-B27 were assayed by RT-PCR. Direct sequencing of MEFV (exons 2,3,5 and 10) and *TNFRSF1A* (exons 2,3,4 and 6) genes were performed. Their analysis confirmed that HLA-B27 was associated with AS; only the TNFA -1031T>C was singly associated with SpA, and the haplotype C/G, resulting from -1031T>C/-308G>A combination, was significantly associated with a reduced risk of developing SpA. Two SNPs were identified in *TNFRSF1A,* the R92Q and c.625+10A>G; none of them was associated with a higher risk of developing SpA. Interestingly, the TNFRSF1A c.625+10 G allele was significantly associated with a later response to anti-TNF-α therapy. Twenty-one SNPs were identified in *MEFV* gene, 10 with a known potential functional significance. Variant alleles were extremely rare in the studied population, except for R202Q; none of them was associated with SpA diagnosis. The authors therefore concluded at first that the risk of developing AS seemed to depend not only on HLA-B27, but also on the protective role of TNF-α haplotype -1031C/-308G; secondly, the *TNFRSF1A* and *MEFV* gene SNPs are not associated with a major risk of developing SpA in the north-east of Italy and finally, that the *TNFRSF1A* c.625+10A>G could impact on the response to anti-TNF-α therapy (13).

Long non-encoding RNAs (lncRNAs) are important mediators of inflammation and in particular in autoimmune diseases such as systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), or PsO, they seem to modulate the immune system. Considering that few data exist on lncRNAs in PsA, Dolcino *et al*. have researched the profile of expression of lncRNA with microarray analysis in a cohort of 10 patients with PsA. They have found 259 lncRNAs that are strongly associated to PsA compared with healthy controls. The role of lncRNAs found in the blood of patients with PsA could be strongly associated with the immunopathogenesis of the disease, owing to their association with B and T lymphocyte gene expression, inflammatory cytokine genes like TNF and type 1 IFN, genes related to bone apposition such as WNT and genes related to metabolic syndrome. From these data it

could be supposed an epigenetic role of lncRNA in PsA pathogenesis, through their role in immunomodulation of adaptative and acquired immunity and in glycolipid metabolism (14).

MicroRNAs (miRNAs) are important mediators of the immune system; only few data on miRNA expression in patients with active PsA is currently availble. Pelosi *et al*. investigated their action in PsA analysing a cohort of 23 PsA patients that were divided into two subgroups based on the phase of their disease (activity or remission). They found that miRNAs changed the expression of TNF, MAPK and WNT signaling pathways only in patients with an active disease, suggesting a possible role of miRNAs on gene expression in PsA transcriptoma. Interestingly, a specific type of miRNA, miR-126-3p was downregulated in patients with active PsA and was usually over expressed in patients with disease in remission. These results highlighted that miRNAs could represent biomarkers of different phases of activity of PsA; besides, they could help as indicators of new possible therapeutic strategies (15).

IL-23 and IL-17 have a well known pathogenetic role in PsA and consequently, they are important specific targets of biological therapy.

Abji *et al*. have analysed the synovial fluid of 14 patients with PsA and 9 with osteoarthritis; in particular, they isolated RNA from synovial fluids and used RT-PCR to study the different expression of 84 genes of the Th17 pathway between the two subgroups. They found that synovial fluid from patients with PsA was characterised by increased expressions of STAT and FOXP3 genes than in patients with osteoarthritis. The differences in the gene expression of synovial fluid between PsA and osteoarthritis could be useful as a possible biomarker of PsA (16).

Comorbidities

A consensus on a list of practical recommendations promoting the early identification of patients with PsA in the dermatology setting was developed based on a narrative literature review, expert review and Delphi consensus, adding further strategies to implement the early identification of patients with PsA (17) and supporting the importance of a multidisciplinary management of PsA in strict collaboration between the rheumatologist and the dermatologist (18). Finally, duration of PsO disease has been reported to be associated with an increased incidence of PsA in a large cohort of 10,011 patients (19).

A screening clinical questionnaire – Simple Psoriatic Arthritis Screening (SIPAS) – to facilitate the discrimination between PsO and PsA has been proposed and validated by Salaffi *et al*. and can be used to identify patients that warrant referral to a rheumatologist (20).

Another novel questionnaire (CONTEST) was developed using the most discriminative items to detect undiagnosed PsA amongst patients with PsO and compared to the previously used Psoriasis Epidemiology Screening Tool (PEST). CONTEST showed acceptable sensitivity/specificity (0.53 and 0.71, respectively), but no superiority to the available PEST tool (21).

The prevalence of dactylitis in patients with early SpA has been reported by 609 patients included in the ESPeranza cohort (including patients with suspected SpA). The study showed that dactylitis occurred in 9.5% of patients and was mainly associated, but not exclusive, of peripheral disease and PsO (22).

An interesting approach to the assessment of comorbidities was proposed by Patel *et al*., analysing whether patients recognise that they are being assessed and monitored for comorbidities associated with PsA or PsO. The authors reported that patients feel they are being moderately well screened for comorbidities, but are mostly unsure about having their blood sugar and cholesterol levels monitored, underlying a discrepancy between patients' responses and physician practice. These results highlight the need to optimise patients' education and endorsement in a comprehensive approach to their health, that would be of benefit on the outcome of the rheumatologic disease itself (23).

The well-established association of PsA with metabolic syndrome and CV risk was still confirmed by the literature published in the past 12 months, particularly in terms of endothelial dysfunction, subclinical atherosclerosis and plaque instability.

Szentpetery *et al*. assessed the frequency and characteristics of coronary plaque burden in 50 patients with PsA and 50 age- and sex-matched controls. Plaques were significantly more frequent in PsA compared to controls. Interestingly, among patients with PsA, the presence of concomitant metabolic syndrome did not influence the plaque burden, which was associated with signs of active inflammatory disease rather than with traditional CV risk factors (24).

A cohort of 340 patients from a tertiary hospital-based polulation with PsA was studied in a retrospective and cross-sectional way for type II diabetes and other CV comorbidities comparing with 600 controls without infammatory arthropathies. Queiro *et al*. found that diabetes was significantly more prevalent in PsA patients (13.8%) than controls (5%). Interestingly, the presence of diabetes was strongly associated with PsO and arthritis onset after 40 years, a higher count of swollen and tender joints, a lower educational level, pustolar PsO and, as expected, metabolic syndrome. After controlling for age, sex and duration of the disease, in particular, the authors found a strong association with late onset PsO and hypertension. These data confirm that type II diabetes is frequent in patients with PsA, suggesting the need for metabolic screening, particularly in patients with late onset PsO and PsA (25).

Remaining on CV risk associated to SpA, a prospective nationwide study with cohorts of patients with AS (n=6448), PsA (n=16063) and uSpA (n=5190) and a general population (GP) (n=266435) cohort in a Swedish registry, was performed with an 8-year follow up, to observe the incidence of atrioventricular (AV) block II-III, atrial fibrillation (AF), pacemaker (PM) implantation and aortic regurgitation. At the end of the follow-up period, it was observed that the highest incidence rates for CV events were noted for AF (5.5–7.4 events per 1000 person-years), followed by PM implantation (1.0–2.0 events per 1000 person-years). Hazard ratios for AV block, AF, PM and aortic regurgitation were significantly increased in AS (HRs 2.3, 1.3, 2.1 and 1.9), uSpA (HRs

2.9, 1.3, 1.9 and 2.0) and PsA (HRs 1.5, 1.5, 1.6 and 1.8) compared with the GP cohort. With these results Bengsston *et al*. proved that patients with SpA are at increased risk of aortic regurgitation, cardiac rhythm disturbances and, as a probable consequence, also PM implantation (26).

