Abstract: Psoriatic arthritis (PsA) is a heterogeneous chronic inflammatory disease with a broad clinical spectrum and variable course. It can involve musculoskeletal structures as well as skin, nails, eyes, and gut. The management of PsA has changed tremendously in the last decade, thanks to an earlier diagnosis, an advancement in pharmacological therapies, and a wider application of a multidisciplinary approach. The commercialization of tumor necrosis factor inhibitors (adalimumab, certolizumab pegol, etanercept, golimumab, and infliximab) as well as interleukin (IL)-12/23 (ustekinumab) and IL-17 (secukinumab) inhibitors is representative of a revolution in the treatment of PsA. No evidence-based strategies are currently available for guiding the rheumatologist to prescribe biological drugs. Several international and national recommendation sets are currently available with the aim to help rheumatologists in everyday clinical practice management of PsA patients treated with biological therapy. Since no specific biological agent has been demonstrated to be more effective than others, the drug choice should be made according to the available safety data, the presence of extra-articular manifestations, the patient’s preferences (e.g., administration route), and the drug price. However, future studies directly comparing different biological drugs and assessing the efficacy of treatment strategies specific for PsA are urgently needed.

Keywords: psoriatic arthritis, treatment, biological drugs, TNF inhibitors, ustekinumab, secukinumab

Introduction
Psoriatic arthritis (PsA) is a heterogeneous chronic inflammatory disease with a broad spectrum of clinical features and courses.1 In order to underline the great heterogeneity of clinical manifestations and the importance of each feature in therapeutic strategies, the term “psoriatic disease” has been proposed.2 PsA manifestations can involve not only musculoskeletal structures (joints, entheses, synovial sheaths of tendons, axial skeleton), together with the skin and nails, but also gut and eyes.3–5 In addition, in patients with PsA or psoriasis there is a higher risk of obesity, insulin resistance, type 2 diabetes, metabolic syndrome, hypertension, hyperlipidemia, and cardiovascular disease than in the general population.6 In the past, PsA was considered a mild disease. On contrary, in the last decades, much attention has been paid to the erosive and deforming features of PsA (40%–60% of patients), which are often the cause of diminished quality of life (QoL) and functional impairment.7–9

PsA treatment, quite insufficient until some years ago, has been impressively improved in the last 3 half-decades. Thanks to a better understanding in PsA...
pathogenesis, new biotechnological drugs have been developed. Such drugs are able to ameliorate signs and symptoms of inflammation as well as to inhibit joint damage in peripheral joints with an improvement in QoL and functional status. Therefore, it is now possible to efficaciously modify the course of the disease. The current therapeutic goals consist of obtaining the remission of symptoms and preventing the appearance of damage in the early stage of PsA or blocking PsA progression in the established cases.

In order to help rheumatologists in everyday clinical practices, several international and national recommendation sets have been developed for PsA management, such as Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) and European League Against Rheumatism (EULAR) recommendations, all of them suggesting that biological drugs therapies should be reserved for patients with active disease refractory to conventional synthetic drugs or expected to have poor prognosis. Definitions of active disease vary but they generally include more than 1 tender and inflamed joint and/or tender enthesis point and/or dactylitis and/or presence of inflammatory back pain.

**Current non-biological pharmacological treatment**

The main non-biological pharmacological treatment categories for PsA are nonsteroidal anti-inflammatory drugs (NSAIDs), corticosteroids, and conventional synthetic disease-modifying antirheumatic drugs (csDMARDs).

NSAIDs are used as symptomatic drugs since they do not seem to have effects in preventing joint destruction progression. They are mainly used in mild forms of peripheral arthritis, enthesitis, and dactylitis, while they have no effects on psoriasis. Corticosteroids can be used both as local injection (especially in monoarthritis or oligoarthritis, dactylitis, or enthesitis) and orally, although their systemic use is not supported by evidence. Routine use of systemic corticosteroids is not recommended, but some patients require corticosteroids for rescue therapy. In these cases, clinicians should pay attention due to theoretical risk of rebound/worsening of psoriasis on withdrawal of the drug.

csDMARDs are used in peripheral involvement, even if there is no evidence that they prevent or significantly decrease the evolution of structural joint damage. Their use for axial disease is not supported by evidence. Among csDMARDs, methotrexate (MTX), leflunomide (LEF), cyclosporine (CsA), and sulfasalazine (SSZ) are used. MTX, LEF, and CsA have effects both on musculoskeletal and cutaneous diseases, whereas SSZ has effect on arthritis only. Their use in mild disease is preferred because of their low cost.

