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Biological and synthetic target DMARDs in psoriatic arthritis

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Title:Biological and synthetic target DMARDs in psoriatic arthritis

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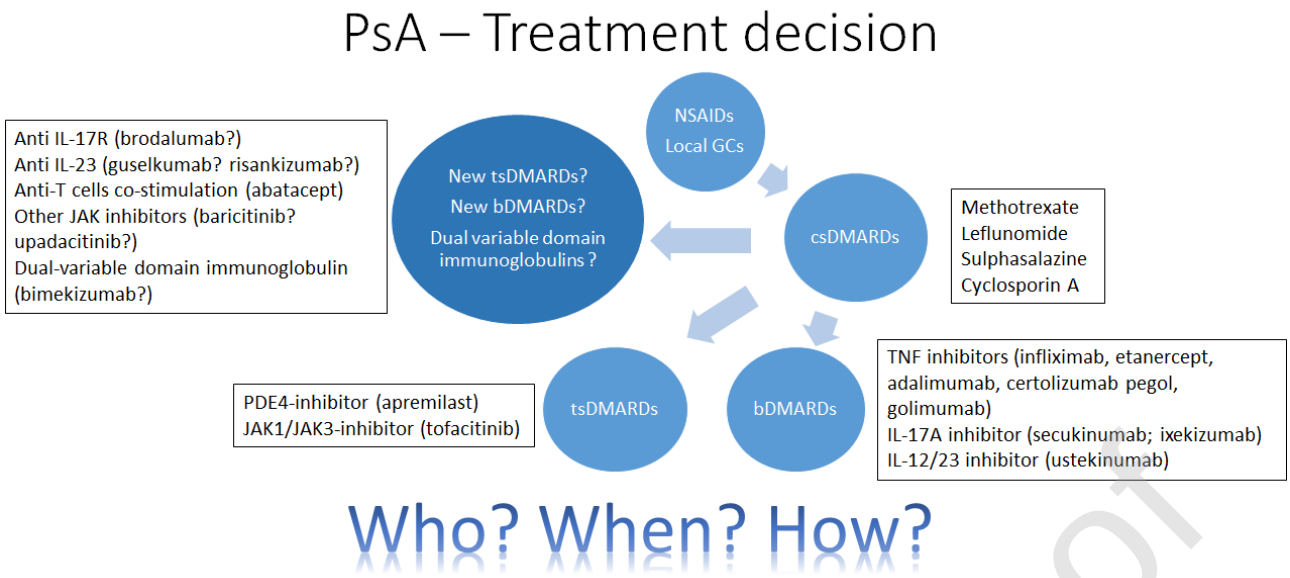
Graphical abstract:



Abstract

Psoriatic arthritis (PsA) is a chronic multi-faceted immune-mediated systemic disorder, characterized by articular, cutaneous, enthesis, nail and spine involvement. Articular manifestations of PsA are particularly common and highly disabling for patients, while the heterogeneous clinical subsets of the disease are challenging for clinicians. In recent years, research has made many advances in understanding the pathogenesis of the disease from genetic, epigenetic and molecular points of view. New drugs are now available for the treatment of this condition, and, in particular, TNF-alfa inhibitors, historically the first biologicals approved in PsA, are now juxtaposed by new biological disease modifying anti-rheumatic drugs (bDMARDs) with different modes of action. Targeting IL-12/IL-23 p40 common subunit with ustekinumab, IL-17A with secukinumab and ixekizumab, T cells co-stimulation with abatacept, is now possible, safe and effective. Moreover, targeted synthetic molecules with oral administration are available, with the possibility to interfere with phosphodiesterase-4 and JAK/STAT pathways. Indeed, new drugs are under development, with the possibility to target selectively IL-17 receptor, IL-23, and other key molecular targets in the pathogenesis of this condition. In this narrative review, we provide an up-to-date overview of the

current application of biological and targeted synthetic DMARDs in the field of PsA, with particular regard to the clinical significance of this possibility to target a higher number of distinct immune-pathways.

Keywords: Psoriatic arthritis, pharmacological treatment, TNF-alfa inhibitors, secukinumab, ustekinumab, JAK/STAT pathway.

Chemical compounds

Chemical compounds enlisted in this article: TNF-alfa inhibitor (PubChem CID: 16079006); Tofacitinib citrate (PubChem CID: 10174505); upadacitinib (PubChem CID: 58557659); methotrexate (PubChem CID: 126941).

1. Introduction

Psoriatic arthritis (PsA) is a chronic immune-mediated inflammatory systemic disease. It is characterized by heterogeneous involvement of joints, enthesis and skin. Dactylitis, nail dystrophy, uveitis, and spine involvement are common manifestations, and associated comorbidities with impact on cardiovascular risk, such as obesity and metabolic syndrome, are intrinsic parts of the psoriatic “disease”. PsA occurs in 6-42% of patients with skin psoriasis or affects familiars of psoriatic patients [1]. Synovitis and progressive cartilage and bone destruction are key pathological elements. New evidence in the pathogenesis of this condition have prompted further insights in our understanding of the molecular pathways involved in either cutaneous or articular manifestations of the disease, and genetic, epigenetic, environmental, cellular and molecular aspects have been clarified, giving rise to a number of different drugs available for treating this condition [2]. In this narrative review, we will overview the current clinical application of different biological disease modifying anti-rheumatic drugs (bDMARDs) and new targeted synthetic (ts) DMARDs (Table 1). Clinical trials have yielded important insights in efficacy and safety of these drugs. Available observational data from international registries support their clinical effectiveness and all these data have been translated into clinical recommendations with the aim to help clinicians in treating such a disabling

condition. Starting from the large body of evidence available for Tumour Necrosis Factor (TNF)-alfa inhibitors (TNFis), there is now increasing application in real life of other bDMARDs with different modes of actions, in particular anti-Interleukin (IL)-12 / IL-23 p40 common subunit ustekinumab, anti-IL-17A secukinumab and ixekizumab, and selective T-cell co-stimulation modulator abatacept. Apremilast and tofacitinib are the only tsDMARDs approved in PsA, and they are already available. Finally, but not at the end, research in PsA treatment is far from being completed, and new drugs are now under evaluation in phase II-III trials, or are currently approved for psoriasis management and promise interesting results even in PsA. Since this large availability of drugs with disease-targeted mechanisms of action (Figure 1), approaching disease remission is now a realistic objective. Moreover, maintaining this condition during years seems feasible, but we do still need to improve our knowledge with the aim to guarantee to each patient the correct and most appropriate treatment, to reduce the number of therapeutic failures, to provide safe decisions and to realize economically sustainable future strategies.