Vitamin D deficiency has been associated with several inflammatory conditions (*i.e*. connective tissue diseases, RA), but has been poorly evaluated in SpA patients. Fernandes *et al*. performed a study with the aim of evaluating the prevalence of hypovitaminosis D in SpA patients (enrolled from the ASAS-COMOSPA study initiative, an international cross-sectional study of patients with SpA) and of understanding the possible association of vitamin D levels with disease phenotype, activity severity or comorbidities. Of the 1030 patients, more than half (51.2%) had vitamin D deficiency, thus confirming the higher prevalence of this condition in inflammatory diseases. Moreover, vitamin D deficiency was also associated with active SI, suggesting an association between low levels of vitamin D and more severe forms of SpA (27).

Hyperuricaemia (HU) is a laboratory finding typically associated with PsA. Lai *et al*. performed a multicentre cross-sectional obervational study on 160 Asian patients, to analyse the possible association in patients with PsA between HU and overweight, obesity, body area involved by PsO, severity of skin disease (using PASI score) and joint count. More than 30% of patients had HU. They found a significant association only between HU and BMI score, thus highlighting the importance of body weight control and daily practice attention on this specific clinical aspect in patients with PsA (28).

Imaging

Modern imaging is a useful tool for the diagnosis, prognosis, and monitoring of therapeutic response in SpA, by providing sensitive measures of the extent of disease (also detecting a subclinical synovitis or enthesitis) and being able to monitor both inflammation and damage. PsA is a heterogeneous disease with various manifestations of musculoskeletal inflammation. Recent advances in imaging, including ultrasound (US) and magnetic resonance imaging (MRI), allow for the accurate evaluation of the extent of inflammation and damage in the peripheral joints, spine, and enthesis. The development and validation of outcome measures are critical steps in creating standardised evaluations of musculoskeletal inflammation and damage in psoriatic patients. At the 2017 meeting of the Group for Research and Assessment of Psoriasis and PsA (GRAPPA), the GRAPPA US group developed and validated a sonographic enthesitis scoring system in PsA, which will improve the standardisation of disease assessment (29).

US is the easiest and reliable way to investigate joint swelling. Macia-Villa *et al*. investigated 27 PsA patients with clinical involvement of metacarpophalangeal joints, particularly evaluating by US the frequency and reliability of peritenon extensor tendon inflammation (PTI) and intra articular synovitis (IAS). It was observed that both IAS and PTI caused metacarpophalangeal joints swelling, where PTI is almost as frequent as IAS as a cause of swelling and that the reliability of PTI is at least as good as for IAS (30).

Predictive signs of PsA in patients with early arthritis have been described. Furlan *et al*. have investigated the frequency of thickening of pulleys for hands flexor tendons in a prospective study involving 228 consecutive patients with early arthritis. The authors observed that the thickening of the pulleys in the flexor tendons was an easy-to-detect sign, with a good sensitivity (80%) of thickened pulleys for the diagnosis of PsA; however, the specificity (70%) and positive predictive value (2.71) were not as high. Nevertheless, the authors concluded that sonographers should report it during hand evaluations of patients with arthritis. Patients with diabetes were excluded as potential confounders, owing to the high frequency of trigger finger pathology in this group of patients (31).

Nail psoriasis disease is associated with an increased probability of PsA, and its clinical signs may have different correlates with the pathogenesis of adjacent bone destruction and have different prognostic value. Moya Alvarado *et al*. attempted to describe which US characteristics of nail psoriasis were associated with the presence of subclinical enthesopathy in patients with PsO and asymptomatic PsA. Forty-eight patients with PsO and asymptomatic PsA were included in the study and the US assessment included Achilles tendon, extensor digitorum tendon and US scan of the nail plate, nail matrix, nail bed and adjacent skin over nail matrix of the five nails of each hand. The authors observed that 33 patients presented US evidence of extensor digitorum tendon enthesopathy. The nails of the patients with subclinical enthesopathy had a higher Nail Psoriasis Severity Index (NAPSI) and skin thickness than the nails of the patients without subclinical enthesopathy, confirming that there is a close relationship between subclinical enthesopathy of the extensor digitorum tendon and the presence of nail alterations (32).

US assessment of changes in fingernails (thickness of the nail plate, nail bed, and matrix) have been reported to correlate with the duration of arthritis (r=0.399; p=0.022) and with the number of swollen digits (r=0.278; p=0.041) in PsA patients (33). Moreover, US findings at the level of the nail unit might be of use to differentiate between PsA and PsO and healthy controls, showing a trend for onycholisis and crumbling in PsA compared to the other groups (34).

A comprehensive US evaluation of finger flexor tendon entheseal soft tissue and bone changes can offer useful information to differentiate PsA from RA. Peri-tendinous dermal soft tissue oedema with power Doppler signal was only found in PsA patients (p=0.003). Flexor tendon enthesopathy including new insertional bone formation and tenosynovitis were both significantly more frequent in PsA compared to RA (35).

US can be used to investigate multiple superficially located entheses and abnormalities can be quantified with a combined score, for example, the MAdrid Sonographic Enthesitis Index (MASEI). Last year, Wervers *et al*. performed a cross-sectional study to investigate the frequency of US changes at

the entheses of 25 patients with a recent diagnosis of PsA, 25 patients with established PsA, and 25 young healthy volunteers. They analysed by US the triceps, quadriceps, patellar, Achilles and elbow extensor tendon insertion, and plantar fascia entheses for structural changes, erosions, calcifications, increased thickness, bursitis, and power Doppler (PD) signal. Sonographic changes in the entheses were observed in young, healthy volunteers, patients with recently diagnosed PsA, and in patients with established PsA. After having excluded patellar tendon enthesis thickness and applying a new method of scoring PD, the modified MASEI was able to distinguish between PsA patients and healthy controls; furthermore, the authors found US abnormalities were very common from the early stages of PsA (36).

As a result of its sensitivity, MRI can be used to detect any subclinical sign of arthritis. Mathew *et al*. performed an observational study evaluating inflammation at the small joints of feet in PsO patients without clinical arthritis (53) as against clinically overt PsA (30) patients, using a low field magnet extremity MRI (eMRI). The authors observed that there was no statistical difference between the median eMRI inflammatory scores in PsA and PsO patients; in particular, evidence of inflammation was present in 33.9% and 50% patients in the PsO and PsA groups, respectively. Early arthritis for psoriatic patients screening questionnaire (EARP) score of ≥3 was significantly associated with imaging features of inflammation in PsO group, suggesting a high proportion of subclinical inflammation in PsO patients and the need to predict risk factors for progression to future PsA development in this kind of patient (37).

Chen *et al*. investigated the reliability of three-dimensional ultrashort echo time cones (3D UTE Cones) MR sequences in 7 healthy volunteers and 9 PsA patients, evaluating the Achilles tendon and its enthesis; they concluded that 3D UTE Cones provided high resolution imaging of entheses and tendons and could be used for morphological and quantitative evaluation of abnormal entheses and tendons in PsA patients, while no reliable T2 measurement could be achieved with a Carr-Purcell Meiboom-Gill (CPMG) sequence, due to insufficient signal from entheses and tendons (38).

Disease activity, quality of life and working ability

It is well known that psychological problems tend to be underrecognised and undertreated in patients with PsA; however, little is known on how people with PsA cope with and manage their disease. The Common Sense Self-Regulatory Model (CS-SRM) suggests illness beliefs, mediated by coping, may influence health outcomes. Therefore, Howells *et al*. planned a cross-sectional observational study to investigate the role of disease severity, illness beliefs and coping strategies in predicting depression, anxiety and QoL in PsA patients; moreover, they tried to assess the role of depression and anxiety in predicting QoL. One hundred and seventy-nine adult PsA patients completed validated measures of predictor (illness beliefs, coping strategies, disease severity) and outcome variables (depression, anxiety, QoL), using an online survey distributed via social media. After controlling for disease severity, hierarchical multiple regression models indicated that more negative beliefs about consequences and behavioural disengagement as a coping method, predicted levels of depression, and self-blame predicted anxiety. Beliefs about consequences and the presence of depression predicted QoL scores after controlling for disease severity. These data may support the use of the CS-SRM in explaining variation on psychological outcomes in individuals with PsA. Moreover, the illness beliefs and coping strategies identified as predictors in this study could be potential targets for interventions, addressing PsA-related distress and QoL (39).