Apremilast, a new targeted synthetic DMARDs, is a phosphodiesterase 4 inhibitor inducing the suppression of several inflammation mediators including interleukin (IL)-2, IL-12, interferon-γ, tumor necrosis factor (TNF)-α, and inducible nitric oxide synthase. It is given orally at the dose of 30 mg twice a day. Its efficacy and safety in PsA have been evaluated through 4 multicentric, randomized trials compared to placebo in patients who have failed other biological drugs (PALACE1, PALACE2, PALACE3) or csDMARDs (PALACE4). At 52 weeks, results of the 4 trials showed efficacy of apremilast in peripheral arthritis, enthesitis, dactylitis, and functional impairment. Apremilast has been recently approved by both the United States Food and Drug Administration (FDA) and European Medicines Agency (EMA) for the treatment of active PsA patients.

**Biological drugs**

The development of biological agents have opened new horizons since it is now possible to better control signs and symptoms of inflammation, improve QoL and functional status, and inhibit the progression of structural damage in peripheral joints. The biological agents available for PsA treatment include anti-TNF-α (etanercept [ETN], infliximab [INF], adalimumab [ADA], golimumab [GOL], and certolizumab pegol [CZP]; INF and ETN biosimilars), anti-IL-17 (secukinumab [SEC]) and anti-IL-12/23 (ustekinumab [UST]) (Tables 1 and 2).

INF is a chimeric (mouse-human) monoclonal antibody that binds both to soluble and membrane-bound TNF-α. It is given intravenously at a dosage of 5 mg/kg body weight over a period of at least 2 hours at weeks 0, 2, and 6 and every 6–8 weeks thereafter. INF efficacy has been mainly evaluated in the IMPACT 2 trial enrolling 200 patients with active PsA despite the use of previous csDMARDs or NSAIDs. At week 24, compared with placebo, INF-treated patients had significantly better response rates for ACR 20 (54% vs 16%), Psoriatic Arthritis Response Criteria (PsARC) (70% vs 32%), and Psoriasis Area and Severity Index (PASI) 75 (60% vs 1%), and there was an improvement in dactylitis (12% vs 34%) and enthesopathy (20% vs 37%) too. Moreover, disability and QoL measures were also significantly improved. INF was generally well tolerated, with a similar incidence of adverse events in each group. Long-term safety was confirmed by a 2-year study showing serious adverse events in 5% of the patients. At week 54, INF was able to inhibit radiographic progression as measured by PsA-modified Sharp (mean changes from baseline score were −0.94 in the INF group and +0.53 in the placebo group).
ETN is a soluble TNF receptor p75-IgG1 fusion protein. It is given subcutaneously, either as a single 50 mg weekly dose or as two 25 mg doses. ETN efficacy in PsA has been assessed by Mease et al in a trial enrolling 205 patients with active PsA despite previous use of NSAIDs. A significant improvement was observed in patients treated with ETN compared to placebo for ACR 20 (59% vs 15%) and PsARC (72% vs 31%) at 12 weeks, and for PASI 75 (23% vs 3%) at 24 weeks. Health Assessment Questionnaire (HAQ) decreased significantly in the ETN group. A good response was also obtained in inhibiting radiographic disease progression: at 12 months, the mean annualized rate of change in the modified Sharp score was −0.03 in the ETN group compared with +1.00 in the placebo group. ETN was well tolerated without substantial differences in frequency of adverse events and infections compared to placebo. Efficacy and safety of ETN have been confirmed in several open long-term studies.

