One year in review 2019: psoriatic arthritis

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ABSTRACT

Psoriatic arthritis (PsA) is an inflammatory arthritis belonging to spondyloarthritides (SpA), a group of rheumatologic diseases characterised by a wide spectrum of different clinical manifestations that tend to associate with various comorbidities and that may significantly compromise the quality of life of patients. Nowadays, it is well known how PsA may manifest in different clinical domains, in particular peripheral articular and periarticular involvement, axial involvement, skin and nail psoriasis. Moreover, the majority of patients with PsA develop comorbidities such as inflammatory bowel diseases, uveitis, but also cardiovascular diseases, psychiatric or pulmonary pathologies. The therapeutical armamentarium of PsA has been enriched during the last years, in relation to an advance in the knowledge of the immunological mechanisms at the basis of the disease; in particular, the future frontier of “personalised medicine” could lead to a further improvement in the quality of care of this group of patients. In this paper we review the literature on PsA of 2019 (Medline search of articles published from 1st January 2019 to 31st December 2019).

Introduction

Psoriatic arthritis (PsA) is an inflammatory arthritis belonging to spondyloarthritides (SpA), a group of rheumatologic diseases characterised by a wide spectrum of different clinical manifestations that tend to associate with various comorbidities and that may significantly compromise the quality of life (QoL) of patients. Nowadays, it is well known how PsA may manifest in different clinical domains, in particular peripheral articular and periarticular involvement (arthritis, tenosynovitis, dactylitis, enthesitis), axial involvement (spondylitis), skin and nail psoriasis (PsO). Moreover, patients might develop some extra-articular manifestations, such as inflammatory bowel diseases (IBD), or uveitis. Finally, PsA is a risk factor for some comorbidities, in particular metabolic syndrome [a cluster of classic cardiovascular (CV) risk factors], mood disorders, osteoporosis, malignancies and fibromyalgia (reported in up to 17% of cases). The therapeutical armamentarium of PsA has been enriched during the last years, in relation to an advance in the knowledge of the immunological mechanisms at the basis of the disease; in particular, the future frontier of “personalised medicine” could lead to a further improvement in the quality of care (QoC) of this group of patients (1, 2).

In this paper we review the literature on PsA of 2019 (Medline search of articles published from 1st January 2019 to 31st December 2019).

Methods

Following our regular annual reviews on different aspects of rheumatology (3-10) we here provide a critical digest of the recent literature on PsA of 2019 (Medline search of articles published from 1st January 2019 to 31th December 2019). In particular, we performed an on-line search on the MESH database, using as key terms “blood”, “complications”, “diagnosis”, “diagnostic imaging”, “drug therapy”, “economics”, “epidemiology”, “genetics”, “metabolism”, “mortality”, “prevention and control”, “psychology”, “rehabilitation”, “therapy”.

Epidemiology

In 2019, three major epidemiologic studies were conducted. The Nordic Patient survey of PsO and PsA (NORPAPP), on a sample of Swedish, Danish and Norwegian populations, showed a prevalence of reported PsO and/or PsA of about 10%. Skin involve-
Genetics

Genetic studies are relevant to describe more comprehensively PsA patient populations, to properly direct PsA patients to the most suitable drugs and to identify specific biologic pathways as possible targets of new therapies. The expansion of genetic data for PsA was guided by genome-wide association studies (GWAS), sequencing and HLA fine mapping analysis, which identified new HLA and not-HLA complex regions associated with this disease. In a small Spanish group of PsA patients with moderate-to-severe plaque PsO, treated with anti-tumour necrosis factor alpha (TNF-α) drugs, Ovejero-Benito et al. identified a significant association between TNFAIP3 gene polymorphisms and improvement of the quality of life (QoL) at 3 months, both in the univariate and multivariate analysis (14). Moreover, Zhao et al. observed that Chinese patients with PsA and PsO differed from healthy controls for a variant in the region rs12883343 of NFKBIA gene and for the prevalence of the haplotype HLA-A*01:01 (15, 16).