The data in the literature show that PsO and PsA impact sexuality and intimate relationships in both men and women, and can be associated with sexual dysfunctions. Esteve *et al*. performed a study aimed at developing and validating a specific questionnaire to assess the impact of these conditions on patients' sexuality. Two focus groups of patients, concerned by sexuality, were conducted in February 2015. Based on the verbatim transcripts, a content analysis was performed by a psychologist trained in qualitative procedures. After an analysis of the verbatim reports by the research group, a preliminary questionnaire comprising 22 questions was drawn up; it covered the following areas: the quality of daily life, tolerance of the cutaneous state by the patient, tiredness, mobility and flexibility of the joints and outside activities involving movement of all or part of the body. Subsequently, the questions were submitted to a panel of experts for selection using a Delphi method; they were questioned about item relevance and content. After expert consensus had been reached, the instructions to participants completing the questionnaire, the wording of items, and the possible answers were finalised. The questionnaire entitled "Questionnaire of sexual quality of life perceived by patients with cutaneous and/or articular psoriasis" comprised 14 questions. However, the authors specified that the quantitative step, aiming at evaluating the metrologic qualities (reliability, validity, and responsiveness) of the questionnaire, had not yet been performed (40).

PSOdisk is a 10-item visual instrument, aimed at assessing the burden of disease in patients with psoriasis. An Italian study group performed an analysis which aimed to compare PSOdisk with the Dermatology Life Quality Index (DLQI), a scientifically validated questionnaire, and assessing both tools in relation to Psoriasis Severity Index (PASI) and patient acceptance. They studied both patients with cutaneous psoriasis and PsA. Correlation analysis between PSOdisk and DLQI was performed using Pearson's product-moment correlation coefficient. A multivariate linear regression was carried out to investigate the effect of PASI on PSOdisk and DLQI scores. Moreover, the authors evaluated completion times as well as patient satisfaction for both PSOdisk and DLQI. The mean value of Cronbach's coefficient alpha was 0.88 for PSOdisk and 0.90 for DLQI, suggesting good reliability. A significant

correlation was found between PSOdisk and PASI. It also was associated with a good patient satisfaction, and required a short completion time. A multivariate linear regression analysis demonstrated a statistically significant effect of PASI on both the DLQI score and PSOdisk score, thus demonstrating a good correlation between PSOdisk and both DLQI and PASI (41).

A Dutch cross-sectional study was conducted to clarify whether PsA patients with an acceptable disease state according to the treating rheumatologist have quiescent disease defined as minimal disease activity (MiDA). An acceptable disease state was defined by asking rheumatologists to refer those patients whom they considered sufficiently treated. Patients were evaluated for current disease activity including clinical assessments and PROs. A total of 250 patients with PsA were screened. The authors found that more than 35% of the patients with acceptable disease state according to the rheumatologist did not fulfill the MiDA definition, most frequently owing to tender joints, patient pain and global disease activity scores. Moreover, also objective signs of disease activity as swollen joint count >1, enthesitis >1 and PASI >1, were higher in patients who did not reach MiDA. Residual disease was more frequent in females, elderly patients and those with a raised BMI, independently of the treatment schedule; it negatively influenced PROs of function and QoL. These data showed that one third of the PsA patients with acceptable disease state according to the treating rheumatologist did not fulfil the MiDA criteria and had residual disease activity on both subjective and objective disease activity measurements, which is associated with worse PROs evaluation. Future strategy trials should be performed, to evaluate whether treatment adjustments could be beneficial for this PsA patient subgroup (42).

The Psoriatic Arthritis Impact of Disease (PsAID) Questionnaire is a tool that was developed by a EULAR task force to assess patient-reported outcome measures (PROs) to reflect the impact of PsA from the patients' perspective. The PsAID was tested and validated on an independent cohort of patients, assessing the minimally important clinical difference for improvement. The PsAID proved to be a reliable tool of the impact of disease, with a sensitivity to change. The minimal detectable change was 1.41. There was a strong correlation with other PROs (such as the EQ-5D index of the FACIT-fatigue score), and a moderate correlation with clinical outcomes (43).

Van Mens *et al*. analysed a real-life cohort of 250 patients to compare the different composite measures used to define remission or LDA for PsA. The following tools were used to assess disease activity: the Disease Activity Index for Psoriatic Arthritis (DAPSA), the clinical DAPSA (cDAPSA), very low disease activity (VLDA) defined if all seven items of the Minimal Disease Activity (MiDA) were fulfilled, and the Psoriatic Arthritis Disease Activity Score. The VLDA was only reached by a minority (19.5%) of the cohort. The different measures used allowed for significantly different grades of residual disease activity that need to be taken into account in clinical practice (44).

A modified version of the Psoriatic Arthritis Disease Activity Score (PASDAS) has been recently proposed demonstrating similar results using a shorter version of the SF36 Questionnaire comprising only 12 domains (SF12) (45).

The treat-to-target strategy in PsA aims at the attainment of remission, or, alternatively, low disease activity (LDA). The GRAPPA and OMERACT groups met to develop consensus-based recommendations for the use of composite measures and treat-to-target in PsA. The most popular measures voted by health care professionals and patients were the PsA disease activity score and the GRAPPA composite index to be used in randomised controlled trials, and an average on 3 visual analogue scales and disease activity in the PsA score for clinical practice. Nevertheless, the group failed to achieve a consensus on the best composite measure to be used. The treatment target proposed by the group is that of a VLDA or MiDA. The group agreed that the assessment of disease activity should comprise musculoskeletal disease, skin disease and HRQoL (46).

DAPSA was validated for PsA in 2010 and is based on the simple summation of visual analogue scales (0-10 cm) of patient's global and pain assessments, 66 swollen joint count, 68 tender joint count and CRP (mg/dL). 28-joint counts have been found to be sufficiently valid in comparison to more comprehensive joint counts in patients with RA; consequently Michelsen *et al*. tested the potential validity of a simplified DAPSA score including 28 instead of the original 66/68 joint counts in patients with PsA. Data were analysed from a cohort of 3157 patients from the Danish national quality registry DANBIO compared to a cohort of 3154 controls. The authors observed that data obtained with only 28-joint counts available can be used to calculate DAPSA28, especially in patients with low disease activity. DAPSA28 showed good criterion, correlational and construct validity and sensitivity to change. Still, it was not recommended the use of DAPSA28 in clinical practice, as the 66/68 joint counts should be used in PsA whenever feasible; despite this, to our knowledge, DAPSA28 is the first 28 joint disease activity score developed and validated in PsA (47).

Therapy

bDMARDs

Kavanaugh *et al*. directly compared the disease burden and use of biologic drugs between 2002 and 2013 in patients with PsA or RA who had been referred to the rheumatology setting and enrolled in the Consortium of Rheumatology Researchers of North America (Corrona) registry, to discover whether the disease burden of PsA was different from that of RA, whether this difference had changed over time, and whether biologic treatment patterns had altered in the wake of increases in published efficacy and safety data. They retrospectively evaluated PsA and RA patients enrolled from January 2002 and March 2013 and grouped in 2-year intervals, assessing clinical outcomes and biologic use. They found an increasing in biologic use over time in both cohorts, with 62 and 52% of patients with PsA and RA,

respectively, receiving biologics by 2012-2013. However, 25 and 35% of patients with PsA and RA, respectively, continued to experience moderate/high disease activity. The progressive increase in biologic use seemed to be associated to progressive decreases in Clinical Disease Activity Index and mean Health Assessment Questionnaire scores. Quite surprisingly, the mean patient pain, the proportion of patients reporting morning stiffness, and the mean duration of morning stiffness remained similar for both cohorts. Therefore, if these data showed that patients with PsA and RA treated in the rheumatology setting had a comparable impact on patient quality of life and functional ability and confirmed that the increased biological utilisation improved the disease burden in both groups, they highlighted that a significant proportion of PsA and RA patients did not reach a good control of disease activity, remaining with a moderate/severe arthritis (48).