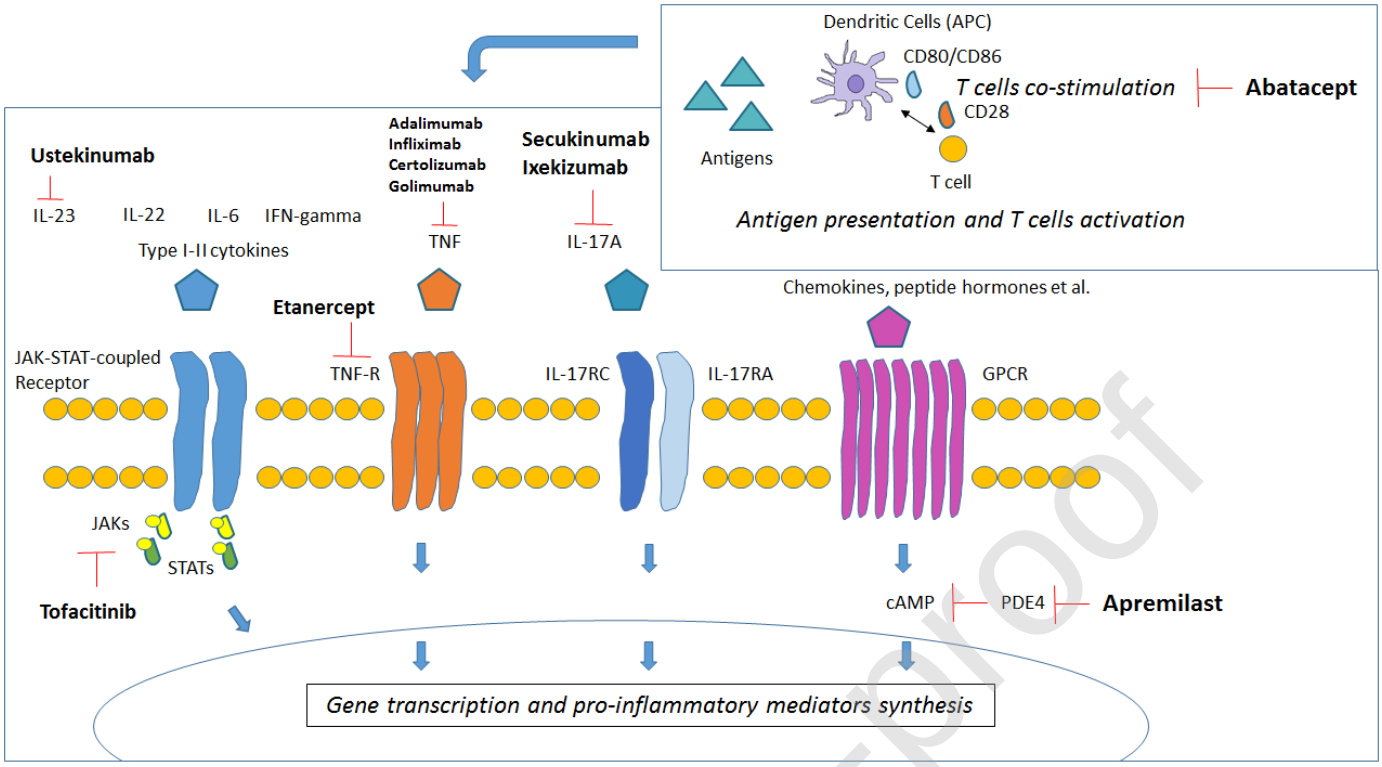
Table 1. Different b/tsDMARDs available in the PsA treatment armamentarium.

Type of drug	Mechanism of action	Available biosimilar (Y/N)	Phase of development / Approval
TNF-inhibitors			
Etanercept	TNF receptor inhibitor	Y	Approved in PsA
Infliximab	TNF inhibitor	Y	Approved in PsA
Adalimumab	TNF inhibitor	Y	Approved in PsA
Golimumab	TNF inhibitor	N	Approved in PsA
Certolizumab	TNF inhibitor	N	Approved in PsA
Anti IL-23/IL-17A axis drugs			

Ustekinumab	P40 common subunit of IL-12 and IL-23 inhibitor	N	Approved in PsA
Risankizumab	P19 subunit of IL-23 inhibitor	N	Phase III ongoing, approved in psoriasis
Guselkumab	IL-23 inhibitor	N	Phase III ongoing, approved in psoriasis
Secukinumab	IL-17A inhibitor	N	Approved in PsA
Ixekizumab	IL-17A inhibitor	N	Approved in PsA
Bimekizumab	IL-17A and IL-17F inhibitor (dual variable domain immunoglobulin)	N	Phase III ongoing
Brodalumab	IL-17RA inhibitor	N	Phase III completed, approved in psoriasis
T cells co-stimulation inhibiton			
Abatacept	CD80/CD86-mediated co-stimulation inhibitor	N	Approved in PsA
tsDMARDs			
Apremilast	PDE4 inhibitor	N	Approved in PsA
Tofacitinib	JAK-1/JAK-3 inhibitor	N	Approved in PsA
Baricitinib	JAK-1/JAK-2 inhibitor	N	Phase IIb in psoriasis
Upadacitinib	JAK-1 inhibitor	N	Phase III ongoing

bDMARDs: biological disease modifying anti-rheumatic drugs; tsDMARDs: targeted synthetic disease modifying anti-rheumatic drugs; TNF: tumour necrosis factor; IL: Interleukin; tsDMARDs: targeted synthetic disease modifying anti-rheumatic drugs; PDE4: phosphodiesterase-4; JAK: Janus kinase.

Figure 1. Selective mechanisms of action of b/tsDMARDs approved for the treatment of PsA.



Different b/tsDMARDs are approved for the treatment of PsA, with different mechanisms of action. Abatacept is a selective modulator of T cells co-stimulatory signal, essential for their activation and differentiations; it acts inhibiting binding of T-cells CD28 with CD80/CD86 co-stimulatory molecules on APCs. Different TNF-inhibitors are available (adalimumab, infliximab, certolizumab, golimumab), with etanercept able to inhibit TNF Receptor. Ustekinumab is a selective inhibitor of P40 common subunit of IL-12 ad IL-23, while secukinumab and ixekizumab inhibit IL-17A. Oral small molecules apremilast and tofacitinib act at intra-cellular level. Apremilast inhibits PDE4, with subsequent increase in cAMP levels and further inhibition of several pro-inflammatory downstream signals, while tofacitinib inhibits JAK1/JAK3 (with lower inhibition on JAK2) preventing STATs phosphorylation and subsequent gene transcription activation.

APC: Antigen-presenting cell; IL: Interleukin; TNF: tumour necrosis factor; JAK: Janus Kinase; STATs: signal transducers and activators of transcription; GPCR: G protein-coupled receptors; cAMP: Cyclic adenosine monophosphate; PDE4: phosphodiesterase-4.

2. Role of TNF-inhibitors in the management of psoriatic arthritis

2.1 Historical, histopathologic and pathogenic view

Over past years, pharmacological improvement in the setting of PsA resulted in enormous advances in clinicians' capability of treating such a disabling condition. However, many pitfalls remain and unsolved problems (or newly emerging problems) are still of interest. Since initial development of highly effective biological treatments, in particular TNFis, and their application to the field of chronic autoimmune arthropathies (in particular rheumatoid arthritis (RA) and spondyloarthropathies (SpA)), a revolution in the management of these conditions has happened [3]. Following early studies in RA patients, in which total synovial cell cultures were treated with TNF blockers showing a significant reduction in IL-1 levels [4], the central role of TNF in the pathogenesis of inflammatory arthritis has emerged [5], giving rise to further development of effective drugs licensed for RA. First adoption of TNFis in the field of PsA goes back to early 2000s and, since then, many things have changed.

From a "synovial membrane" point-of-view, chronic inflammatory arthritis are histologically characterized by marked hyperplasia of the intimal lining layer (containing fibroblast-like synoviocytes (FLS) and macrophages) and infiltration of the synovial sublining with both innate and adaptive immune cells. This inflammatory infiltrate is responsible of inflammatory mediators release (cytokines, chemokines, matrix metallo-proteinases (MMPs)), neoangiogenesis promotion, adjacent cartilage damage and bone destruction. In PsA synovitis, differing from RA, neoangiogenesis is particularly marked, with tortuous, immature and elongated vessels [6], while lymphoid aggregates are fewer. CD163-positive macrophages (both in lining and sublining layer) are enriched in synovial tissues from PsA [6,7], and their number in lining (but not in sublining) layer is higher than in RA synovitis [8]. Macrophages are among the main producers, at synovial level, of key inflammatory mediators, such as TNF [9], and two different populations of macrophages are described in patients with chronic synovitis: lining mature CD163-positive and sublining infiltrating MRP8/MRP14-positive macrophages [7]. Effective TNF inhibition resulted in reduction of sublining infiltrating macrophages in SpA patients [7,10], and, with less validated significance with respect

to RA [11], this remains a sensitive change after effective treatment in PsA [12–14]. Apart from macrophages, other leading cellular actors are present, and mast cells, polymorphonuclear (PMN) cells, and lymphocytes (B cells, T cells, plasma cells) play an important role [2,6,10,15–18], with abundant overexpression of pro-inflammatory cytokines, including TNF, IL-1β, IL-6, IL-22, IL-17A, IL-18. Both T helper (Th) and CD8-positive cells are involved in the pathogenesis, with clonally expanded populations of cytotoxic T cells resistant to effective treatment [17]. Moreover, bone metabolism is altered in PsA: bone formation biomarkers are inter-connected with catabolic ones and bone erosions coexist with new bone growth [19] (Figure 2).