Take home messages

• Chinese patients with PsO and/or PsA significantly differ from healthy controls for a variant in the region rs12883343 of NFKBIA gene and for the prevalence of the haplotype HLA-A*01:01.

• Genetic variation at the glycosaminoglycan metabolism pathway seems to be specifically associated with PsA (17).

• Epigenetics could play a central role to determine the genetic susceptibility for PsA (18).

Biomarkers

Alivernini et al. tried to solve the clinical practice challenge of the differential diagnosis among PsA and rheumatoid arthritis (RA) analysing the histological characteristics of synovial tissue; they found that the synovial tissue of PsA patients was enriched in CD117+ mast cells in the sublining area (in the context of tissue lymphoid aggregates) compared to seronegative RA, whose synovial tissue was found to be enriched in CD138+ B cells (19). Colak et al. observed that vaspin and neutrophil gelatinase-associated lipocalin (NGAL) levels were significantly higher in PsA patients than in the healthy controls, in contrast with the Apolipoprotein A1 levels; however, further studies are needed to elucidate the role and the possible use as biomarkers of these molecules in PsA (20, 21). Coras et al. found that serum levels of some trimethylamine metabolites correlated with parameters of both skin and clinical activity, with Health Assessment Questionnaire (HAQ) and fatigue. Therefore, these molecules could be biomarkers of PsA, but future studies are needed to explore the mechanistic association with skin and joint inflammation (22).

Low molecular mass hyaluronan (HA) can cause inflammatory processes and can act as a pro-inflammatory cytokine in skin and other sites of activity in PsA. Interestingly, Hellmann et al. observed that in anti-TNF naïve PsA patients who started adalimumab (ADA) therapy, the serological concentration of HA was higher in older patients, with a later onset of arthritis, more deformed joints, a higher number of swollen joints and a higher concentration of circulating inflammatory biomarkers. Molecular weight also showed a differential distribution: in more severe disease a wide spectrum of high-molecular-mass HA accompanied by low mass HA was observed; this distribution partially normalised after treatment. Therefore, HA concentration and mass could be potentially related to PsA pathogenesis and be feasible biomarkers of disease severity (23).

Finally, Fassio et al. added new data on the effects of biologic therapy on bone turnover markers and WNT modulation, showing that, in PsA patients, serum Dkk-1 level significantly decreased. Moreover, both Dkk-1 and sclerostin demonstrated a significant increase from baseline up to the 6th month, suggesting that SEC could restore normal Dkk-1 serum levels (24).

Take home messages

• The synovial tissue of PsA patients was found to be enriched in CD117+ mast cells (19).

• Serum trimethylamine-N-oxide metabolites could represent PsA biomarkers for both skin and articular involvement (22).

• HA concentration and mass seemed to be related to PsA pathogenesis and might represent feasible biomarkers of disease severity (23).

• Serum Dkk-1 levels tend to be low in active PsA and seem to be restored after treatment with SEC (24).
Imaging

During the last year, many papers have been published on imaging techniques applied to PsA. The bulk of the works assessed the importance of ultrasound (US) as a reliable, fast and “bed-side” tool, either to early identify the pivotal features of the disease, to monitor disease activity and response to therapy, or to detect joint alterations in asymptomatic subjects at risk for the condition. In particular, in a recent multicentre study, US has proved to be a precise technique to describe the alterations of tendinous, peri-tendinous and articular structures in hand dactylitis in PsA; it was very interesting to observe how a “symptomatic” dactylitis tended to be associated with an active inflammation of tendons and peri-tendinous structures, while the “asymptomatic” dactylitis was more frequently associated with joint inflammation (25). Furthermore, growing evidence confirms that US is, together with the clinical exam, a feasible and reproducible diagnostic tool. On this topic the Madrid Sonographic Enthesis Index (MASEI) has proved to be a reliable, fast and precise score to detect all the key features of OMERACT’s definition of enthesitis (26).