ADA is a fully human anti-TNF-α monoclonal antibody. It is administered subcutaneously at the dosage of 40 mg every other week. ADEPT trial assessed its efficacy in PsA patients with moderately to severely active disease despite the use of previous NSAIDs. At 24 weeks, significant data were obtained for ACR 20 (57% vs 15%), PsARC (60% vs 23%), and PASI 75 (59% vs 1%) compared with placebo, as well as disability and QoL measures. ADA was well tolerated with a similar incidence of adverse events and infections in the placebo group. Such data were confirmed by a 2-year open-label extension study. As far as radiographic progression is concerned, at week 48 the mean change from baseline in the modified Sharp score was 0.1 in patients receiving ADA and 1.0 in those receiving placebo for 24 weeks followed by ADA for 24 weeks.

### Table 1 Biological drugs currently licensed for PsA

<table>
<thead>
<tr>
<th>Molecule</th>
<th>Mechanism of action</th>
<th>Route</th>
<th>Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infliximab</td>
<td>Chimeric monoclonal antibody against TNF-α</td>
<td>IV</td>
<td>5 mg/kg at weeks 0, 2, and 6–8 weeks</td>
</tr>
<tr>
<td>Etanercept</td>
<td>Soluble TNF receptor p75-IgG1 fusion protein</td>
<td>SC</td>
<td>50 mg/week</td>
</tr>
<tr>
<td>Adalimumab</td>
<td>Fully human anti-TNF-α monoclonal antibody</td>
<td>SC</td>
<td>40 mg every 2 weeks</td>
</tr>
<tr>
<td>Golimumab</td>
<td>Fully human IgG1 anti-TNF-α antibody</td>
<td>SC</td>
<td>50 mg/month</td>
</tr>
<tr>
<td>Certolizumab pegol</td>
<td>Fab fragment of anti-TNF-α monoclonal antibody</td>
<td>SC</td>
<td>400 mg at 0, 2, 4 weeks and then 200 mg every 2 weeks</td>
</tr>
<tr>
<td>Ustekinumab</td>
<td>Fully human IgG1 monoclonal antibody against the shared P40 subunit of human IL-12 and IL-23</td>
<td>SC</td>
<td>45 mg at weeks 0 and 4 and every 12 weeks (90 mg if weight &gt;100 kg)</td>
</tr>
<tr>
<td>Secukinumab</td>
<td>Monoclonal antibody against IL-17A</td>
<td>SC</td>
<td>150 (or 300) mg at weeks 0, 1, 2, 3, and 4 every 2 weeks or directly 150 mg/month</td>
</tr>
</tbody>
</table>

**Abbreviations:** PsA, psoriatic arthritis; TNF, tumor necrosis factor; IV, intravenous; SC, subcutaneous; IL, interleukin.

### Table 2 Currently approved biological drugs for PsA: efficacy data from registrative trials

<table>
<thead>
<tr>
<th>Molecule</th>
<th>PASI 75 (at week 24)</th>
<th>ACR 20 (at week 24)</th>
<th>ACR 50 (at week 24)</th>
<th>ACR 70 (at week 24)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infliximab (5 mg/kg weekly)</td>
<td>60% (1%)</td>
<td>54% (16%)</td>
<td>41% (4%)</td>
<td>27% (2%)</td>
</tr>
<tr>
<td>(5 mg/kg at weeks 0, 2, 6, 14, and 22)</td>
<td>(15%)</td>
<td>(15%)</td>
<td>(6%) (1%)</td>
<td>(2%) (1%)</td>
</tr>
<tr>
<td>Adalimumab (25 mg twice weekly)</td>
<td>59% (3%)</td>
<td>57% (12%)</td>
<td>39% (6%)</td>
<td>23% (1%)</td>
</tr>
<tr>
<td>(40 mg every 2 weeks)</td>
<td>(1%)</td>
<td>(15%)</td>
<td>(6%) (1%)</td>
<td>(1%) (2%)</td>
</tr>
<tr>
<td>Golimumab (50 mg every 4 weeks)</td>
<td>56% (1%)</td>
<td>52% (12%)</td>
<td>– – (1%)</td>
<td>– – (1%)</td>
</tr>
<tr>
<td>(400 mg at weeks 0 and 2 and then 200 mg every 4 weeks)</td>
<td>62% (1%)</td>
<td>64% (1%)</td>
<td>44% (2%)</td>
<td>28% (2%)</td>
</tr>
<tr>
<td>Ustekinumab (300 mg/kg monthly)</td>
<td>57% (1%)</td>
<td>42% (15%)</td>
<td>25% (2%)</td>
<td>12% (2%)</td>
</tr>
<tr>
<td>(45 mg at weeks 0 and 4 and then every 12 weeks)</td>
<td>(15%)</td>
<td>(3%) (9%)</td>
<td>(2%) (1%)</td>
<td>(1%) (2%)</td>
</tr>
<tr>
<td>Secukinumab (150 mg at weeks 0, 1, 2, 3, and 4 and every 4 weeks)</td>
<td>48% (1%)</td>
<td>51% (15%)</td>
<td>35% (7%)</td>
<td>21% (1%)</td>
</tr>
</tbody>
</table>