The increasing use of bDMARDs for the treatment of PsA have significantly changed the disease course, but have introduced potential issues in terms of sustainability and costs. Goeree *et al*. analysed the cost-effectiveness of secukinumab compared to other bDMARDs (ADA, certolizumab pegol, ETN, GOL, ustekinumab, IFX and biosimilar-IFX) for the treatment of active PsA over a life-time horizon. Secukinumab dominated in ensuring a better response to treatment (PsA Response criteria -PsARC) and was cost-effective against all other bDMARDs (49).

Another cost analysis was published in 2018, assessing the value of a tight control strategy in early PsA from the Tight Control of Psoriatic Arthritis (TICOPA) study (50); it reported no clear cost-effectiveness of the tight control strategy in PsA. Despite being a demonstrated clinically effective intervention, other issues such as drug prices, ideal target populations and frequency of rheumatologic assessment should be improved in the management of PsA (51).

The persistence on therapy of PsA patients treated with bDMARDs is not optimal as confirmed by a recent study analysing administrative claims data in the USA. Of 1235 patients, the mean duration of persistence with a new bDMARD – different TNFi or ustekinumab – was less than 12 months. Patients persisting on the first index biologic for over one year were 44.5% of the population (52).

Interestingly, extracting data from 329 patients from an Icelandic database (ICEBIO), Runarsdottir *et al*. observed that the majority of patients with PsA were not eligible for randomised clinical trials. ICEBIO registered patients with PsA who received ADA, ETN, GOL, or IFX as their first-line treatment in the period from January 1, 2000 to February 4, 2016. The authors described that only 34% of the patients with complete data available met the inclusion criteria; particularly the proportion of patients who met the inclusion criteria was highest among those who received ADA or ETN (53%) while those who received IFX had the lowest inclusion rate (23%). The main reason of exclusion was an inadequate number of swollen or tender joints (45% of the cases) and the second was comorbidity (15.8%). In conclusion, the vast majority of PsA patients from ICEBIO register are in treatment with a biologic agent but would have been excluded from randomised clinical trial with the same therapy. Further studies with regards to whether outcomes would be different between those that met the inclusion criteria and those that did not remain to be performed (53).

TNF alpha inhibitors

Thomas *et al*. analysed the long-term survival on drug (SOD) of patients with RA, PsA and AS treated with GOL, enrolled from 2010 to 2014 in 4 Academic Centres in Greece. SOD was analysed using Kaplan-Meier survival analysis. They included 328 patients (RA: 166, PsA: 82, AS: 80). The estimated SOD at 2 and 3 years was 68% and 62% overall; data for AS (79% and 76%) were significantly better than those for RA (69% and 60%, p=0.067) or PsA (58% and 53%, p=0.001) patients; no difference was noted between RA and PsA patients. No difference in SOD was observed between biologic-naïve or -experienced patients, nor between non-biologic association therapy or GOL monotherapy treated patients. The rates of serious adverse events serious infections were 2.3 and 1.0/100-patient-years, respectively; a quite low proportion of patients discontinued the drug owing to adverse events (about 11%), thus confirming an acceptable safety profile of GOL in real life, with good values of SOD, particularly in AS patients (54).

Ruwaard *et al*. investigated if there were any differences in SOD and clinical outcomes in patients with AS treated with ADA or ETN. They enrolled biological-naïve consecutive AS patients; 163 were treated with ETN and 82 with ADA. Disease activity was assessed by the ASDAS-CRP; in particular, a stage of moderate disease activity (MDA) was defined as an ASDAS-CRP <2.1. They found 32.9% treated with ADA and 18.4% with ETN discontinued treatment, owing to inefficacy, adverse events, loss to follow-up, planning a pregnancy, or uveitis. Besides, they did not find any significant difference at 2 years of follow-up between the two groups both in mean ASDAS-CRP value, nor in the percentage of patients who reached MDA (respectively 67.6% for ADA and 60.7% for ETN). Therefore, they conclude that ETN seems to have a higher SOD than ADA in their cohort of AS patients, however, no difference was noted in the reduction of disease activity between the two groups, thus suggesting that probably more data are needed to correctly compare these drugs (55).

A recent observational cohort Danish study investigated gender differences in disease manifestations, patient-reported outcomes (PROs), comorbidities and treatment effectiveness among patients with PsA treated with their first TNF-α inhibitor. The DANBIO register provided prospectively collected data on PsA patients who initiated their first TNF inhibitor in 2000–2015. Comorbidity informations were achieved from the Danish Nationwide Patient Register. Response to treatment was assessed according to EULAR and ACR criteria at 3 and 6 months. Cox and logistic regression models analysed the impact of gender on anti-TNF alpha persistence and response, respec-

tively. The authors enrolled 1750 PsA patients (935 women). At baseline, women were significantly older, more often smokers, with significantly worse PROs scores, with a significantly higher frequency of hospital-diagnosed anxiety or depression and with a higher prevalence of chronic pulmonary disease than men. Median persistence on anti-TNF alpha was 3.8 years in men *vs*. 1.4 in women ($p<0.001$). These data showed a better efficacy profile of anti-TNF alpha in men than women with PsA; taking into account that the adjustment for baseline risk factors including PROs, disease activity, comorbidities and lifestyle factors did not influence this relationship, biological factors may exert a major role in establishing this gender difference (56).

An Italian multicentre retrospective study aimed to compare the drug survival and efficacy of different anti-TNF agents for the treatment of both PsO and PsA patients. A database of PsO/PsA patients treated with ADA, ETN, and IFX from May 2013 to May 2014 was analysed. PASI 75, 90, and 100 were calculated at each time point to evaluate efficacy. Drug survival rate and probability of maintaining PASI response were evaluated. The impact of dependent variables on probability of PASI 75 loss was evaluated by logistic regression. The authors evaluated data from 577 patients with PsO and 685 with PsA. The highest survival rates were observed with ADA followed by ETN and IFX in both groups of patients. The probability of maintaining PASI response was significantly higher for patients treated with ADA, followed by IFX. For PsA patients, the odds of losing PASI 75 was higher in ETN-treated patients or IFX *vs*. ADA, similarly to what was observed in the PsO group. Therefore, these results highlighted a significantly better efficacy profile of ADA, compared with ETN and IFX (57).

Damjanov *et al*. analysed data from Psoriasis Randomised Etanercept Study in subjects with psoriatic Arthritis (PRESTA) cohort, to evaluate the efficacy of ETN in PsA patients from Central and Eastern Europe (CEE). In PRESTA, patients were randomised to receive ETN 50 mg BIW or 50 mg QW for 12 weeks (double-blind phase) and ETN 50 mg QW for 12 additional weeks (open label). In this analysis, only 307 patients from Czech Republic, Hungary, Poland and Serbia were included. The primary efficacy variable was the proportion of subjects achieving a physician global assessment (PGA) of psoriasis status: "clear" or "almost clear" at week 12. The Authors found that 54% BIW/QW compared with 40% (QW/QW) ($p=0.02$), achieved "clear"/"almost clear" for PGA of psoriasis at week 12, increasing, to 68% and 60%, respectively (p=ns) by week 24. Mean improvement from baseline in PASI were 59% versus 49% ($p=0.005$) at week 6 and 87% versus 81% ($p<0.05$) at week 24, for the BIW/QW and QW/QW groups, respectively, thus showing that both dose regimens of ETN provided significant improvements in efficacy in PsO treatment in PsA patients from CEE (58).