It has been shown that US is useful to study PsA nail alterations as well: two groups of researchers demonstrated that patients with PsA had a higher thickness of both the nail bed and the nail plate than controls (27, 28). Moreover, the first group showed that this damage seemed to be linked to an active enthesitis of the distal extensor tendon (27). An increasing number of papers have confirmed the already-known data that people with skin PsO can subclinically harbour the joint alterations typical of PsA (29-31). Although the US detection of an active enthesitis (described as an enthesis with grey-scale alterations associated with power Doppler signal) has been found only in PsO subjects when compared to healthy controls (30), the grey-scale modifications of the enthesis has been extensively demonstrated also in healthy subjects, suggesting that they have a limited role as an early sign of PsA in PsO patients (30, 31). Nevertheless, the observations by Zuliani and Elnady confirmed that a significantly higher number of PsO patients showed US signs of synovitis when compared to healthy subjects, stressing the usefulness of US as a key tool to help rheumatologists in diagnosing PsA from its earlier phases, particularly in patients at greater risk of developing it, such as those with PsO (30, 31).

US has been used also to compare the entheseal micro-anatomical features of AS and PsA: it was observed that PsA enthesis was characterised by more elementary lesions (namely hypoechogenicity, power Doppler) than AS. The authors suggested that this data could be related to the different responses to enthesis damage among the conditions (32).

Interestingly, a radiographic study showed that a high level of occupation-related mechanical stress could be associated with increased radiographic joint damage among subjects with PsA, stressing the point of a possible role of micro-trauma in its pathogenesis (33). A study by Salaffi et al. assessed the reliability and feasibility of a novel radiological PsA scoring system, the Simplified Psoriatic Arthritis Radiographic Score (SPARS), aiming at its validation as a score. The authors validated the score underlining its potential utility in daily clinical practice due to the very short amount of time it takes (34).

Moreover, a recent paper showed how current radiographic scoring systems, such as INSPIRE and the Domjan, could be valuable tools to assess the spinal lateral flexion in PsA (35). Nevertheless, together with the standard imaging techniques applied to PsA, new methodologies have been taken into account, in particular, some novel applications of computed tomography. It has been stated that either dual-energy computed tomography (DE-CT) (36) or high-resolution peripheral tomography (HRpQCT) (37) are interesting novel techniques to depict synovitis and bony erosions, respectively. On the other hand, optical coherence tomography (OCT) has been used to assess nail alterations during the illness (38). Although the potential of these novel methodologies could be significant in the long run, the evidence provided is still limited to small case series.

Take home messages

• US clarified how a “symptomatic” dactylitis is usually associated with a prevalent involvement of tendinous and peri-tendinous structures (25).
• US study of nails during PsA showed an increased thickness of both nail bed and nail plate, probably correlated with an enthesitis of the distal extensor tendon (27, 28).
• Grey-scale modifications of the enthesis has been extensively demonstrated also in healthy subjects (30, 31); nevertheless, US was confirmed to be extremely useful to early detect PsA in patients with PsO (29-31).
• PsA enthesis was characterised by more elementary US lesions than AS enthesitis (32).
• Both SPARS and INSPIRE could be valuable tools to score PsA damage in clinical practice (34, 35).
• Novel methodologies such as DE-CT, HRpQCT and OCT might become useful in the future for the assessment of joint and nail involvement during PsA (36-38).

Quality of care

The identification of the best disease activity indices is a major issue for clinicians treating PsA, since it may affect the strategies aimed at achieving the therapeutic goal of remission (REM) or low disease activity (LDA). Several composite score are available, each one with strengths and weaknesses. Grolier et al. observed that the Disease Activity in Psoriatic Arthritis index (DAPSA) performed better than very low disease activity (VLDA) and minimal disease activity (MDA) indexes for REM, LDA and for pooled REM/LDA. Better performances were obtained for pooled REM/LDA, thus suggesting that it is probably difficult for patients to distinguish them. Furthermore, physician-perceived status appeared too lenient, whereas VLDA/MDA were too stringent compared to the patients’ perspective (39).

Similarly, a cross sectional study showed the agreement between Psoriatic Arthritis Impact of Disease questionnaire and VLDA was lower than with DAPSA and clinical DAPSA (40).