While inflammation is not restricted to the context of synovium, but also extends to systemic parts, the intimate link between synovial membrane inflammatory burden and systemic inflammation (with skin, nails, enthesis, cardiovascular system or gut involvement) is far from being understood. Moreover, it is actually not known if different pathogenic immune-pathways are active and distinguishable depending on the different anatomical site, with tissue-specific responses varying across different organs [20]. Genomic profiling studies in PsA could help to understand this issue. Belasco and co-workers [21] have analysed paired PsA synovial tissue and skin samples and demonstrated higher IL-23/IL-17-related gene expression in cutaneous biopsies, while TNF- and Interferon-gamma (IFN-gamma)-signatures were quite homogenously expressed at both levels. To this regard, therapeutic targeting of crucial mediators, such as TNF, confirmed, in numbers of studies, major effects on both synovial and systemic inflammation [22]. Genetic association studies strongly support the role of different cytokines in the pathogenesis of PsA and several molecular variants of non-Major Histocompatibility Complex (MHC) genes associated with disease susceptibility [2,23]. In particular, genome-wide association (GWA) studies, performed exploiting several international consortia dedicated to sample collection, highlighted a role for polymorphisms in different genes related to TNF-dependent signal transduction, either in ankylosing spondylitis (AS)[24] and in PsA [25]. Genes like TNFAIP3 and TNIP1 are under consideration [25,26] and these associations remark the relevant role of TNF in SpA pathogenesis, unveiling further rationale for its pharmacological inhibition.

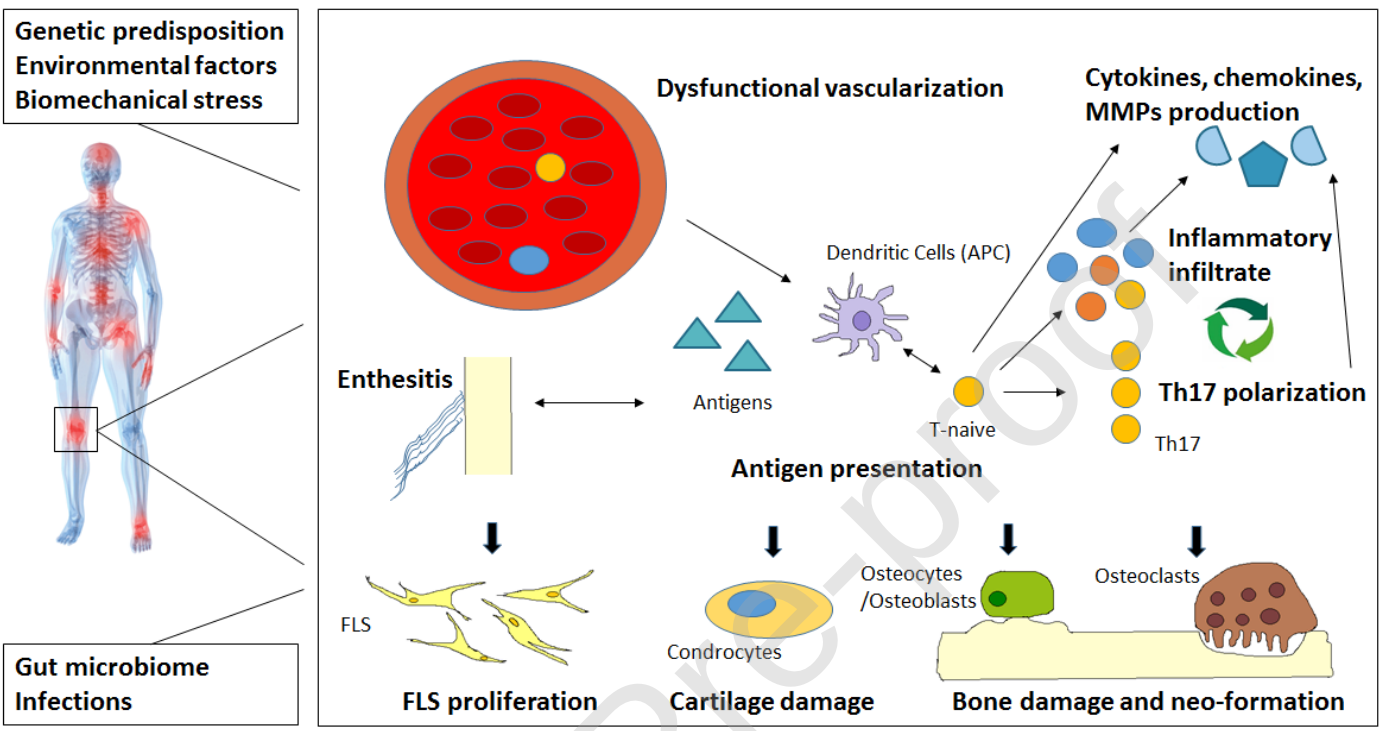
Major changes after effective TNFis treatment in PsA synovium consist, apart from reduction in number of sublining macrophages, in significant reduction of sublining CD3-positive T cells [10,27], vascular endothelial growth factor (VEGF) and other markers of neovascularization expression [14], matrix metallo proteinases-3 (MMP-3) and MMP-13 [27]. Synovial fluid (SF) cytokines [28], but even serum cytokines' [29] modifications are relevant. TNFis have demonstrated, in addition, effectiveness in variation of relevant cellular and molecular biomarkers at cutaneous level, with reduction in CD3-positive and CD163-positive cells, CD161-positive and elastase-positive dermal cells, dendritic cells, IL-17, IL-22, IL-23, IFN-gamma, inducible Nitric Oxide synthase (iNOS), TNF, IL-20 expression and increase in Langerhans cells [30–35].

All these evidence point towards a crucial role for TNF inhibition in the treatment of PsA. However, what we have learnt from synovial histopathology studies (but even from studies on serum, SF or skin biomarkers) is not enough to develop *ad hoc* short-term early phase randomized clinical trials (RCTs), aimed to identify early reliable biomarkers of response to effective treatments. It is reasonable to imagine that more recent and sophisticated approaches, most of them derived from studies in RA [36–39], could help in isolating single cells populations from synovial biopsies, characterizing cell heterogeneity within joints and performing single-cell RNA sequencing or mass cytometry [16,40], while targeted proteomics approaches could be applied at whole-tissue level to discover early modifications or *a-priori* models of response [41,42].

Given these histologic modifications of cellular and molecular biomarkers after TNFis treatment, another relevant aspect to consider concerns the issue of remission and its histologic counterpart. A recent study by Alivernini et al. performed in PsA remitting patients after successful TNFi treatment showed high residual amounts of sublining CD68-positive, CD3-positive cells, and CD31-positive vessels [43], and this aspect could partially explain the high proportion of patients relapsing after treatment discontinuation [44]. The challenge of treatment discontinuation remains open and synovial histopathology findings might help in discovering biomarkers of disease relapse. To date, clinical outcomes (usually evaluated by composite disease activity measures) remain the only validated ones to define response to treatment and to guide

therapeutical strategies, being either TNFis or other conventional synthetic (cs) DMARDs, bDMARDs or tsDMARDs [45–48].

Figure 2. Main pathogenic features of chronic PsA synovitis.



Chronic synovitis of psoriatic arthritis is characterized by dysfunctional vascularization, with tortuous, immature and elongated vessels. Enthesitis and antigen-presentation to naïve T cells are early pathogenic processes, resulting in Th17 polarization of T cells, rich inflammatory infiltrate with macrophages, T cells, B cells, polymorphonuclear cells, and mast cells and subsequent production of different cytokines (TNF, IL-17, IL-6, IL-1, IL-22, IL-21, IFN-gamma), matrix metallo-proteinases (MMPs) and chemokines. Fibroblast-like synoviocytes (FLS), chondrocytes, osteoblast and osteclasts activation result in secretion of different matrix-degrading enzymes and RANKL, with final cartilage degradation, bone erosion along with bone neo-formation, and joint damage.