Zangrilli *et al*. conducted a retrospective study aimed at evaluating the long-term efficacy and effects on lipid profile and AIP of ADA in patients with moderate-to-severe PsO or PsA. Sixty-nine PsO patients treated with ADA 40 mg every other week were included. Patients were treated continuously for 4 years; follow-up visits were performed every 24 weeks. Disease severity indices, disease burden indices (PSOdisk), serum lipid concentrations, AIP and inflammatory markers were assessed at each visit. After 24 weeks, the NAPSI score, articular pain and disease burden had improved significantly. The 4 years of uninterrupted treatment with ADA was well tolerated. Lipid serum concentrations and inflammatory markers were overall stable and within the range of normality; high-density lipoprotein cholesterol concentrations increased significantly and AIP improved, thus highlighting long-term treatment of moderate-to-severe psoriatic disease with ADA is effective, well tolerated, and potentially beneficial also in terms of lipid pattern and atherogenic risk (59).

Stober *et al*. performed a study to analyse persistence on therapy with anti-TNF alpha, when used as first- or second-line therapy in patients with PsA; they also evaluated baseline clinical and laboratory parameters associated with persistence on anti-TNF. They retrospectively evaluated from their cohort of PsA patients, those who began anti-TNF therapy as first or second-line between 2003 and 2015. Demographic, clinical and laboratory characteristics were compared with TNFi persistence, using Kaplan-Meier survival and Cox proportional hazards models. They found 188 PsA patients had began TNFi as a first line biological treatment; after 12 months, 79% of patients persisted with TNFi therapy, and 73% at 24 months. Discontinuation was due to primary inefficacy in 35% of cases, secondary inefficacy in 22% and adverse events in 43%. Female sex and the presence of metabolic syndrome-related comorbidities were significant predictor of a lower persistence on therapy. TNFi persistence was 2-fold less likely in patients taking the drug as a second line therapy compared with first-line TNFi users. These data showed discontinuation of anti-TNF therapy is higher in PsA female patients or in those with metabolic syndrome; patients who switched to another anti-TNF had a lower persistence on therapy, however, a substantial proportion of these cases responded, thus advocating switching to a second TNFi as a valid therapeutic strategy (60).

The impact of comorbidities on disease severity and response to TNFi was assessed on a large population-based cohort including 1750 patients with PsA recruited in the Danish DANBIO registry. Higher scores on the Charlson Comorbidity index (CCI) were significantly associated with greater disease activity at baseline, reduced response to treatment (EULAR response), and shorter persistence on treatment (HR 1.72; 95%CI 1.26; 2.37; p=0.001). The persistence on treatment decreased with increasing values of CCI from 2.6 years (95% CI 2.2-2.9) for CCI=0 down to 1.3 years (95% CI 1.0-1.6) for CCI ≥2; log-rank <0.001. Persistence on therapy was also lower for patients with anxiety and depression (61).

Based on the data of 216 patients enrolled in a randomised controlled trial of GOL in PsA patients, GO-REVEAL,

Schoels *et al*. performed diagnostic testing analyses using 3- and 6-month disease activity as tests for treatment outcomes to understand the implications of early response. In regression analyses, they estimated the probabilities for achieving at least LDA. Disease activity was measured by DAPSA. Their results showed that an early response to therapy at 3 months can be predictive of future accomplishment of the target, predicting 6-month and 1 year disease activity outcomes and stressing the need for a tight disease control based on a treat-to-target strategy (62).

Interleukin-17A inhibition

In a study by Nicola *et al*., 13 patients with PsO and PsA who failed at least one previous anti-TNF alpha, were treated with secukimumab and methotrexate, showing a rapid clinical response of both cutaneous and articular involvement; improving of PsO took place after 4 weeks and that of arthritis within 16 weeks, including also normalisation of the inflammatory indices and improvement of the quality of the life parameters (63).

Ixekizumab (IXE) is a high-affinity monoclonal antibody that selectively targets IL-17A and is an approved treatment for moderate-to-severe psoriasis. In a recent phase III, multicentre, double-blind, randomised study (SPIRIT-P1) van der Heijde *et al*. evaluated the efficacy and safety of IXE over 52 weeks in patients with active PsA who were naive to bDMARD. Patients were randomised (1:1:1:1) to receive subcutaneous injections of placebo (PBO), adalimumab 40 mg every 2 weeks (ADA), and IXE 80 mg every 2 weeks (IXEQ2W) or 80 mg every 4 weeks (IXEQ4W). At Week 24 (Week 16 for inadequate responders), ADA (8-week washout before starting IXE) and PBO patients were re-randomised to IXEQ2W or IXEQ4W. Both IXE dose regimens included an initial 160-mg starting dose. Of 417 patients randomised, 381 completed the double-blind period (52 weeks), at the end of witch was observed that the IXEQ4W and IXEQ2W groups (EPP), respectively, ACR20 (69.1% and 68.8%), ACR50 (54.6% and 53.1%), and ACR70 (39.2% and 39.6%) response rates were sustained. A similar pattern was observed for PASI outcomes, while radiographic progression in all groups was minimal. Furthermore, the safety profile was consistent and the most frequently reported treatment-emergent adverse events (≥4%) were nasopharyngitis, injection site reaction, injection site erythema, upper respiratory tract infection, and back pain. No deaths were reported, and serious adverse event frequency was 0–4% (64).

The role of IL17A is a well known target of biological therapy; the role of the IL-17F seems to be similar in inflammatory processes. A new biological therapy, bimekizumab, could be a strategic double-targeted therapy for the treatment of patient with PsA. Indeed, bimekizumab is directed against both these cytokines. It was studied in a placebo-controlled proof-of-concept clinical trial in which the double action of bimekizumab showed a fast and strong ability to improve skin and articular disease in patients with PsA (65).

IL-12/23 inhibition

The real-life effectiveness of ustekinumab in patients with PsA, both naïve or showing insufficient response to previous TNFi, was assessed on a prospective observational study including 65 patients, with a long-term follow-up (24 months). Ustekinumab was prescribed as first-line therapy only in 20% of cases, and mainly as second-line bDMARD (33.8% of cases). The effectiveness and safety of ustekinumab were confirmed (66).

Another Italian study, the real-life data from the biologic Apulian registry (BIOPURE) reported on the drug survival and effectiveness of ustekinumab, showing the best performance (DAPSA-based remission) of the drug when used in bDMARDs-naïve patients. Interestingly, co-medication with methotrexate did not increase the persistence on therapy (67).

Small molecules

Nash *et al*. evaluated Apremilast efficacy across various PsA manifestations in biological-naïve patients with PsA. Patients were randomised (1:1) to apremilast 30 mg twice daily or placebo. At week 16, patients whose swollen and tender joint counts had not improved by ≥10% were eligible for early escape. At week 24, all patients received apremilast through week 52. Among 219 randomised patients (apremilast: n=110; placebo: n=109), a significantly greater American College of Rheumatology 20 response at week 16 (primary outcome) was observed with apremilast versus placebo (38.2 *vs*. 20.2%); at week 16, apremilast significantly reduced PsA disease activity *versus* placebo, with changes in DAS-28 CRP, HAQ-DI and Gladman Enthesitis Index (p=0.001); these improvements were maintained with continued treatment through week 52. Over 52 weeks, apremilast's safety profile was consistent with prior phase 3 studies in psoriasis and PsA; in particular, during weeks 0–24, the incidence of protocol-defined diarrhoea was 11.0% *versus* 8.3% of placebo group; serious adverse event rates were 2.8% in the treated patients *versus* 4.6% of the placebo group. These data seemed to show that in biological-naïve patients with PsA, the onset of the effect of apremilast was observed at week 2 and continued through week 52, with a safety profile in agreement with previous reports (68).

New biological drugs

A new biological therapy anti-interleukin 23p19, guselkumab, that has been approved to treat moderate-to-severe PsO, in a study by Deodhar *et al*., showed efficacy to treat also active PsA, controlling its symptoms and mantaining a good profile of safety. Therefore, guselkumab could be a promising choice to treat both skin and articular involvement in PsA (69).