Conversely, a cross-sectional study
on patients with PsA showed that the stringency of the MDA criteria resulted in better outcomes. The authors noted that, although MDA performed better in identifying patients free from disease burden, they may still have residual symptoms, thus suggesting the need for better definitions of LDA and remission. Interestingly, residual symptoms were observed mainly in PROs (41). Accordingly, Bakirci et al. found that MDA achievement was mainly hampered by PROs. In particular, they found biologic treatment predicted the achievement of MDA, whereas axial disease and DIP involvement were negative predictors (42).

A Thai study revealed that DAPSA, clinical DAPSA, HAQ and MDA were all associated with Health Utility (HU) assessed by EuroQol-5 Dimensions-5 Levels. Patient Acceptable Symptom State (PASS), on the other hand, related to pain/discomfort domain of HU and, notably, to disease duration; in addition, more than half PASS+ patients were not in remission/LDA, suggesting that adaptation and expectations may also play a major role in disease perception (43). Interestingly, in a northern European cohort, patients with PsA who also presented cutaneous symptoms of PsO perceived their disease as significantly more severe than patients without PsO; in particular, symptoms of itching or flaking seemed to compromise QoL more than body surface area (11).

A poor treatment response was found to affect patients’ functionality: a multinational cohort of PsA patients who received >1 immunosuppressor due to different reasons, showed worse HRQoL (measured with EQ-5D-3L and SF-36), HAQ and work impairment compared to patients who experienced treatment success. Interestingly, the time for initiating a new treatment after a failure was 9.4 months on average, making the authors wonder whether a timely switching could improve outcomes in poor-responders (44).

The great effort made in analysing different tools to assess disease activity is mainly aimed at reaching a satisfying treat-to-target (T2T) approach for PsA, similarly to what happens in RA. Nisar et al. confirmed that an early assessment, aimed at a prompt beginning of treatment (within 3 weeks from first assessment) and rapid escalation of methotrexate (MTX) regimen according to the level of disease activity, was effective in achieving good clinical response for PsA (45).

On the other hand, a proper T2T approach seemed hard to be obtained when using MDA as treatment goal (46). Conversely, in a report by Lubrano et al., a DAPSA-driven T2T strategy seemed to be feasible and effective in achieving treatment goals (47).

With reference to treatment adherence, the ALIGN study, conducted in Denmark, found that 75% of patients with PsA were highly adherent to treatment according to the Morisky Medication Adherence Scale. In a multivariable regression analysis, factors positively associated with adherence were older age and TNF inhibitor (TNFi) treatment, whereas concerns about medication overuse were strongly associated with poor adherence. Notably, about 30% of patients thought “if doctors had more time they would prescribe fewer medicines” (48).

On the other hand, a Scandinavian study showed that about 33% and 23% of patients were dissatisfied with treatment with MTX and biologics, respectively. Dissatisfaction with MTX was mainly due to the side-effects, whereas for biologics it was due to both side effects and lack of efficacy. Interestingly, about 35% of patients never discussed systemic treatment with their physician (49).

An analysis of health service-related costs of Finnish patients with rheumatic diseases (RDs) showed a small proportion of PsA patients were high-utilisation subjects; they tended to show worse PROs outcomes and a more severe disease than low-utilisation ones. Notably, about the 2/3 of the costs were due to comorbidities (50).

Another study assessed the quality of informative contents about SEC on YouTube and concluded that patients should be helped in choosing high-quality videos, since the number of views, likes, dislikes, and comments per day is not a predictor of reliable high-quality videos (51).

**Take home messages**

- DAPSA seems to perform better than others clinimetric indices for REM, LDA and for the impact of PsA on the patients’ life (38, 39).
- MDA achievement was mainly hampered by PROs (40, 41).
- HAQ showed a stronger association with HU than disease activity indices (42).
- Both cutaneous symptoms of PsO (11) and poor treatment response (44) might significantly affect the HRQoL of PsA patients.
- A T2T approach in PsA could be useful to achieve LDA or remission (45-47); MDA did not seem the right outcome measure to be taken into account (46).
- Concerns about medication overuse or side effects and a suboptimal communication with physicians seemed to be strongly associated with poor adherence in PsA patients (48, 49).