APC: Antigen-presenting cell; MMPs: matrix metallo-proteinases; Th17: T helper 17; FLS: fibroblast-like synoviocytes; TNF: tumour necrosis factor; IL: Interleukin; IFN-gamma: Interferon gamma; RANKL: receptor activator of nuclear factor-kappa B ligand.

2.2 Data from randomised clinical trials

RCTs form the major source for evidence-based medicine. TNFis, until recently, were the only bDMARDs licensed for PsA management, as they have shown highly reproducible efficacy across different studies, similar for all the approved agents (infliximab (IFX), adalimumab (ADA), certolizumab pegol (CTZ), etanercept (ETA) and golimumab (GOL)) [49,50]. Phase III trials involving TNFis were designed mostly in csDMARDs-insufficient responders (IR), with some exceptions involving TNFis-IR patients [51]. American College of Rheumatology (ACR)20 response rate (primary outcome measure in phase III RCTs), is in the order of 50-65% across studies for both short-term and long-term evaluations [51–60]. Important results have been demonstrated regarding other efficacy outcomes, as well for functional [61,62] and structural outcomes [57,63–66], and for either spine, cutaneous, entheseal manifestations [49,67,68] or dactylitis [69]. For relevant psoriatic skin manifestations or coexisting active inflammatory bowel disease, ETA (receptor-blocker) seems less efficacious, or at least slower in the onset, than other TNFis [70,71].

Combination of bDMARDs with csDMARDs is highly effective in the treatment of RA, in particular this is true for TNFis [72]. When considering PsA, RCTs have shown similar response rates in patients receiving TNFis with or without concomitant csDMARDs [73–75], and recent results from the SEAM-PsA trial (NCT02376790) [76,77] confirmed no relevant differences in efficacy endpoints in etanercept monotherapy arm compared to ETA-methotrexate (MTX) arm, apart from numerically higher improvements in the skin endpoints for the combination regimen. As a matter of fact, some registries have shown improved drug survival for combination therapy, mainly with infliximab [78–80].

In the absence of head-to-head clinical trials comparing TNFis and newer IL-17A-targeting agents, it is difficult to ascertain a better efficacy on peripheral arthritic manifestations for TNFis over the others. Strand and colleagues [81] have recently indirectly evaluated the efficacy of ADA and secukinumab in RCTs, and found higher efficacy for ADA at week 24, while Nash and co-workers [82], prolonged the matching-adjusted indirect comparison through one year, adjusting for previous TNFis exposure, and claimed higher

efficacy for secukinumab. It is remarkable the need for head-to-head RCTs directly comparing different treatments strategies [83,84].

2.3 Use of TNFis in “real life”

The role of TNFis in PsA patients has been confirmed by numbers of results from long-term observational studies, registries and healthcare databases [79,85–87]. As persistence in treatment is considered a good indirect and composite measure of effectiveness, safety and tolerability, it is used to underline the long-term impact of the drug. After initial approval of TNFis for the treatment of PsA, five-year persistence rate approached 50% with first-line TNFis and the rate was similar even with subsequent lines of treatment [88]. However, this tendency tends to differentiate in the last years, with lower persistence for subsequent lines of therapy [89]. It is conceivable that wider availability of new drugs (with similar but also with different molecular targets) could affect persistence, with more therapeutical chances to use in refractory patients. Observational studies have shown that TNFis’ persistence is mainly reduced by comorbidities (including depression and/or anxiety) [88,90], body mass index (BMI) [80], and baseline disease activity [80,89], while a longer disease duration associates with higher persistence [80,89], maybe due to acceptance of sub-optimal control of the disease in patients with long-standing disabling conditions.

Following results of RCTs and observational studies, systematic literature reviews (SLRs) and expert judgement were translated into guidelines, which describe the state of the art, in order to help clinicians making treatment decisions at individual patient level. Treatment of PsA has been systematically organized by different sets of international recommendations, and among the most important ones there are those provided by European League against Rheumatisms (EULAR) [91] and Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) [92]. TNFis remain among first-line biological treatment strategies in both sets of recommendations [93]; this is a consequence, in particular, of long-term experience gained across time, most in terms of adequate efficacy/safety profiles. In a stepwise approach, after treatment with csDMARDs for an appropriate time (usually 3–6 months) without achieving at least

low disease activity, a bDMARD has to be considered. Patients with more prominent axial or entheseal involvement, instead, could be treated with biologics even if csDMARDs have not been undertaken (just after failure of non-steroidal anti-inflammatory drugs (NSAIDs) and/or local injections of glucocorticosteroids (GCs)) [91]; in these cases csDMARDs have proven less efficacy [94]. The recently published set of recommendations from American College of Rheumatology (ACR) / National Psoriasis Foundation (NPF) [95] suggest the adoption of TNFis even in early csDMARD-naïve patients, and this is supported by recently-developed RCTs [96].

The central role of TNFis in the management of PsA is remarkable even when considering the correct treatment strategy. At present, recommended treatment approach in the field of chronic inflammatory arthritis refers to treat-to-target (T2T) implementation, and T2T guidelines for PsA management have recently been published and updated [97]. The key points of T2T approach refer to measuring disease activity and adjusting tailored treatment accordingly, with the final objective to improve long-term quality of life, controlling signs and symptoms, preventing structural damage, and minimising comorbidities and toxic effects of drugs. The main goal of T2T is to reach clinical remission / inactive disease, but low/minimal disease activity is acceptable in selected cases, and measuring using available instruments is suggested [45,46]. In the TIght COntrol in Psoriatic Arthritis (TICOPA) trial, a randomized controlled open-label trail including 206 patients [47], a T2T approach was compared with standard of care management. Patients receiving the intensive treatment strategy tailored at achieving remission or minimal disease activity (MDA) gained positive outcomes in terms of efficacy and patient reported outcomes (PROs) for both articular and skin domains, despite higher costs and overall increase in adverse events. As stated in recent recommendations for T2T in SpA [97], this targeted-approach has stressed the role of an early introduction of effective treatments (including TNFis) in the management of refractory PsA patients that are not able to achieve MDA, while a delay in diagnosis is associated with poor long-term outcomes and structural damage [48]. However, in clinical settings, adherence to T2T approach is sub-optimal, performed by only half of healthcare professionals [98]. Elements able to drive clinicians' decisions in the choice of a TNF-inhibitor versus other drugs with different modes of action in bDMARD-naïve patients are, at present, more related

to clinical manifestations and to clinical strategies than to available biomarkers able to drive treatment decisions, as therapeutic choice in chronic arthritis are substantially based on 'trial-and-errors' basis. What is remarked by T2T recommendations is the search for a relevant clinical outcome, irrespective of the drug adopted [99]. Moreover, if in first-line treatment strategies the choice of the drug might be challenging, similar difficulties are present in subsequent treatment lines. In case of first bDMARD failure (due to adverse events, primary inefficacy or effect loss), in fact, a large amount of data is available supporting the possibility of switching either to an alternative bDMARD within same drug class or to a drug with a different action modality [100], but a definite recommendation lacks [91,92]. Switching to another TNFi is considered useful in PsA, and this aspect has been investigated by many registries. Observational data of initial courses of TNFis (2002-2006), in fact, have shown similar persistence rates, independent of the line of treatment [88]; treatment courses including those started in recent years, however, clearly show lower persistence and response rates in lines different from the first one [89,100,101]. To this regard, the possibility to swap to other biologics with different modes of action is intriguing, and recent RCTs have included patients who have previously failed treatment with one or more TNFis [51,102–106], trying to investigate the aspect of the best choice in second-line therapy. In the PSUMMIT 2 trial [106], ustekinumab efficacy decreased depending on the number of previous TNFis' failures, thus introducing the concept of merely refractory synovitis instead of the possibility of different activated immune-pathways. As, to the best of our knowledge, no clinical trial has investigated differences in clinical effectiveness between these opposite treatment strategies (switching to TNFis compared to swapping to other bDMARDs) in PsA, this is definitely expected in next years.