Supplementation therapy

Kristensen *et al*. performed a randomised, double-blind, placebo-controlled study to evaluate whether the use of n-3 polyunsatured fatty acids (n-3 PUFA) in patients with PsA could exert some effect on disease activity, use of analgesics, and inflammatory biomarkers levels. They enrolled 145 PsA patients who received a supplement of 3g n-3 PUFA/day or 3 g olive oil/day

(control) for 24 weeks. Outcome measures for disease activity, use of analgesics, and leukotriene formation from activated granulocytes were assessed at baseline and at study end. At the end of the observation period, the n-3 PUFA group showed a decrease in DAS28-CRP, 68 tender joint count, enthesitis score, and PASI, although not significantly different from the controls. Interestingly, there was a significant reduction in NSAID and paracetamol use compared with controls. Moreover, the participants in the n-3 PUFA group had significantly lower formation of leukotriene B4 from stimulated granulocytes and significantly higher formation of leukotriene B5 compared with controls. These data showed a decrease in disease activity parameters after n-3 PUFA supplementation, even if not significantly different from the controls; on the contrary, the authors found a significant reduction in the use of NSAIDs and paracetamol and in the production of inflammatory cytokines, in particular significantly lower levels of leukotriene B4 (70).

Therapy for comorbidities

Navarro-Millàn *et al*. analysed patients from the Reasons for Geographic And Racial Differences in Stroke (REGARDS) study to understand whether 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 cardiovascular disease (CVD) risk factor. Subjects from the REGARDS study were classified as having IA (without diabetes and hypertension), diabetes (without IA and hypertension), hypertension (without IA and diabetes), or no IA, diabetes or hypertension. Multivariable logistic regression models examined the odds of medical treatment among those with hyperlipidaemia. Thirty-nine participants had IA, 5423 had diabetes, 7534 had hypertension, and 5288 had no diabetes, hypertension, or IA. The fully adjusted odds of treatment were similar between participants with IA and those 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, who should be considered as an independent risk factor for CVD, to optimise the treatment and the clinical assessment in this kind of patient (71).

Abbreviations

SpA: spondyloarthritis
AAU: acute anterior uveitis
PsO: psoriasis
IBD: inflammatory bowel disease
PsA: psoriatic arthritis
ax-SpA: axial spondyloarthritis
SIj: sacroiliac joint
SI: sacroiliitis
nr ax-SpA: non radiographic axial spondyloarthritis
CVD: cardiovascular disease
OP: osteoporosis
HRQoL: health-related quality of life
IBP: inflammatory back pain
CRP: C-reactive protein
TNF: tumour necrosis factor
ETN: etanercept
IFX: infliximab
ADA: adalimumab
GOL: golimumab
SNPs: single nucleotide polymorphisms
MEFV: Mediterranean fever
TNFRSF1A: TNF receptor superfamily member 1A
FMF: familial Mediterranean fever
TRAPS: tumour necrosis factor receptor-associated periodic syndrome
lncRNAs: long non-encoding RNAs
RA: rheumatoid arthritis
IFN: interferon
WNT: wingless/integrated
miRNAs: microRNAs
MAPK: mitogen-activated protein kinase
IL: interleukin
RT-PCR: reverse transcription polymerase chain reaction
STAT: signal transducer and activator of transcription
FOXP3: forkhead box P3
PEST: psoriasis epidemiology screening tool
CV: cardiovascular
GP: general population
AV: atrioventricular
AF: atrial fibrillation
PM: pacemaker
HU: hyperuricaemia
BMI: Body Mass index
US: ultrasound
MRI: magnetic resonance imaging
GRAPPA: Group for Research and Assessment of Psoriasis and PsA
PTI: peritenon extensor tendon inflammation
IAS: intra articular synovitis
NAPSI: Nail Psoriasis Severity index
MASEI: MAdrid Sonographic Enthesitis index
PD: power Doppler
eMRI: extremity MRI
EARP: early arthritis for psoriatic patients screening questionnaire
3D UTE Cones: three-dimensional ultrashort echo time cones
CPMG: Carr-Purcell Meiboom-Gill
CS-SRM: common sense self-regulatory model
QoL: quality of life
DLQI: Dermatology Life Quality index
PASI: Psoriasis Severity index
MiDA: minimal disease activity
PRO: patient-reported outcome
PsAID: psoriatic arthritis impact of disease
LDA: low disease activity
DAPSA: Disease Activity index for Psoriatic Arthritis
cDAPSA: Clinical Disease Activity index for Psoriatic Arthritis
VLDA: very low disease activity
PASDAS: Psoriatic Arthritis Disease Activity score
PsARC: PsA response criteria
TICOPA: tight control of psoriatic arthritis
MDA: moderate disease activity
TNFi: tumour necrosis factor inhibitors
SOD: survival on drug
PRESTA: Psoriasis Randomised Etanercept STudy in subjects with psoriatic Arthritis
CEE: Central and Eastern Europe
PGA: physician global assessment
AIP: atherogenic index of plasma
CCI: Charlson Comorbidity index
IXE: ixekizumab
PUFA: polyunsatured fatty acids
NSAID: non-steroidal anti-inflammatory drug
REGARDS: Reasons for Geographic And Racial Differences in Stroke
IA: inflammatory arthritis

