An Italian shared dermatological and rheumatological proposal for the use of biological agents in psoriatic disease

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Abstract

Background As psoriatic disease (PD) is a condition characterized by the combination of inflammatory skin (psoriasis) and osteo-articular manifestations (psoriatic arthritis), its treatment should cover both its clinical components.

Objective The objective of this study was to propose a flexible framework for the use of biological agents in PD.

Methods The proposal was drawn up by a group of dermatologists and rheumatologist expert in PD and was based on existing evidence and personal opinion.

Results The three TNF-α inhibitors (adalimumab, etanercept, infliximab) are effective in all of the psoriatic manifestations and should be used in the case of moderate/severe disease refractory to systemic treatment with non-biological drugs. We propose the following definitions of moderate/severe disease: PASI > 10 or BSA > 10 or DLQI > 10 for plaque-psoriasis; BSA ≥ 10 or DLQI ≥ 10 for the other psoriatic skin lesions; DLQI ≥ 10 or meaningful values of the NAPSI or mNAPSI for psoriatic nail involvement; ≥ 1 inflamed joint + patient global VAS ≥ 34 + physician’s judgement or arthritic joint deformities or radiographic joint damage plus ≥ 5 inflamed small joints or ≥ 1 large joints for peripheral joint involvement; ≥ 1 digit with dactylitis and ≥ 1 enthesitic sites + patient global VAS ≥ 34 + physician’s judgement for dactylitis and enthesitis. BASDAI ≥ 4 + physician’s judgement for spondylitis; recurrent flares or risk of developing irreversible damage for uveitis. Other assessment instruments can be used if the physician is more familiar with them and if they have been validated.

Conclusion We provide a shared dermatological and rheumatological proposal for the use of biological agents in PD.

Keywords
adalimumab, etanercept, infliximab, psoriasis, psoriatic arthritis

Conflict of interest
None declared.

Introduction

The huge variety of extension, type and severity of lesions typical of psoriatic disease (PD) makes its treatment a highly challenging task. Traditionally, PD is treated by dermatologists or rheumatologists, both with a vision limited to the respective field of competence. Dermatologists are often not aware of mild concomitant arthritis and do not seem to treat severe arthritis in the proper way. On the other hand, rheumatologists do not seem to pay right attention to the skin involvement.
Three agents targeting the tumour necrosis factor-α (TNF-α) (infliximab, etanercept and adalimumab) are the only biological agents currently available in Europe for the therapy of PD. However, several other biological therapies for the treatment of this condition have been studied and are likely to be commercialized soon.

Guidelines for the treatment of psoriasis (Ps) and psoriatic arthritis (PsA) have been published recently and recommendations for the use of biological agents in Ps and PsA have been suggested independently by Dermatological and Rheumatological Societies. To provide a therapeutic approach to the psoriatic patient as a whole, we present a conjunct dermatological and rheumatological proposal for the use of biological agents in the treatment of PD in adult patients.

Methods
The proposal presented in this study was framed by five dermatologists and six rheumatologists, experts in Ps and PsA respectively, through the following steps: definition of the unifying concept of PD, literature research and evaluation, first draft of the proposal, collegial evaluation and discussion of the first draft to find consensus, and final version of the manuscript. A thorough literature research on the treatment of Ps and PsA has already been performed by the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) and published in 2006. A further review of the literature concerning the use of biological agents in Ps and PsA published since 2005 was carried out. The final proposal was based on both evidence-based medicine and expert opinion but was not validated in a clinical context.

Biological therapies for PD
The three TNF-α inhibitors commercially available in Europe have been licensed for the treatment of both Ps and PsA. Several other biological agents have been studied in PD. The efficacy results of the most relevant randomized controlled trials (RCTs) of these drugs are reported in Tables 1 and 2.

Adalimumab. Adalimumab is a recombinant, fully human IgG1 monoclonal antibody specific for human TNF-α. Its recommended dose is 40 mg subcutaneously every other week. This drug was significantly more effective than placebo in improving joint inflammation and skin involvement and in inhibiting radiographic joint progression (level 1B, grade A). Dactylitis was shown to improve more in adalimumab than in placebo-treated patients, but the difference was not statistically significant. No data about the efficacy of this drug in enthesitis and axial involvement were reported. However, in ankylosing spondylitis (AS), adalimumab was better than placebo in improving both spine inflammation and enthesitis (level 1B, grade A).

Etanercept. Etanercept is a fusion protein consisting of the extracellular ligand-binding portions of two human TNF receptors and the Fc portion of a human IgG1 antibody. TNF-α bound to etanercept is functionally inactive. Its recommended dose is 50 mg twice a week subcutaneously for 12 weeks followed by a dose reduction to 25 mg twice weekly in Ps, and 25 mg twice a week or 50 mg weekly in PsA. Etanercept was significantly more effective than placebo in reducing joint inflammation and radiographic progression (level 1B, grade A). Spondylitis, dactylitis and enthesitis were not evaluated in the PsA studies. In AS RCTs, etanercept was significantly more effective than placebo in improving these clinical manifestations (level 1B, grade A). Etanercept was significantly effective in improving psoriatic skin lesions in a dose-dependent fashion (level 1B, grade A). For Ps, but not for PsA, the current European label requires etanercept discontinuation after 24 weeks. However, retreatment is safe and effective.