**Comorbidities**

The analysis of US Administrative Claims Data on newly diagnosed cases of PsA confirmed a higher risk of CV diseases (CVD), together with a higher incidence of diabetes, anxiety, fatigue, obesity or overweight, depression, osteoporosis, uveitis, eczema and gout. Moreover, PsA patients had higher rates of all-cause hospitalisation compared to controls, in particular for coronary artery disease (52).

A large UK Clinical Practice Research Datalink study confirmed the association between PsA and both CVD and type 2 diabetes. A retrospective cross-sectional study confirmed the association of PsA with obesity, showing that a family history of PsA, an axial involvement and a dyslipidaemia increased the risk of developing it (53). On the other hand, Bridgan and colleagues did not confirm the hypothesis that a diet with higher Empirical Dietary Inflammatory Pattern, associated with higher levels of TNF-α, IL-6 and adiponectin, would be related with the occurrence of PsA (54).

Data from two recent studies on PsA patients showed that age at onset of PsO >40 years, a polyarticular evolution with a higher number of swollen joints, a longer disease duration and an
axial involvement could be considered as disease-specific factors associated with CVD development (55, 56).

The effect of a better control of the disease activity in preventing the development of risk factors associated with CV events has been assessed in a recent study evaluating the impact of achieving MDA on the progression of subclinical atherosclerosis and arterial stiffness by high-resolution carotid ultrasound. The authors found that achieving a condition of sustained MDA could have a protective effect on carotid atherosclerosis progression (57).

Sparks et al. observed that after a CV event, approximately 30% of patients discontinued or switched disease-modifying anti-rheumatic drugs (DMARDs). The study did not find any association between the DMARD mechanism of action and the risk of subsequent CV event (58).

Several CV risk scores have been proposed for the general population and, with adaptations, for patients with rheumatic diseases; EULAR recommendations, for example, suggest applying a 1.5 multiplication factor to score these algorithms in patients with RA. The ASSIGN risk is one of the algorithms used to assess CV risk. A recently published study tested this score in patients with PsA, demonstrating its potential usefulness in this condition (59).

These data underline the importance of incorporating CV risk assessments in the management of PsA and of improving our knowledge on the conditions associated with an increased CV risk in this population.

As already mentioned, PsA tends to associate with a number of comorbidities different from CVD, which have been also explored during the past year. The association between PsA and gout was confirmed in a study conducted in Taiwan, particularly in patients aged 41–50 years old, but it did not seem to be influenced by gender (60).

Another study from Taiwan showed that PsA patients seem to be at higher risk of developing thyroid diseases, highlighting the opportunity to periodically screen them for the occurrence of these conditions (61).

Chimenti et al. evaluated that only about one-third of patients with chronic arthritis (PsA and RA) did not show any signs of alexithymia, which were associated, as expected, with female sex, but also with both the levels of inflammatory markers and clinimetric parameters; these data confirm the need to evaluate this group of patients in a more comprehensive way, including a psychiatric assessment (62).

Comorbidities, together with disease activity and permanent damage, may have a significant impact on disability. A study assessing the causes of disability certificate requests in an Argentinian city showed that PsA was listed among the five most common causes of disability (63).

The analysis of the British Society for Rheumatology Biologics Register confirmed that PsA is not associated to an increased risk of malignancy, except for non-melanoma skin cancer, and that the increased risk of death was again mainly driven by CV causes, specifically coronary heart disease (64).

Finally, an Italian study on the Gruppo Italiano per lo Studio delle Early Arthritis (GISEA) registry, highlighted that the incidence of infections was higher in PsA and AS than in undifferentiated SpA and in patients treated with infliximab (INF), with respect to those treated with ADA or etanercept (ETN). Interestingly, male sex, therapy with glucocorticoids and comorbidities could be considered as predictive factors of serious infections (65).