References

1. PARMA A, COMETI L, LEONE MC, LEPRI G, TALARICO R, GUIDUCCI S: One year in review 2016: spondyloarthritis. *Clin Exp Rheumatol* 2017; 35: 3-17.
2. TERENZI R, MONTI S, TESEI G, CARLI L: One year in review 2017: spondyloarthritis. *Clin Exp Rheumatol* 2018; 36: 1-14.
3. STRAND V, SINGH JA: Patient burden of axial spondyloarthritis. *J Clin Rheumatol* 2017; 23: 383-91.
4. CALABRESI E, PETRELLI F, BONIFACIO AF, PUXEDDU I, ALUNNO A: One year in review 2018: pathogenesis of rheumatoid arthritis. *Clin Exp Rheumatol* 2018; 36: 175-84.
5. DI BATTISTA M, MARCUCCI E, ELEFANTE E *et al*.: One year in review 2018: systemic lupus erythematosus. *Clin Exp Rheumatol* 2018; 36: 763-77.
6. BORTOLUZZI A, FURINI F, GENERALI E, SILVAGNI E, LUCIANO N, SCIRE CA: One year in review 2018: novelties in the treatment of rheumatoid arthritis. *Clin Exp Rheumatol* 2018; 36: 347-61.
7. ZABOTTI A, MANDL P, ZAMPOGNA G, DEJACO C, IAGNOCCO A: One year in review 2018: ultrasonography in rheumatoid arthritis and psoriatic arthritis. *Clin Exp Rheumatol* 2018; 36: 519-25.
8. MARASCO E, CIOFFI E, COMETI L *et al*.: One year in review 2018: idiopathic inflammatory myopathies. *Clin Exp Rheumatol* 2018; 36: 937-47.
9. FIGLIOMENI A, SIGNORINI V, MAZZANTINI M: One year in review 2018: progress in osteoporosis treatment. *Clin Exp Rheumatol* 2018; 36: 948-58.
10. MARCHESONI A: Oligoarticular psoriatic arthritis: addressing clinical challenges in an intriguing phenotype. *Rheumatol Ther* 2018; 5: 311-6.
11. DE SOCIO A, PERROTTA FM, GRASSO GM, LUBRANO E: Incidence of rheumatoid arthritis, psoriatic arthritis and polymyalgia rheumatica in an inland area of central Italy: results of the CAMPO-RHE study. *Postgrad Med* 2018; 130: 137-41.
12. CRETU D, GAO L, LIANG K, SOOSAIPILLAI A, DIAMANDIS EP, CHANDRAN V: Differentiating psoriatic arthritis from psoriasis without psoriatic arthritis using novel serum biomarkers. *Arthritis Care Res* 2018; 70: 454-61.
13. AITA A, BASSO D, RAMONDA R *et al*.: Genetics in TNF-TNFR pathway: A complex network causing spondyloarthritis and conditioning response to anti-TNFalpha therapy. *PloS One* 2018; 13: e0194693.
14. DOLCINO M, PELOSI A, FIORE PF *et al*.: Long non-coding RNAs play a role in the pathogenesis of psoriatic arthritis by regulating microRNAs and genes involved in inflammation and metabolic syndrome. *Front Immunol* 2018; 9: 1533.
15. PELOSI A, LUNARDI C, FIORE PF *et al*.: MicroRNA expression profiling in psoriatic arthritis. *Biomed Res Int* 2018; 2018: 7305380.
16. ABJI F, POLLOCK RA, LIANG K, CHANDRAN V, GLADMAN DD: Th17 gene expression in psoriatic arthritis synovial fluid and peripheral blood compared to osteoarthritis and cutaneous psoriasis. *Clin Exp Rheumatol* 2018; 36: 486-9.
17. GISONDI P, ALTOMARE G, AYALA F *et al*.: Consensus on the management of patients with psoriatic arthritis in a dermatology setting. *J Eur Acad Dermatol Venereol* 2018; 32: 515-28.
18. LUCHETTI MM, BENFAREMO D, CAMPANATI A *et al*.: Clinical outcomes and feasibility of the multidisciplinary management of patients with psoriatic arthritis: two-year clinical experience of a dermo-rheumatologic clinic. *Clin Rheumatol* 2018; 37: 2741-9.
19. EGEBERG A, SKOV L, ZACHARIAE C, GISLASON GH, THYSSEN JP, MALLBRIS L: Duration of Psoriatic Skin Disease as Risk Factor for Subsequent Onset of Psoriatic Arthritis. *Acta Derm Venereol* 2018; 98: 546-50.
20. SALAFFI F, DI CARLO M, LUCHETTI MM *et al*.: A validation study of the Simple Psoriatic Arthritis Screening (SiPAS) questionnaire to screen psoriasis patients for psoriatic arthritis. *Clin Exp Rheumatol* 2018; 36: 127-35.
21. COATES LC, SAVAGE LJ, CHINOY H *et al*.: Assessment of two screening tools to identify psoriatic arthritis in patients with psoriasis. *J Eur Acad Dermatol Venereol* 2018; 32: 1530-4.
22. TEVAR-SANCHEZ MI, NAVARRO-COMPAN V, AZNAR JJ, LINARES LF, CASTRO MC, DE MIGUEL E: Prevalence and characteristics associated with dactylitis in patients with early spondyloarthritis: results from the ESPeranza cohort. *Clin Exp Rheumatol* 2018; 36: 879-83.
23. PATEL P, ROSEN CF, CHANDRAN V, YE YJ, GLADMAN DD: Addressing comorbidities in psoriatic disease. *Rheumatol Int* 2018; 38: 219-27.
24. SZENTPETERY A, HEALY GM, BRADY D *et al*.: Higher coronary plaque burden in psoriatic arthritis is independent of metabolic syndrome and associated with underlying disease severity. *Arthritis Rheumatol* 2018; 70: 396-407.
25. QUEIRO R, LORENZO A, PARDO E, BRANDY A, COTO P, BALLINA J: Prevalence and type II diabetes-associated factors in psoriatic arthritis. *Clin Rheumatol* 2018; 37: 1059-64.
26. BENGTSSON K, FORSBLAD-D'ELIA H, LIE E *et al*.: Risk of cardiac rhythm disturbances and aortic regurgitation in different spondyloarthritis subtypes in comparison with general population: a register-based study from Sweden. *Ann Rheum Dis* 2018; 77: 541-8.
27. FERNANDES S, ETCHETO A, VAN DER HEIJDE D *et al*.: Vitamin D status in spondyloarthritis: results of the ASAS-COMOSPA international study. *Clin Exp Rheumatol* 2018; 36: 210-4.
28. LAI TL, YIM CW, WONG PY, LEUNG MC, NG WL: Hyperuricemia in Asian psoriatic arthritis patients. *Int J Rheum Dis* 2018; 21(4): 843-9.
29. EDER L, AYDIN SZ, KAELEY GS, MAKSYMOWYCH WP, OSTERGAARD M: Options for assessing joints and entheses in psoriatic arthritis by ultrasonography and magnetic resonance imaging: how to move forward. *J Rheumatol Suppl* 2018; 94: 44-7.
30. MACIA-VILLA C, FALCAO S, GUTIERREZ M, MEDINA J, HAMMER HB, DE MIGUEL E: What is metacarpophalangeal joint swelling in psoriatic arthritis? Ultrasound findings and reliability assessment. *Clin Exp Rheumatol* 2018; 36: 896-9.
31. FURLAN A, STRAMARE R: The thickening of flexor tendons pulleys: a useful ultrasonographical sign in the diagnosis of psoriatic arthritis. *J Ultrasound* 2018; 21: 309-14.
32. MOYA ALVARADO P, ROE CRESPO E, MUNOZ-GARZA FZ *et al*.: Subclinical enthesopathy of extensor digitorum tendon is highly prevalent and associated with clinical and ultrasound alterations of the adjacent fingernails in patients with psoriatic disease. *J Eur Acad Dermatol Venereol* 2018; 32: 1728-36.
33. KRAJEWSKA-WLODARCZYK M, OWCZARCZYK-SACZONEK A, PLACEK W, WOJTKIEWICZ M, WIKTOROWICZ A, WOJTKIEWICZ J: Ultrasound assessment of changes in nails in psoriasis and psoriatic arthritis. *Biomed Res Int* 2018; 2018: 8251097.
34. IDOLAZZI L, GISONDI P, FASSIO A *et al*.: Ultrasonography of the nail unit reveals quantitative and qualitative alterations in patients with psoriasis and psoriatic arthritis. *Med Ultrason* 2018; 20: 177-84.
35. TINAZZI I, MCGONAGLE D, ZABOTTI A, CHESSA D, MARCHETTA A, MACCHIONI P: Comprehensive evaluation of finger flexor tendon entheseal soft tissue and bone changes by ultrasound can differentiate psoriatic arthritis and rheumatoid arthritis. *Clin Exp Rheumatol* 2018; 36: 785-90.
36. WERVERS K, VIS M, RASAPPU N *et al*.: Modification of a sonographic enthesitis score to differentiate between psoriatic arthritis and young healthy volunteers. *Scand J Rheumatol* 2018; 47: 291-4.
37. MATHEW AJ, BIRD P, GUPTA A, GEORGE R, DANDA D: Magnetic resonance imaging (MRI) of feet demonstrates subclinical inflammatory joint disease in cutaneous psoriasis patients without clinical arthritis. *Clin Rheumatol* 2018; 37: 383-8.
38. CHEN B, ZHAO Y, CHENG X *et al*.: Three-dimensional ultrashort echo time cones (3D UTE-Cones) magnetic resonance imaging of entheses and tendons. *Magn Reson Imaging* 2018; 49: 4-9.
39. HOWELLS L, CHISHOLM A, COTTERILL S, CHINOY H, WARREN RB, BUNDY C: Impact of disease severity, illness beliefs, and coping strategies on outcomes in psoriatic arthritis. *Arthritis Care Res* 2018; 70: 295-302.
40. ESTEVE E, MACCARI F, DELAVIERRE D *et al*.: Preliminary development of a questionnaire assessing the impact of psoriasis and psoriatic arthritis on patient's perception of sexuality. *Medicine* 2018; 97: e12807.
41. COZZANI E, LINDER D, BURLANDO M *et al*.: PSOdisk is a reliable, intuitive instrument for the evaluation of psychological distress, which strongly correlates with DLQI: a preliminary study. *Eur J Dermatol* 2018; 28: 332-7.
42. VAN MENS LJJ, TURINA MC, VAN DE SANDE MGH, NURMOHAMED MT, VAN KUIJK AWR, BAETEN DLP: Residual disease activity in psoriatic arthritis: discordance between the rheumatologist's opinion and minimal disease activity measurement. *Rheumatology* 2018; 57: 283-90.
43. HOLLAND R, TILLETT W, KORENDOWYCH E *et al*.: Validation of the Psoriatic Arthritis Impact of Disease (PsAID) Questionnaire and its potential as a single-item outcome meas-