**Notes:** The percentages within the brackets refer to the related placebo values. *At week 12. Data are only presented for an illustrative purpose but not for a direct comparison.

**Abbreviations:** PsA, psoriatic arthritis; PASI, Psoriasis Area and Severity Index; ACR, American College of Rheumatology improvement criteria.
GOL is a fully humanized IgG1k anti-TNF-α given by monthly subcutaneous injection (50 mg every month). Its efficacy in PsA was assessed through GO-REVEAL trial showing a significant improvement of ACR 20 (GOL 100 mg 61%, GOL 50 mg 52%, placebo 12%), PsARC (GOL 100 mg 85%, GOL 50 mg 70%, placebo 29%), and PASI 75 (GOL 100 mg 66%, GOL 50 mg 56%, placebo 1%) at week 24. Significant improvement was observed for other major secondary endpoints including HAQ, 36-Item Short Form Health Survey (SF-36), Nail Psoriasis Severity Index, and PsA-modified Maastricht Ankylosing Spondylitis Enthesitis Score. GOL was generally well tolerated in this trial. Moreover, an inhibition of joint damage was observed in comparison with placebo at week 52.

CZP is a humanized anti-TNF monoclonal antibody Fab fragment. Because lacking the Fc portion of the immunoglobulin, CZP does not induce any Fc- receptor-mediated immune effects such as complement or antibody-ependent cell-mediated cytotoxicity. It is able to neutralize membrane TNF-α monovalently rather than divallynt. CZP is pegylated so that its half-life is longer (14 days) and stability and solubility are increased, whereas its immunogenicity is reduced. It is given subcutaneously with a starting dose of 400 mg at weeks 0, 2, and 4 and then 200 mg every other week. CZP efficacy in PsA has been evaluated through a multicentric, randomized, double-blind randomized controlled trial (RCT) (RAPID-PsA) showing a significant improvement in ACR 20 (CZP 400 mg Q4W 56%, CZP 200 mg Q2W 64%, placebo 24%), PASI 75 (CZP 400 mg Q4W 61%, CZP 200 mg Q2W 62%, placebo 15%) and an improvement in disability and QoL measures at week 24. No differences in adverse events when compared to placebo were found. With regard to radiographic progression, at week 24 the mean change from baseline mTSS score was 0.06 in patients receiving CZP and 0.28 in those receiving placebo.

UST is a fully human IgG1 monoclonal antibody that binds with high affinity to the shared p40 subunit of human IL-12 and IL-23, inhibiting their binding to the IL-12Rβ1 receptor on the surface of T cells, NK cells, and antigen-presenting cells (APCs). Since 2009, it has been used for treating moderate-to-severe psoriasis, and it has been recently approved for PsA. It is given subcutaneously with a starting dose of 45 mg (or 90 mg if weight >100 kg) at weeks 0 and 4 and then 45 mg every 12 weeks. Its safety and efficacy have been evaluated in 2 multicentric, double-blind, placebo-controlled trials (PSUMMIT 1 and PSUMMIT 2). The first trial enrolled patients naive to biological therapy, the second one also included patients who failed anti-TNF-α agents. TNF-α agents. At week 24, there was a significant improvement in ACR 20 in PSUMMIT 1 (UST 90 mg 50%, UST 45 mg 42%, placebo 23%) as well as in PSUMMIT 2 (UST 90 mg 44%, UST 45 mg 44%, placebo 20%). A following study integrated data from PSUMMIT 1 and PSUMMIT 2 showing an inhibition of radiographic progression.