**Take home messages**

- PsA patients are at higher risk of CV disorders, but also type 2 diabetes and obesity (53, 54, 64).
- PsA patients are at higher risk of hospitalisation, in particular for coronary artery disease, also related to a high risk of death (54, 64).
- Some disease-specific characteristics could be related with a higher CV risk (56); accordingly, a better control of the disease activity might prevent carotid atherosclerosis progression (57).
- CV risk scores could be useful in evaluating the CV risk of PsA patients in clinical practice (59).
- Patients with PsA are at higher risk for thyroid disfunctions and alexithymia (61, 62).
- The therapy of PsA patients might influence the risk of SIs (65).

**Therapy**

It has already been demonstrated that early initiation of effective treatment in RA can favour remission, but this is still uncertain in the field of PsA. A recent multicentre double blind, randomised, placebo-controlled trial showed how initiation of a combination therapy with golimumab (GOL) plus MTX in patients with early, MTX-naïve PsA, might double the number of patients achieving DAS remission when compared with placebo+MTX; moreover, the frequency of adverse events was similar in the two groups, thus suggesting the value of early intervention also in PsA rather than the classical step-up approach (66).

Adding MTX to TNFi has been demonstrated to improve their effectiveness in RA; this data is not clear for PsA. Three different studies on this issue in the last year suggested that a combination therapy with MTX does not seem to significantly improve the efficacy of ETN, ADA and GOL in PsA, respectively (67-69).

Considering the lack of studies assessing the effectiveness of certolizumab pegol (CZP) across its approved indications in current clinical practice, a workgroup analysed data from an Italian registry (BIOPURE) and observed at first a significant clinical improvement from baseline for RA, PsA and SA; secondly, while biologic-naïve RA patients achieved significantly higher survival rates than switchers taking CZP as a second-line or third- or next-line biologic agent, PsA and SA patients showed similar drug retention rates regardless of the line of treatment. In addition, the data confirmed that an early response within 3 months was a predictor of CZP effectiveness (70).

Allard et al. confirmed a role of TNFi in slowing radiographic progression in PsA patients, similarly to what happens in RA (71).

Using an existing real-world cohort of Canadian patients with inflammatory
arthritis (BioTRAC), Coates et al. observed that among PsA patient treated with GOL a residual activity in dactylitis and skin despite DAPSA remission might affect patient function. This difference could be explained by the fact that DAPSA only focuses on peripheral joint disease (and C-reactive protein) while MDA covers additional extra-articular manifestations such as skin and enthesitis (72). The decrease in costs and the possibility of expanding treatment to a larger proportion of patients have made biosimilars an attractive alternative, although most regulatory agencies have approved them for PsA as an extrapolation of the efficacy confirmed in studies on other diseases (RA and AS).

Data on efficacy, safety, and immunogenicity of biosimilars for PsO and PsA are still limited. In a recent observational cohort study based on the DANBIO registry it was observed that almost 80% of ETN-treated patients switched to biosimilar; one-year adjusted retention rate values for non-switchers and for switchers were similar; besides, patients not in remission had lower retention rates than patients in remission, independently in switchers and non-switchers. In addition, the reasons for biosimilar withdrawal seemed mainly subjective, suggesting that switch outcomes in routine care should be more related to patient-related factors than to specific drug effects (73).

The first interleukin-17A (IL-17A) available for treatment of PsA was SEC. Mann et al. tried to describe real life experience of SEC by collecting data from the ATTRA registry. The data showed that rheumatologists in a real-life setting tended to switch to another anti-TNF after the failure of a first-line TNF inhibitor, while they preferred to switch to SEC after failure of at least 3 anti-TNFs. Besides, the proportion of patients receiving SEC as first-line bDMARD and their baseline characteristics were comparable with those of anti-TNF treated patients, thus underlining that the prescribing rheumatologists considered SEC equivalent to TNF inhibitors for bDMARD-naive patients (74). Safety data of ixekizumab (IXE) showed injection site reactions were very common; overall, no active tuberculosis, invasive Candida infections, anaphylaxis, or suicide/self-injury behaviours were reported (75).

Kavanaugh et al. analysed PRO results in a cohort of IXE-treated patients with PsA, extrapolating data from the SPIRIT-P2 trial. They concluded that in patients with PsA and an insufficient response or intolerance to TNF inhibitors, IXE could be a valid alternative, acting on disease activity, HRQOL, work productivity and skin involvement (76).