Finally, another point to consider, with few lights and numbers of shadows, deals with treatment interruption and/or tapering after obtaining remission or MDA. The wide availability of effective drugs has made possible to achieve remission in many patients, however, clinicians are concerned of avoiding non-necessary prolongation of treatment, thus exposing patients to possible side effects. While in the context of RA some more evidence is available [107,108], it is difficult to drag conclusions in the field of PsA. Small clinical studies have been performed, demonstrating high rate of relapses (more than half of patients) after

bDMARD withdrawal [44,109]. Data from CORRONA registry [110] have recently shown that, among 302 patients discontinuing TNFis when in low disease activity, a higher clinical disease activity index (CDAI) (Hazard Ratio, unadjusted HR 1.43 (95% Confidence Interval, 95%CI 1.03-2.00)) and smoking habits (adjusted HR 1.76 (95%CI 1.13-2.27) were predictive factors for subsequent relapse. Similar effect was demonstrated for severe skin involvement and presence of synovial hypertrophy at ultrasonographic (US) evaluation [44]. Restoring TNFi treatment that was interrupted is efficacious in most patients in order to attain disease control [111]. Apart from TNFis withdrawal, the possibility of dose reduction (with time-spacing of administrations or dosage reduction for intra venous (IV) protocols) has been taken into account and seems more feasible than drug interruption [111,112]. At the moment, however, this practice is considered off-label, despite money-saving [113].

2.4 Biosimilars

In recent years, the availability of biosimilar DMARDs (bsDMARDs) has changed relevantly the complex therapeutic scenario of chronic inflammatory arthropathies, rendering the access to biologicals more sustainable for healthcare systems. However, the advent of bsDMARDs has also been harbinger of further challenges for both patients and clinicians. Biosimilar is a biological product highly similar to an existing reference medicinal product (RPM). To be approved by Food and Drugs Administration (FDA) and European Medicines Agency (EMA), bsDMARDs have to be proven similar to the RPM (which cannot be considered bio-equivalence at all) and comparable in efficacy and safety [114,115]. bsDMARDs have been developed after patent expiration of the RPM and currently there are 16 bsDMARDs approved in Europe for the treatment of RA (4 infliximab, 3 etanercept,6 adalimumab, 3 rituximab), with others awaiting approval. In addition to RA ([116–118], RCTs involving bsDMARDs for TNFi were developed in plaque psoriasis [119,120] and ankylosing spondylitis (AS)[121] and, according to guidance for regulatory approval of biosimilars, the indication was extended to other indications of the RPM, including PsA [122], with no relevant new safety concerns. However, there are still lights and shadows regarding their use. With the same efficacy and

safety, their added value depends exclusively on the significant cost reduction compared to the RPM (from 20 to 40%), which can ensure healthcare system sustainability and access to treatment for a greater number of patients [115]. Furthermore, the transition from the original drug to the biosimilar agent has proved to be safe and effective, as demonstrated by RCTs [123,124] and SLRs [125,126]. The NOR-SWITCH trial [123] is the first randomized, double-blind, non-inferiority study which has investigated, in patients with inflammatory bowel disease, SpA, RA, PsA, or chronic plaque psoriasis, receiving stable treatment with infliximab originator for at least 6 months and switching from the RPM to a biosimilar anti-TNF agent (CT-P13), the non-inferiority of switching compared to continuing treatment with the originator drug. The adjusted relative risk of disease worsening in the IFX biosimilar group was 1.17 (95%CI 0.82–1.52) compared with the infliximab originator group, so switching was deemed not inferior to continuing RPM. In this trial, however, only 6% of patients had PsA (30/481), and the trial was not powered to clearly assess non-inferiority in each disease group. Observational data from registries, moreover, are useful in understanding the significance of switching at single disease level. Data from the DANBIO registry have reported that in 802 patients with RA, PsA, and axial SpA treated with IFX for a median of more than 6 years, switching to CT-P13 had no negative impact on 1-year clinical outcomes and disease activity [127], and similar data are now available for 1,621 patients switching to ETA biosimilar SB4 [128]. Retention rates appear similar both in PsA and in RA.

However, the increasing availability of different bsDMARDs of the same biologic agent involves both the problem of selection (which one to prefer), as well as the repeated switch between biosimilars in the pursuit of the right drug, with the associated implications in treatment delay, pharmacovigilance issues and risks consequent to different immunogenicity patterns [129]. The lack of evidence to support switching between different biosimilars or multiple switches is now under the lens of researchers. Additionally, when a bsDMARD is prescribed, the nocebo effect should be considered, which occurs when a patient has the expectation that a given treatment will have no benefit [130]. Nocebo effect might have a negative impact on treatment adherence and outcomes and it can be particularly troublesome when switching real-world patients from original bDMARDs to bsDMARDs [131]. To avoid contributing to the nocebo effect, it is very

important that clinicians carefully consider how they communicate with their patients, and make an effort to frame communications in a positive context [132]. In conclusion, biosimilars will play an important role in treating rheumatic diseases offering cost savings and healthcare system sustainability. Education and effective communication between physicians and patients are the winning weapon for eliminating the concerns that patients may have about biosimilars, avoiding the nocebo effect and ensuring long-term adherence to drugs.

2.5 Safety concerns

Despite up to 20-year experience with TNFis, safety aspects are still among most important points to evaluate [49,50], and the majority of evidence is borrowed from studies regarding RA patients [133]. In RA, TNFis might impact the overall risk for serious infections, with adjusted hazard ratios (HRs) ranging from 0.9 to 2.4 with respect to patients treated with csDMARDs, and with higher values when considering general population [133]. This is not a peculiarity of TNFis, however, and non-TNFis, as well, present higher risk of infections compared with csDMARDs-users and general population. No meaningful difference among single TNFis was highlighted. Encompassing published randomized studies in RA, AS and PsA, a recent SLR has stated that TNFis affect the risk for serious infections, any infections and tuberculosis (compared with placebo or no treatment) across different indications, also taking into account heterogeneity among studies [134]. Apart from infections, other relevant adverse events concern infusion reactions, injection site reactions, and hepatotoxicity. Moreover, TNFis carry the risk of worsening pre-existing heart failure (HF). Despite univocal conclusions are lacking [135], to date, they are not contraindicated in patients with mild HF, while they should be avoided in those with moderate-to-severe HF (New York Heart Association (NYHA) class III or IV). The global impact of TNFis on cardiovascular risk, however, seems to be reduced after lowering systemic inflammation both in psoriasis and in PsA [136].

Analyses of registries and RCTs have shown that patients on bDMARDs have not an increased risk for solid malignancies, either in comparison to general population or to patients on csDMARDs [133,137–139], and

conclusion in PsA patients are similar to those in other chronic inflammatory arthritis [137]. Several studies, however, highlighted an increased risk for melanomas and non-melanoma skin cancers (NMSC) after TNFis exposure [138,140]. To this regard, it is important to underline that patients with psoriasis are at higher risk for developing melanomas [141] and NMSCs [142]. A recent analysis of pooled data in 11 European registries, including 130,315 RA patients treated with TNFis, demonstrated an increased risk for invasive melanomas, but statistical significance was not achieved (standardised incidence ratios (SIR) 1.2, 95%CI 0.99-1.6) [143]. Conversely, in the analysis of the British Society for Rheumatology Biologics Register, Fagerli and colleagues [138] found a relevant increase in incidence rates for NMSC (SIR 2.12, 95%CI 1.19-3.50) among 709 PsA patients treated with TNFis, and the risk was higher among females. Careful skin evaluations in all patients receiving TNFis remain recommended, before treatment initiation and, relevantly, during follow-up, independent of the clinical indication for TNFi prescription. Other relevant cutaneous side effects of TNFis are xerosis, eczema, and psoriasiform eczema. In addition, numerous cases have been reported in which TNFis have induced or worsened symptoms of psoriasis [144] and palmoplantar pustulosis [145]; in such cases, switching to another agent with similar mechanism of action is not advisable. Finally, TNFis are generally not recommended as first-line bDMARD therapy in patients with coexisting systemic lupus erythematosus (SLE), demyelinating diseases such as multiple sclerosis (MS), and other autoimmune systemic or neurological disorders, as numbers of case-reports and case series point towards an increased risk of various autoimmune conditions in TNFis-treated patients [146–148].