ure in clinical practice. *Ann Rheum Dis* 2018; 77: 343-7.
44. VAN MENS LJJ, VAN DE SANDE MGH, VAN KUIJK AWR, BAETEN D, COATES LC: Ideal target for psoriatic arthritis? Comparison of remission and low disease activity states in a real-life cohort. *Ann Rheum Dis* 2018; 77: 251-7.
45. HELLIWELL PS, WAXMAN R: Modification of the Psoriatic Arthritis Disease Activity Score (PASDAS). *Ann Rheum Dis* 2018; 77: 467-8.
46. COATES LC, FITZGERALD O, MEROLA JF *et al*.: Group for Research and Assessment of Psoriasis and Psoriatic Arthritis/Outcome Measures in Rheumatology Consensus-Based Recommendations and Research Agenda for Use of Composite Measures and Treatment Targets in Psoriatic Arthritis. *Arthritis Rheumatol* 2018; 70: 345-55.
47. MICHELSEN B, SEXTON J, SMOLEN JS *et al*.: Can disease activity in patients with psoriatic arthritis be adequately assessed by a modified Disease Activity index for PSoriatic Arthritis (DAPSA) based on 28 joints? *Ann Rheum Dis* 2018; 77: 1736-41.
48. KAVANAUGH A, SINGH R, KARKI C *et al*.: Disease activity and biologic use in patients with psoriatic arthritis or rheumatoid arthritis. *Clin Rheumatol* 2018; 37: 2275-80.
49. GOEREE R, CHIVA-RAZAVI S, GUNDA P *et al*.: Cost-effectiveness analysis of secukinumab for the treatment of active psoriatic arthritis: a Canadian perspective. *J Med Econ* 2018; 21: 163-73.
50. COATES LC, MOVERLEY AR, MCPARLAND L *et al*.: Effect of tight control of inflammation in early psoriatic arthritis (TICOPA): a UK multicentre, open-label, randomised controlled trial. *Lancet* 2015; 386: 2489-98.
51. O'DWYER JL, MEADS DM, HULME CT *et al*.: Cost-effectiveness of tight control of inflammation in early psoriatic arthritis: economic analysis of a multicenter randomized controlled trial. *Arthritis Care Res* 2018; 70: 462-8.
52. WALSH JA, ADEJORO O, CHASTEK B, PALMER JB, HUR P: Treatment patterns among patients with psoriatic arthritis treated with a biologic in the united states: descriptive analyses from an administrative claims database. *J Manag Care Spec Pharm* 2018; 24: 623-31.
53. RUNARSDOTTIR EE, GUNNARSDOTTIR AI, LOVE TJ, GUNNARSSON PS, GUDBJORNSSON B, ICEBIO: The majority of patients with psoriatic arthritis are not eligible for randomised clinical trials. *Clin Exp Rheumatol* 2018; 36: 1068-73.
54. THOMAS K, FLOURI I, REPA A *et al*.: High 3-year golimumab survival in patients with rheumatoid arthritis, ankylosing spondylitis and psoriatic arthritis: real world data from 328 patients. *Clin Exp Rheumatol* 2018; 36: 254-62.
55. RUWAARD J, L'AMI MJ, MARSMAN AF *et al*.: Comparison of drug survival and clinical outcome in patients with ankylosing spondylitis treated with etanercept or adalimumab. *Scand J Rheumatol* 2018; 47: 122-6.
56. HOJGAARD P, BALLEGAARD C, CORDTZ R *et al*.: Gender differences in biologic treatment outcomes-a study of 1750 patients with psoriatic arthritis using Danish Health Care Registers. *Rheumatology* 2018; 57: 1651-60.
57. POTENZA MC, PERIS K, BERARDESCA E *et al*.: Use of biological drugs in patients with psoriasis and psoriatic arthritis in Italy: Results from the PSONG survey. *Dermatol Ther* 2018; 31.
58. DAMJANOV N, KARPATI S, KEMENY L *et al*.: Efficacy and safety of etanercept in psoriasis and psoriatic arthritis in the PRESTA study: analysis in patients from Central and Eastern Europe. *J Dermatolog Treat* 2018; 29: 8-12.
59. ZANGRILLI A, BAVETTA M, SCARAMELLA M, BIANCHI L: Long-term treatment of psoriatic patients with adalimumab reduces disease severity and maintains a favorable lipid pattern and a low Atherogenic Index. *G Ital Dermatol Venereol* 2018; 153: 146-54.
60. STOBER C, YE W, GURUPARAN T, HTUT E, CLUNIE G, JADON D: Prevalence and predictors of tumour necrosis factor inhibitor persistence in psoriatic arthritis. *Rheumatology* 2018; 57: 158-63.
61. BALLEGAARD C, HOJGAARD P, DREYER L *et al*.: Impact of comorbidities on tumor necrosis factor inhibitor therapy in psoriatic arthritis: a population-based cohort study. *Arthritis Care Res* 2018; 70: 592-9.
62. SCHOELS MM, LANDESMANN U, ALASTI F, BAKER D, SMOLEN JS, ALETAHA D: Early response to therapy predicts 6-month and 1-year disease activity outcomes in psoriatic arthritis patients. *Rheumatology* 2018; 57: 969-76.
63. NICOLA S, ROLLA G, MONTI R, BRUSSINO L: Treatment of psoriatic arthritis with secukinumab: a case series. *J Dermatolog Treat* 2018; 29 (Suppl.): 6-8.
64. VAN DER HEIJDE D, GLADMAN DD, KISHIMOTO M *et al*.: Efficacy and safety of ixekizumab in patients with active psoriatic arthritis: 52-week results from a Phase III Study (SPIRIT-P1). *J Rheumatol* 2018; 45: 367-77.
65. GLATT S, BAETEN D, BAKER T *et al*.: Dual IL-17A and IL-17F neutralisation by bimekizumab in psoriatic arthritis: evidence from preclinical experiments and a randomised placebo-controlled clinical trial that IL-17F contributes to human chronic tissue inflammation. *Ann Rheum Dis* 2018; 77: 523-32.
66. CHIMENTI MS, ORTOLAN A, LORENZIN M *et al*.: Effectiveness and safety of ustekinumab in naive or TNF-inhibitors failure psoriatic arthritis patients: a 24-month prospective multicentric study. *Clin Rheumatol* 2018; 37: 397-405.
67. IANNONE F, SANTO L, BUCCI R *et al*.: Drug survival and effectiveness of ustekinumab in patients with psoriatic arthritis. Real-life data from the biologic Apulian registry (BIOPURE). *Clin Rheumatol* 2018; 37: 667-75.
68. NASH P, OHSON K, WALSH J *et al*.: Early and sustained efficacy with apremilast monotherapy in biological-naive patients with psoriatic arthritis: a phase IIIB, randomised controlled trial (ACTIVE). *Ann Rheum Dis* 2018; 77: 690-8.
69. DEODHAR A, GOTTLIEB AB, BOEHNCKE WH *et al*.: Efficacy and safety of guselkumab in patients with active psoriatic arthritis: a randomised, double-blind, placebo-controlled, phase 2 study. *Lancet* 2018; 391: 2213-24.
70. KRISTENSEN S, SCHMIDT EB, SCHLEMMER A, RASMUSSEN C, JOHANSEN MB, CHRISTENSEN JH: Beneficial effect of n-3 polyunsaturated fatty acids on inflammation and analgesic use in psoriatic arthritis: a randomized, double blind, placebo-controlled trial. *Scand J Rheumatol* 2018; 47: 27-36.
71. NAVARRO-MILLAN I, GAMBOA CM, CURTIS JR, SAFFORD MM: Lipid management among individuals with inflammatory arthritis in the national REasons for Geographic And Racial Differences in Stroke (REGARDS) cohort. *J Int Med Res* 2018; 46: 62-9.