Arthritis in PsA patients may share some clinical features with RA, while, on the contrary, enthesitis is highly typical of PsA and IL-23 is considered to play a central role for its development. The ECLIPSIA trial showed UST achieved superior responses to TNFi on both enthesitis and psoriatic skin disease, but not on arthritis, thus suggesting that the presence or absence of enthesitis might represent a discriminator of response among different approaches to treat PsA (77).

Tofacitinib (TOF), an oral Janus kinase inhibitor, might be a valid therapeutic option for PsA patients who had an insufficient response to csDMARD and bDMARD. The efficacy and safety of TOF 5 and 10 mg twice daily in combination with a csDMARD had been demonstrated in two phase 3 trials of up to 12 months’ duration in patients with active PsA and an inadequate response to conventional therapy. In particular, Ruija Xie et al. found that TOF did not require dose modification or restrictions for age, body weight, sex, race, ethnicity, or baseline disease severity in patients with active PsA, while dosing adjustments for renal impairment have to be considered (78).

Apremilast is a phosphodiesterase-4 inhibitor that had been found to be an effective and safe option in the treatment of PsO and PsA in randomised controlled trials, with real world data now emerging. Although TOF and apremilast have shown considerable efficacy in placebo-controlled trials of active PsA, the relative efficacy and safety remain unclear because of a lack of head-to-head comparisons in the scientific literature. A recent meta-analysis by Gwan Gyu Song et al. showed that TOF 10 mg and apremilast 30 mg were among the most effective treatments for active PsA; interestingly, no significant differences in the incidence of serious AEs was described between treatments and placebo (79).

The persistence on therapy is a crucial concept for biologic therapies, because they are usually prescribed on a long-term basis. In particular, updated data on the levels of adherence, persistence and switches, reflecting the use of different therapies for PsA in real life, could be very helpful to have more accurate insight into the profile of efficacy of each drug. In this regard, a workgroup recently tried to retrospectively compare ADA and ETN use in PsA in a real-life setting, confirming that persistence and switches are a relevant problem for patients who cannot follow a consistent therapy over time, for clinicians who have to manage therapy suspension and changes, and for the National Health System that must procure and pay for a high number of drugs (80).

Another study published last year compared the persistence on therapy of GOL and other anti-TNF. Data collected in one Slovenian registry (Bio. Rx.si) showed that the overall proportions of RA, AS and PsA patients being persistent on GOL versus other TNFi did not differ significantly. In the PsA subgroup, the bDMARD-naïve status was significantly associated with a better treatment persistence. Interestingly, anti-TNF different from GOL were more discontinued in PsA and AS patients who were bDMARD-experienced, underlining a tendency to higher values of persistence on GOL in SpA than in RA (81).

Similarly, data from the Spanish registry of patients with rheumatic disorders receiving biological drugs (BIOBADASER) showed the probability of retention over the years was not significantly different between RA, PsA or AS. Moreover, they found that GOL use as a first-line therapy and its combination with MTX were associated with higher values of retention, while a concomitant use of corticosteroid (CS) seemed to compromise it (82). Interestingly, in a recent retrospective
study, Kaste et al. took data from German registry (IQVIA) of patients with PsA, RA and axial SpA who received a first prescription of biological drugs and observed that persistence varied widely depending on the definition of discontinuation (gap of 90, 180 or 360 days, respectively). Moreover, the majority of non-persistent patients seemed to restart biological therapy shortly after its discontinuation (83).

By analysing the same data, Jacob et al. observed that patients under 30 years of age seemed more likely to discontinue their biological therapy than those over 70, with persistence values globally low (84).

Intra-articular glucocorticoid (IAGC) injection treatment is known to be an easy and effective way to treat arthritis, in particular mono- or oligoarticular manifestations. Despite its widespread use, there is a limited knowledge on the adequate dosing for different joints. Weitof et al. found the lower 20 mg THA dose should be preferred to 40 mg in IAGC treatment for knee synovitis in chronic polyarthritis (85).