To sum-up, despite a huge body of evidence, still a high proportion of patients may necessitate of second-line therapies, with treatment failures occurring in at least 30–40% of the overall PsA population (for primary non-responses, loss of efficacy, relapses, but even for side effects). ACR20 response rates with TNFis rarely exceeded 60% in RCTs. Subjects refractory to more than one biologic remain a challenge for clinicians, and this interesting aspect may unveil a true biological refractory state or a distinct pathogenic phenotype, but even unidentified factors, such as epigenetic alterations, are possible. Even more, it is difficult to establish when it is possible to reduce doses, space administration frequencies or even discontinue, thus exposing patients to long-term treatment schedules with possible accrual of side effects.

Many patients, affected by particular comorbidities that raise doubts about administration of TNF-inhibitor agents, may necessitate of alternative biologics. Therefore, what we have learned from literature evidence (RCTs, observational studies, SLRs) and from clinical practice with five different TNFis (and their available biosimilars) is not yet enough, and adoption of new drugs with different mechanisms of action, new treatment strategies targeting free-drug regimens as well as the development of new-targeted drugs still necessitate.

3. New biological treatments: IL-23/IL-17 axis

There is extensive evidence that IL-23/IL-17 pathway has a crucial role in the pathogenesis of psoriasis and PsA [149]. IL-23 is a heterodimeric cytokine consisting of two subunits (respectively known as p40, which is shared with IL-12; and p19) that binds IL-23R and IL-12Rβ1 [150]. It is produced by T-cells and antigen presenting cells (APCs) in response to multiple factors such as biomechanical stress, abnormalities in human leucocyte antigen (HLA) B27 protein folding and intestinal dysbiosis [151]. IL-23 induces differentiation, activation and expansion of Th-17 cells, which are effector of the inflammatory process and the main source of IL-17A, a member of the IL-17 family. The latter includes six homodimer cytokines (IL-17A to IL-17F) and one heterodimeric protein (IL-17A/IL-17F) [152]. IL-17A and, albeit in varying degrees, the entire IL-17 family, have been reported to be implicated in natural host defense, neutrophil differentiation, activation, migration to the site of inflammation, and in the control of infections, especially Staphylococcus aureus and Candida infections [152,153]. However, IL-17A and IL-17F are the most implicated in inflammatory responses and in the development of autoimmune conditions, with a less prominent role for IL-17F compared to IL-17A [152]. The IL-17A/IL-17A homodimer and IL-17A/IL-17F heterodimer are the biological active forms of IL-17. Their receptor consists of two chains: IL-17RA and IL-17RC, and their combination is required for functional receptor activity [152,154].

In addition to Th-17 cells, IL-17A and IL-17F are produced by a large variety of innate and adaptive immune cells, such as CD8-positive T lymphocytes, γδ T cells, natural killer (NK) cells, innate lymphoid cells (ILCs)

[152], while mast cells are considered a storage unit [155,156]. IL-17A producing cells are found at sites of inflammation in PsA, both in the skin and joints. This finding strongly supports the theory of a master role for IL-17A in the inflammatory response in PsA through its action on different cell types such as neutrophils, keratinocytes, synoviocytes, endothelial cells, chondrocytes and osteoblasts, whose activation causes the release of several pro-inflammatory cytokines [157,158]. Noteworthy, secretion of IL-17A as well as IL-22, IL-6 and CXCL1 by specific resident CD3+CD4−CD8−RORγt+IL-23R+ T cells at entheseal level leads to secondary synovitis, osteitis, bone destruction, and bone hyper proliferation, typical of PsA, and epidermal proliferation and inflammation, typical of psoriasis, in mice models of SpA [159]. Again, genetic association studies highlighted an important role for different single nucleotide polymorphisms (SNPs) in IL-23/IL-17A axis-related genes in the susceptibility to the disease [160], with different alleles involved, like the IL-12 p40 subunit, the IL-23 p19 subunit, IL-23R, IL-17A and IL-17RA [25,161–164]. Variants in TRAF3IP2 (Act-1), an ubiquitin mediating signal transduction after IL-17R activation for subsequent induction of the NF-kB pathway, are associated with PsA, psoriasis and inflammatory bowel diseases [165]. At present, the IL-23/IL-17 axis can be targeted by inhibiting IL-23, IL-17A or their receptors.

3.1 IL-23 inhibitors

Ustekinumab is a fully human monoclonal IgG1 antibody with high affinity for the p40 subunit of IL-12 and IL-23 [166]. It is administered subcutaneously and has been approved for the treatment of adults with active PsA in United States of America (USA) and Europe. Several clinical trials have examined ustekinumab as a treatment for PsA. A phase II, randomized, double-blinded, placebo-controlled crossover trial highlighted the efficacy, tolerability and safety of ustekinumab in adult patients with active PsA unresponsive to csDMARDs, NSAIDS, TNFis or a combination of the three [167]. The two subsequent larger phase III, double-blind, randomized, placebo-controlled clinical trials PSUMMIT-1 [168] and PSUMMIT-2 [106] demonstrated the efficacy of ustekinumab in treating peripheral PsA already within 4-8 weeks, reaching the plateau within 24-28 weeks. Ustekinumab worked either with and without MTX and resulted

in a decrease of radiographic progression [169] compared with placebo. Notably, the response among patients previously exposed to TNFis was lower than in TNFis-naïve subjects [106,168]. Safety profile of ustekinumab in PsA RCTs was similar to that provided in psoriasis trials, with no particular safety concerns, low rates of serious infections and absence of opportunistic infections, malignancies or deaths [170].

Concerning real-world experiences, only one study was published, to date, regarding drug survival and effectiveness of ustekinumab using real-world data [171]. The entire cohort (160 PsA patients; 54 biologic-naïve and 106 biologic-experienced) demonstrated a statistically significant reduction in disease activity, disability and skin scores at 6 months. Moreover, biologic-naïve patients achieved the best outcomes with respect to both clinical effectiveness and drug survival at 12 months. In summary, this real-world study has reflected what had been reported in phase III RCTs. Ustekinumab proved great efficacy even for cutaneous involvement, with superiority versus ETA in a head-to-head trial for psoriatic skin disease [166]. The efficacy of the drug in axial manifestations of PsA remains unproven [50].

Promising new drugs in the therapeutic armamentarium of psoriasis and PsA are selective IL-23 inhibitors guselkumab and risankizumab. They are monoclonal antibodies that target the p19 subunit of IL- 23, allowing sparing of the interleukin 12 Th-1 axis, which is important for defence against intracellular pathogens via interferon-γ production [3,172]. These antibodies have shown good efficacy and safety in the treatment of skin psoriasis, with superiority versus adalimumab and ustekinumab [173–176]. Guselkumab is now approved by the US FDA and EMA for this indication [172,177]. Safety and good efficacy of guselkumab have also been reported in patients with active PsA and an inadequate response to csDMARDs or to a single previous TNFi in a multicentre, randomised, placebo-controlled, phase II trial [178]. As regards risankizumab, currently available data have highlighted efficacy even in PsA [179].