SEC is a human monoclonal antibody targeted against IL-17A. Initially approved for psoriasis treatment, it has recently been approved for PsA. The efficacy of SEC in PsA has been investigated in 2 randomized, double-blind, placebo-controlled multinational phase III trials, FUTURE 1 and FUTURE 2. In the first, SEC was given at beginning intravenously and then subcutaneously. In FUTURE 2, patients were treated with subcutaneous SEC since the beginning of trial. At week 24, both trials showed an improvement in ACR 20 (FUTURE 1, SEC 150 mg 50%, SEC 75 mg 50%, placebo 17%; FUTURE 2, SEC 300 mg 54%, SEC 150 mg 51%, placebo 15%), PASI 75 (FUTURE 1, SEC 150 mg 61%, SEC 75 mg 65%, placebo 8%; FUTURE 2, SEC 300 mg 63%, SEC 150 mg 48%, placebo 16%), as well as HAQ and SF-36. Pooled data (SEC 75, 150, and 300 mg) from FUTURE 2 study showed resolution of dactylitis (47% vs 15% of placebo) and enthesitis (40% vs 22% of placebo). SEC effects seemed to be greater in patients naïve to other biological treatments. Radiological progression was considered only in FUTURE 1: at week 24, SEC-treated patients showed significantly less radiographic progression than placebo. SEC was well tolerated, and the most common reported adverse events were mild to moderate, non-serious infections. Exacerbation of inflammatory bowel disease as well as new onset has been reported during treatment with SEC. Therefore, patients should be monitored for bowel signs and symptoms and caution should be exercised in patients with Crohn’s disease.

Pharmacoeconomic issues and biosimilars

Biosimilars to INF (CT-P13, Remsima and Inflectra) and ETN (SB4, Benepali) are currently licensed for PsA treatment. Although their impact on rheumatic diseases has been remarkable, biological drugs are a very large financial burden for payers. Since a number of patents pertaining to certain biological drugs are expiring, there is a growing interest in developing biosimilar agents. However, it is expected that the decline of biological originator therapies will not be as strong as that given by the introduction of generics for brand synthetic drugs.

According to the World Health Organization, a biosimilar is a “biotherapeutic product which is similar in terms of quality, safety, and efficacy to an already licensed reference
B-cell targeting agents, tyrosine kinase inhibitors) are under evaluation. Several drugs with different mechanisms of action (cytokine blockers, Janus kinase inhibitors, tyrosine kinase inhibitors, as well as small molecule drugs) are quite easy to synthesize, that act by interrupting the intracellular signaling based on the inhibition of kinases. They are low molecular mass compounds that can be demonstrated. Small molecule drugs are low molecular mass compounds that act by interrupting the intracellular signaling based on the inhibition of kinases. They are quite easy to synthesize, not so expensive, and orally bioavailable. Among them are Janus kinase inhibitors, tyrosine kinase inhibitors, as well as the p38 mitogen-activated protein kinase pathway inhibitors.

**Choice of biologicals**

All TNF-α blockers have been studied in RCTs and in observational postmarketing studies with consistent evidence supporting their safety and efficacy in PsA. A systematic review by Ash et al evaluated efficacy and safety of ADA, INF, GOL, and ETN. At 12–14 weeks, there were no significant differences in efficacy and safety among different anti-TNF-α agents and all the 4 drugs were significantly more effective than placebo for PsARC; ACR 20, 50, and 70 response criteria; and PASI as well as for dactylitis and enthesitis. Moreover, an improvement in QoL was observed. Similarly to that observed in rheumatoid arthritis, PsA safety data underline that TNF inhibitors can be associated with an increased infectious risk (bacterial, viral, fungal, and mycobacterial) requiring careful monitoring. Moreover, TNF-α blockers are the first drugs whose efficacy on radiographic progression has been clearly demonstrated. Anti-TNF-α drugs have been compared in a single randomized non-blinded study involving 100 patients with PsA and in 2 indirect comparison meta-analyses showing that significant differences in their effectiveness cannot be demonstrated.