A recent study tried to characterise the use of systemic glucocorticoids (SGC) in PsA patients living in Latin-American countries, through an online anonymous survey administered to 195 rheumatologists. The results showed the great majority of physicians prescribed SGC, usually at low doses, for short periods of time, mostly in association with DMARDs (cs/b/ts) and usually with the aim of treating peripheral joint involvements (86). Dual cytokine inhibition is being explored as an innovative treatment for PsA, RA and other immune-mediated diseases.

ABT-122 is a dual-variable-domain IgG1 immunoglobulin that concurrently neutralises TNF-α and IL17A and was studied for PsA treatment. Recently it was observed that plateau of ABT-122 efficacy was achieved at exposures associated with the 120 mg every week in patients with PsA, which were comparable to molar exposures of ADA 40 mg EOW. Of greater significance, the shape of the exposure-response relationships for ABT-122 and ADA did not differ significantly, with similar efficacy at comparable molar exposure ranges, indicating no clear evidence that inhibition of the IL-17 pathway provided incremental benefit in the presence of TNF-α inhibition (87). The cytometry, describing the phenotype of peripheral blood lymphocytes, can be useful to classify individual patients based on their immunological characteristics. The precision medicine, based in particular on therapies targeted to the immunological patient’s profile, could represent a future intriguing perspective for PsA treatment.

A very interesting study by Miyagawa and colleagues showed in PsA patients the use of bDMARDs guided from the immunophenotype was associated to a significantly higher efficacy (both in articular and cutaneous domains) compared to the conventional choice of the drugs (based on EULAR recommendations); moreover, the clinical improvement testified from clinimetric indices was widely distributed in the subgroup, thus suggesting a more personalised therapy could really optimise the quality of care of patients with PsA (88).

Immunogenicity of biologics is usually assessed by the detection of anti-drug antibodies (ADAs), specifically binding the biologic drug molecule and able to neutralise or eliminate it, with possible adverse impacts on bDMARDs safety and/or efficacy. A recent study compared the original Enzyme Immunoassay (EIA) with the novel highly sensitive DT-EIA (drug tolerant-EIA) to determine the presence of antibodies versus GOL, highlighting a higher sensitivity of DT-EIA in detecting ADAs. However, the clinical relevance of ADAs was consistent with previously observed original-EIA results; indeed, even if present at higher titres, they did not seem to significantly impact on GOL clinical efficacy or on the risk of injection-site reactions (89).

**Take home messages**

- Early intervention with a combination therapy could be advisable also in PsA patients (66).
- Adding MTX does not seem to significantly improve the efficacy of anti-TNF in PsA (67-69).
- In patients with PsA, IXE can be a valid alternative; unfortunately, ISRs are very common (75, 76).
- The presence or absence of enthesis tis might represent a discriminator of response among different approaches to treat PsA (77).
- Tofacitinib and apremilast could be effective treatments for active PsA (69).
- Persistence on therapy remains a key point in the quality of care of PsA patients; it seems to vary based on not only specific characteristics of the patients, but also on the way the authors define it (80-84).
- The use of GC, both intra-articular, or systemic, continues to play a central role in the treatment of PsA, in particular for the therapy of peripheral involvement (85, 86).
- A personalised therapy guided from peripheral lymphocyte phenotyping could really optimise the quality of care of patients with PsA (88).

**Contraception and pregnancy**

Contraception is an issue of major interest in women with PsA, who are usually in their childbearing age at disease onset and who are often treated with teratogenic medications to control their disease activity. Using three different surveys Leverenz et al. assessed contraceptive methods in women under 40 with RA or PsA and correlated contraceptive method efficacy with the use of concomitant immunosuppressors. Overall, about two-thirds of women with RA and PsA seemed to use effective methods of contraception, though women with PsA were more likely to report no methods of contraception. Interestingly, these proportions do not appear to be influenced by medications and remained similar across subgroups taking MTX, anti-TNF biologics, or novel medications (90).

A large Swedish cohort study and a case control study by Polachek et al. showed that women with PsA are not at higher risk of infertility and confirm that their pregnancies tend to be uneventful. However, higher rates of preterm delivery and Caesarean delivery were observed if compared to healthy controls (91, 92).
references


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