3.2 IL-17 pathway inhibitors

Currently, two monoclonal antibodies targeting IL-17A (secukinumab and ixekizumab) have been approved for the treatment of PsA on the basis of large phase III trials [103,104,180,181]. Secukinumab is a fully

human IgG1κ monoclonal antibody, which selectively binds to IL-17A, thus inhibiting its interaction with IL-17R [182]. The two FUTURE-1 [104] and FUTURE-2 [103] studies demonstrated the efficacy of secukinumab in the treatment of articular symptoms, dactylitis and enthesitis in PsA, with improvement of functional impairment and inhibition of radiographic progression. Efficacy of secukinumab was demonstrated regardless of concomitant MTX therapy and in both TNFi-naive and TNFi-experienced patients [103,104]. Across FUTURE 1 and FUTURE 2, secukinumab was well-tolerated with a good safety profile. The most common adverse events were nasopharyngitis, upper respiratory tract infections, and headache, while serious adverse events (candidiasis) were uncommon. Secukinumab has also proven effectiveness in AS [183], which supports its use in cases of inflammatory spondylitis in PsA. In phase III trial programmes of skin psoriasis, blockade of IL-17A resulted in high PASI skin responses (PASI 75 to PASI 100) [184], with superior efficacy over ustekinumab [185] and etanercept [186] in head-to-head trials.

Ixekizumab is a humanized IgG4 monoclonal antibody that binds IL-17A with very high affinity. It has proved high efficacy in plaque psoriasis with the capacity to provide almost complete clearing of skin and it has been licensed in the USA and most European countries for the treatment of moderate-to-severe plaque psoriasis in adult patients [187,188]. Two phase III trials (SPIRIT-P1 and SPIRIT-P2) evaluated ixekizumab in the treatment of PsA. In these RCTs, ixekizumab has shown to be effective on peripheral joint symptoms, dactylitis, function and progression of structural damage; conversely, it was less effective in improving entheseal manifestations [180,181]. To date, there are not head-to-head studies comparing the efficacy of ixekizumab with secukinumab. The safety profile of ixekizumab in patients with PsA was generally favourable, and candidiasis and/or staphylococcal infections were infrequent. No particular concern in relation to induction/activation of inflammatory bowel disease emerged [103,104].

Promising results derive from studies on bimekizumab, a monoclonal antibody that neutralises both IL-17A and IL-17F [189], and on brodalumab, a human monoclonal antibody against IL-17 receptor A [190]. The latter has been approved for the treatment of skin psoriasis, and phase II data suggest a beneficial effect in PsA [190].

4. T cells co-stimulation inhibition

4.1 Abatacept in the treatment of PsA

Co-stimulation of T cells by APCs is necessary in order to obtain activation of different subsets of T cells. Cytotoxic T lymphocyte–associated antigen 4 (CTLA4) is expressed on T cells membrane and is physiologically able to bind CD80 and CD86 on APCs. It acts as an inhibitor of co-stimulation and it prevents the second signal required for optimal T cells activation by CD28 binding to CD80/CD86. Abatacept is a selective T-cells co-stimulation modulator. It is a human immunoglobulin-G1 linked to the extracellular domain of human CTLA4 protein. In this way, it is able to inhibit the binding of T cell CD28 with APCs' CD80/CD86, blocking the full T cells activation. FDA and EMA have already approved abatacept for the treatment of RA. More recently, following the phase III Active Psoriatic Arthritis Randomized Trial (ASTRAEA) trial [191], it has been approved for the treatment of PsA. In this RCT, subcutaneous abatacept 125 mg weekly (213 patients) was compared with placebo (211 patients) in PsA patients with active arthritis and plaque psoriasis, both TNFis-naïve and TNFis-exposed. Primary outcome was ACR20 response at 24 weeks. Abatacept demonstrated efficacy over placebo with significant achievement of ACR20 response (39.4% in abatacept group vs 22.3% in placebo at 24 weeks; $p<0.001$). At week 44, ACR20 in abatacept group reached 48.4%. ACR50 response at week 24 was 19.2% (28.2% at week 44), while ACR70 10.3% at week 24 (15.5% at week 44). TNFis-experienced patients displayed lower response rate in comparison with TNFis-naïve, and the separation between groups became higher at week 44. Switching from placebo to abatacept significantly improved efficacy in this group of patients. Efficacy on dactylitis and enthesitis was even remarked, while no new and relevant safety issues, in respect to the other studies in RA, were highlighted in this trial. Concerning cutaneous involvement, instead, the number of patients reaching PASI50 response was not statistically different between groups (26.7% in abatacept group versus 19.6% in the placebo arm, $p=0.137$) and even PASI75 response rate was low. "Real-life" data are now

awaited in order to better understand the clinical utility of targeting CD28-dependent T cells co-stimulation in the field of PsA, and the weight of benefits expected for articular domains, as well as for skin lesions.

5. Targeted synthetic disease-modifying anti-rheumatic drugs

csDMARDs and bDMARDs are effective in most PsA patients. However, treatment failure with these drugs can represent a relevant clinical problem. Moreover, treatment with these agents can be hindered in daily clinical practice by different situations, in particular the presence of comorbidities such as chronic and recurrent infectious diseases or history of malignancies. The discovery of pro-inflammatory intracellular pathways involved in PsA pathogenesis, such as the intracellular enzyme phosphodiesterase (PDE)-4 [192,193] and the transcription factors Janus kinase (JAK) and signal transducer of activators of transcription (STAT) [194] has led to the development of different tsDMARDs. Their use, ideally expected in cases of contraindication, primary/secondary ineffectiveness, side effects or intolerance to csDMARDs or bDMARDs, might be independent of the presence of these contraindications, and the acquisition of a relevant placement in the treatment armamentarium of PsA is reasonable [195–197]. The reported evidence of increased risk of PsA in patients with particular SNPs of several proteins involved in JAK/STAT signalling (e.g. TYK2, STAT3) [160,161] confirm the role of this type of inhibition as a treatment option.

5.1 Apremilast

Apremilast is an orally administered small molecule that specifically inhibits intracellular Phosphodiesterase-4 (PDE4) [198,199]. This enzyme is a member of the class of phosphodiesterases that act by hydrolysing cyclic adenosine monophosphate (cAMP), an intracellular second messengers which influences a network of pro-inflammatory and anti-inflammatory mediators [200]. Stimulation of neutrophil chemotaxis, inhibition of anti-inflammatory IL-10 and the increased production of pro-inflammatory cytokines (TNF, IL-12, IL-23, IL-2, IL-8) and chemokines (CCL4, CXCL9, CXCL10) are some of its main pro-inflammatory actions [193,200]. PDE4 is expressed in several cells including immune cells, haematopoietic

cells and keratinocytes [201]. Through its inhibition mediated by apremilast, cAMP levels in immune and non-immune cells increase with consequent reduction of the downstream inflammatory cascade [193,200]. In murine models of arthritis, apremilast has proven efficacy in reducing arthritis and histopathological changes in a dose-dependent manner [192].

Phase II multicentre, randomized, double-blind, placebo-controlled studies [202,203] and the Psoriatic Arthritis Long-term Assessment of Clinical Efficacy (PALACE) program consisting of phase III randomized, placebo-controlled trials with long-term and open-label extension [204–208] evaluated the efficacy and safety of apremilast on active PsA across patients with varying previous therapies (csDMARDs and/or bDMARDs). In particular, PALACE 1–3 included patients with active PsA despite prior traditional csDMARD or biologic treatment [204–207], while PALACE 4 includes patients with no prior csDMARD therapy [208].

Overall, apremilast treatment resulted in moderate improvement of joints signs and symptoms, including enthesitis, dactylitis and physical function, albeit not within the range of the responses achieved by inhibitors of TNF or IL-17 [3]. Regarding safety, apremilast resulted well tolerated with a reassuring profile. Most common adverse events were gastrointestinal ones (diarrhoea, nausea), headache, and upper respiratory tract infections. Nausea and diarrhoea generally occurred early and usually resolved spontaneously [204–206,208]. The good safety profile of apremilast, as well as a better efficacy than csDMARDs, allow to place apremilast as an alternative to biological therapy in patients at high risk of infections or with other contraindications. However, as it is more expensive than other available therapies, it remains to date a second- or third-line treatment option.