To date, there is no RCT trial aimed to assess efficacy on manifestations different from peripheral joint involvement. Only 1 observational study reported on the effect of ETN in 32 patients with axial PsA showing, after a 12-month treatment, a significant improvement of Bath Ankylosing Spondylitis Disease Activity Index and Bath Ankylosing Spondylitis Functional Index. Dactylitis and enthesitis were evaluated as secondary endpoints in some RCTs on GOL and INF showing a significant improvement.
Because of a substantial similarity in efficacy and safety among different anti-TNF-α drugs, the drug choice is taken considering specific safety issues, extra-articular manifestations, and patient’s preference. Indicatively, in patients with bowel or eye involvement, a monoclonal antibody is preferred, whereas in those at risk of tuberculosis ETN is the safer option.

As previously discussed, PsA is a heterogeneous disease with several clinical manifestations. To assist the clinician in the management of PsA, treatment recommendations have been developed (EULAR, GRAPP). In agreement with these, we can have different therapeutic approaches according to the predominant clinical manifestation being present:

1. In peripheral arthritis, biological therapy should be considered in patients with peripheral synovitis not responsive to NSAIDs and csDMARDs. Patients with monoarthritis or oligoarthritis should have also failed steroid injections. The choice of biological drug should be also taken into account when patient develops new erosions or worsening of preexisting erosions.

2. In psoriatic spondylitis and/or sacroiliitis, biological drugs should be taken into consideration in patients who failed NSAIDs. As for ankylosing spondylitis, there are no evidence of efficacy for csDMARDs on axial PsA.

3. In dactylitis, the biological should be started in patients who failed NSAIDs and csDMARDs as well as steroid injections.

4. In enthesitis, biological treatment should be considered in patients who failed NSAIDs and steroid injections.

**Biological switch**

Currently, there are very few data about therapy in case of anti-TNF-α failure. With regard to switch from a TNF-α inhibitor to another in PsA, there are very poor data. However, in clinical practice, switching from an anti-TNF-α to another is a successful strategy. Gossec and Smolen, based on the EULAR and GRAPP recommendations, suggest that every biological drug and/or csDMARDs can be used after biological failure. As for switch from an TNF inhibitor to another, it is currently accepted that patients who failed a previous anti TNF-α may successfully response to another. Moreover, patients with a good clinical and laboratory response but with radiological progression have to be switched to another biological agent or co-treated with a csDMARD. However, there is no evidence of increased efficacy of anti-TNF-α therapy by using csDMARDs, and studies results are quite in contrast on their effects on prolonging anti-TNF-α survival.

With regard to switching to another mode of action, data are limited to SEC and UST trials. In these studies, response to the drug was considered both in patients naive to anti-TNF agents and in those who failed such treatment. Efficacy in anti-TNF failures has been tested in PSUMMIT 2 for UST and in FUTURE 2 for SEC. Both the trials confirm their efficacy both in TNF-naive patients and in those previously treated.

**Conclusion**

The PsA treatment scenario has completely changed with the introduction of biological agents, which are more effective than csDMARDs on symptoms and signs of the disease, improve function and QoL, and inhibit the structural damage in peripheral joints.

No evidence-based strategies are currently available for guiding the rheumatologist to prescribe biological drugs. A conservative approach should suggest their use after the failure of csDMARDs but early PsA may be treated with a delay making less useful the advantage of an early recognition of the disease. In authors’ opinion, a more efficacious intervention with biological agents at an early stage, when tissue injury may still be reversible, could result in a great benefit for the patient. However, one of possible criticisms to this approach is the heterogeneous clinical spectrum of PsA, which includes self-limiting forms.

Several international and national recommendation sets are currently available with the aim to help rheumatologists in everyday clinical practice management of PsA patients treated with biological therapy. These treatment recommendations suggest that biological agents, preferentially TNF blockers, should be reserved for patients with active disease with different starting modalities according to the pattern of presentation of the psoriatic disease, i.e., peripheral arthritis, enthesitis, dactylitis, and axial disease.

To date, there are no direct head-to-head RCTs comparing biological agents. Since no specific biological agent has been demonstrated to be more effective than others, the drug choice should be made according to the available safety data, the presence of extra-articular manifestations, the patient’s preferences (e.g., administration route), and the drug price. However, future studies directly comparing different biological drugs and assessing the efficacy of treatment strategies specific for PsA are urgently needed.

**Disclosure**

The authors report no conflicts of interest in this work.
References