5.2 JAK-inhibitors

Several JAK inhibitors are in clinical development, each having a selectivity for inhibition of one or more of the 4 identified JAKs (JAK-1, JAK-2, JAK-3, Tyk-2). JAKs switch on major regulators of gene expression known as STATs (signal transducers and activators of transcription) [194]. Many cytokines implicated in the pathogenesis of PsA including INF-gamma, IL-12, IL-22, and IL-23 activate JAK/STAT pathway through a variety of combinations of different JAK and STAT family members. Other pivotal cytokines such as TNF-alfa

and IL-17 signal independently of JAKs. However, their production could be indirectly regulated by acting on upstream cytokines (such as IL-23, which signals via JAK/STAT) [2].

A preliminary study in PsA has demonstrated increased levels of JAK1, STAT3, STAT1 in synovial fluid T cells, compared with peripheral blood or healthy control, suggesting activation of JAK/STAT pathway at the site of inflammation [209]. More recently, a pre-clinical study has further investigated the role for JAK-STAT signalling in the pathogenesis of PsA examining primary PsA synovial fibroblasts (PsAFLS) and ex vivo PsA synovial explants [210]. Initial experiments demonstrated increased expression of STAT1 and STAT3 in PsA synovium when compared with osteoarthritis. Tofacitinib, an oral JAK inhibitor, that preferentially inhibits signalling by receptors associated with JAK1 and JAK3, with functional selectivity over JAK2, inhibited STAT3 and STAT1 expression in PsAFLS when compared with vehicle control. In parallel, tofacitinib induced SOCS3 (Suppressor of cytokine signalling) and PIAS3 (protein inhibitor of activated STAT3) expression in PsAFLS and synovial explant cultures [210]. Functionally, tofacitinib decreased PsAFLS invasion, migration and network formation. Finally, tofacitinib significantly decreased spontaneous secretion of key pro-inflammatory cytokines, inhibiting pro-inflammatory and invasive mechanisms critically involved in the pathogenesis of PsA.

5.3 RCTs with JAK-inhibitors in PsA

In the last few months, various studies implemented data on “in vivo” efficacy of tofacitinib inhibitors in PsA. To date, tofacitinib is the only JAK inhibitor that has been approved for the treatment of PsA by the US Food and Drug Administration and recently by the European Commission [211]. In 2017, two studies reported data on safety and efficacy of tofacitinib in PsA. The Oral Psoriatic Arthritis Trial (OPAL) Beyond [102] is a 6-month randomized phase III trial of tofacitinib conducted in patients with PsA with an inadequate response to at least one TNF inhibitor due to lack of efficacy or the occurrence of an adverse event related to treatment [102]. 394 patients were enrolled in the study and received, in a 2:2:1:1 ratio, at least one dose of tofacitinib (5-mg dose of tofacitinib administered orally twice daily or 10-mg dose of tofacitinib administered orally twice daily). The demographic and disease characteristics of the patients at

baseline were similar across the groups, except for the mean number of tender or painful joints that was highest in 10-mg dose of tofacitinib group. At 3 months, 50% of patients in 5-mg dose of tofacitinib and 47% with the 10-mg dose achieved the rates of ACR20 response, as compared with 24% with placebo (P<0.001 for both comparisons). In addition, at the end of the trial, 32 to 38% of the patients who received tofacitinib had an ACR50 response, and 15 to 21% had an ACR70 response. The 10-mg dose of tofacitinib, but not the 5-mg dose, was superior to placebo in treating skin psoriasis enabling a PASI75 response, a key secondary efficacy end-point of the study, in 43% of patients compared with 14% of response in placebo (and 21% in tofacitinib 5 mg group).

The Oral Psoriatic Arthritis Trial (OPAL) Broaden [212], a 12-month, double-blind, active-controlled and placebo-controlled phase III trial, evaluated the efficacy and safety of tofacitinib and adalimumab in patients with active PsA who have previously had an inadequate response to at least one csDMARD. Overall, 422 patients have undergone randomization to one of these regimens: tofacitinib 5-mg orally twice daily (107 patients), tofacitinib 10-mg orally twice daily (104 patients), adalimumab 40-mg subcutaneously once every 2 weeks (106 patients), placebo with a blinded switch to the 5-mg tofacitinib dose at 3 months (52 patients), or placebo with a blinded switch to the 10-mg tofacitinib dose at 3 months (53 patients). At three months, ACR20 response rates were 50% in the 5-mg tofacitinib group, 61% in the 10-mg tofacitinib group, 52% in the adalimumab group as compared with 33% in the placebo group. Also, PASI75, enthesitis and dactylitis, key secondary endpoints, improved with active treatment.

In both trials, Health assessment questionnaire disability index (HAQ-DI) scores improved with tofacitinib 5 and 10 mg twice daily and they were maintained until the end of the studies. Changes from baseline through month 6 (OPAL Beyond trial) or 12 (OPAL Broaden trail) with tofacitinib were numerically similar to those observed at month 3 but could not be compared with placebo at end of the studies because the patients in the placebo group had switched to tofacitinib at month 3. That is why, for example, the OPAL Broaden trial did not provide direct evidence of the effects of tofacitinib on structural radiographic progression, even if a total of 91 to 98% of patients across all trial groups met the radiographic criteria for non-progression [212]. The safety profile displayed in PsA was similar to those in previous trials with

tofacitinib in rheumatoid arthritis (reviewed elsewhere) [107]. In the OPAL Broaden trial, over a period of 12 months, serious adverse events occurred in 7% of patients receiving continuous tofacitinib at a dose of 5 mg, 4% of those receiving continuous tofacitinib at a dose of 10 mg, and 8% of those receiving adalimumab, and discontinuations due to adverse events occurred in 6%, 3%, and 4%, respectively [212]. In both trials, tofacitinib appears to carry an additional risk of herpes zoster infection [102,212]. The results from these two trials, as suggested in the accompanying editorial introducing the aforementioned studies, confirm that tofacitinib display an emerging role in the armamentarium of drugs for the treatment of PsA and may find a place alongside TNFis and phosphodiesterase-4 inhibitors [213]. Other tsDMARDs targeting JAK/STAT signalling mechanisms are under development in PsA: baricitinib, an oral JAK-1/JAK-2 inhibitor, currently approved for the treatment of RA, has given interesting results in a phase IIB trial in patients with psoriasis [214], while two phase III trials are actually ongoing with the selective JAK-1 inhibitor upadacitinib (ABT-494) in PsA patients [215,216].

6. Conclusions

Rheumatologists' ability in treating chronic inflammatory arthritis has mutually ameliorated in recent years along with the advent of new drugs and with growing experience in the use of largely available bDMARDs. However, the availability of different drugs with different modes of actions raises significant questions, in particular regarding the choice of the correct drug for the correct patient and the possible existence of different inflammatory pathways activated in various degree across different tissues and varying from subject to subject. Poor evidence is actually available supporting the choice of different drugs tailored on patients' biological or disease-specific features. A recent study by Miyagawa and co-workers [217] directly compared two different treatment strategies. Before starting treatments for active PsA, the authors performed peripheral blood lymphocyte analysis by flow-cytometry and depicted phenotypic characterization of circulating T cells. Patients with higher Th-1 status received ustekinumab, while those with higher Th-17 were treated with secukinumab. TNFi or secukinumab were given if both Th-1 and Th-17

were enhanced, while only TNFi when both were down-expressed. This tailored approach with specific interventions based on distinct T cells phenotypes resulted in higher clinical effectiveness compared with conventional treatment approach, in which no relevant biologics-dependent treatment decision was made. This finding, in parallel with a relevant body of literature that aims at identifying relevant genetic, synovial, skin, serum biomarkers, opens interesting scenarios in the treatment of this condition. There is great expectation to proceed towards personalized medicine, with the final aim to give the right drug to the right patient in the right moment, and with the hope to avoid, as possible, undesired side effects and time consumptions.

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