Infliximab. Infliximab is a chimeric (Fc portion of human IgG1 plus Fab murine binding portion) monoclonal antibody, which inhibits both soluble and receptor-bound TNF-α and mediates lysis of the TNF-producing cells. Its recommended dose in Ps and PsA is 5 mg/kg intravenously at 0, 26 weeks and then every 8 weeks. Infliximab was significantly superior to placebo in improving joint inflammation, dactylitis, enthesitis and skin manifestation (level 1B, grade A). Radiographic progression was also significantly less in infliximab-treated patients (level 1B, grade A). Like adalimumab and etanercept, data on the effects of infliximab on spondylitis came from the AS trials, where this drug significantly improved all of the measures of spine inflammation (level 1B, grade A).

However, in Ps, infliximab was significantly more effective than placebo and significantly more effective than placebo in improving peripheral joint inflammation and skin involvement (level 1B, grade A), with a tolerability profile comparable with that of placebo. In addition, golimumab was effective on dactylitis and enthesitis. Ustekinumab, a human anti-p40 IL-12/23 monoclonal antibody, was extensively studied in both Ps and PsA. In a PsA RCT, this drug, administered at the dose of 63 or 90 mg once a week, was significantly more effective than placebo in decreasing the number of inflamed joints and was well-tolerated (level 1B, grade A). In two large Ps RCTs, this agent at the dose of 45 or 90 mg given subcutaneously with different time regimens, was significantly superior to placebo in reducing skin involvement (level 1B, grade A). The rate and pattern of adverse events were the same in the treated and control patients. In the following cross-over phases of these two studies, the efficacy of ustekinumab...
| Drug – trial name, if available (trial duration) | Molecule | Dose | Disease | ACR20 | ACR50 | ACR70 | Progression (Sharp score) | Dactylitis | Enthesitis | Spondylitis | PASI75 | Ref. |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Adalimumab ADEPT (week 24) | Human anti-TNF-α monoclonal antibody | 40 mg/eow | PsA | 57%* | 39%* | 23%* | -0.2 (week 24)* | Improv. | NE | NE | 59%* | 15 |
| Adalimumab (week 12) | Human anti-TNF-α monoclonal antibody | 80 mg loading dose, 40 mg/eow | Ps | NE | NE | NE | NE | NE | NE | NE | 53%* | 16 |
| | | 80 mg/week for 2 weeks, 40 mg/week | | | | | | | | | 80%* | 16 |
| Etanercept (week 12) | TNF-α receptor (fusion protein) | 25 mg/twice weekly | PsA | 73%* | 50%* | 13%* | NE | NE | NE | NE | 26%* | 18 |
| Etanercept (week 12) | TNF-α receptor (fusion protein) | 25 mg/twice weekly | PsA | 59%* | 39%* | 11%* | -0.03 (month 12)* | NE | NE | NE | 23%* | 19 |
| Etanercept (week 12) | TNF-α receptor (fusion protein) | 25 mg/twice weekly | Ps | NE | NE | NE | NE | NE | NE | NE | 34%* | 22 |
| Etanercept (week 12) | TNF-α receptor (fusion protein) | 50 mg/twice weekly | Ps | NE | NE | NE | NE | NE | NE | NE | 50%* | 23 |
| Infliximab IMPACT (week 16) | Chimeric anti-TNF-α monoclonal antibody | 5 mg/kg @ 0, 2, 6 and every 8 weeks | PsA | 65%* | 46%* | 29%* | NE | 85% improv. in score* | -11% pts from bsl* | NE | 75%* | 24 |
| Infliximab IMPACT2 (week 14) | Chimeric anti-TNF-α monoclonal antibody | 5 mg/kg @ 0, 2, 6 and every 8 weeks | PsA | 59%* | 36%* | 15%* | -0.70 (week 24)* | -12% pts from bsl* | -12% pts from bsl* | NE | 64%* | 25, 29 |
| Infliximab (week 10) | Chimeric anti-TNF-α monoclonal antibody | 3 mg/kg @ 0, 2, 6 and every 8 weeks | Ps | NE | NE | NE | NE | NE | NE | NE | NE | 72%* | 28 |
| | | 5 mg/kg @ 0, 2, 6 and every 8 weeks | | | | | | | | | 88%* | 28 |

*Significantly statistically different from placebo.
Ps, psoriasis; PsA, psoriatic arthritis; ACR20, 50, 70: 20, 50, 70% improvement according to American College of Rheumatology response criteria; PASI, Psoriasis Activity and Severity Index; NE, not evaluated.
Table 2  Efficacy data of other biological drugs tested in Ps and PsA (from phase II-III RCTs) but not licensed in Europe

<table>
<thead>
<tr>
<th>Drug – trial name, if available (trial duration)</th>
<th>Molecule</th>
<th>Dose</th>
<th>Disease</th>
<th>ACR20</th>
<th>ACR50</th>
<th>ACR70</th>
<th>Progression (Sharp score)</th>
<th>Dactylitis</th>
<th>Enthesitis</th>
<th>Spondylitis</th>
<th>PASI75</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Golimumab GO-REVEAL (14 weeks)</strong></td>
<td>Human anti-TNF-α monoclonal antibody</td>
<td>50 mg q4 weeks</td>
<td>PsA</td>
<td>51%*</td>
<td>~31%*</td>
<td>~15%*</td>
<td>NE</td>
<td>Improvement in score</td>
<td>−20% pts from bsl*</td>
<td>NE</td>
<td>40%*</td>
<td>31</td>
</tr>
<tr>
<td></td>
<td></td>
<td>100 mg q4 weeks</td>
<td>PsA</td>
<td>45%*</td>
<td>~29%*</td>
<td>~18%*</td>
<td>100% score improvement*</td>
<td>−18% pt from bsl*</td>
<td>NE</td>
<td>58%*</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Ustekinumab (12 weeks)</strong></td>
<td>Human anti-p40 IL-12/23 monoclonal Ab</td>
<td>63 or 90 mg once weekly</td>
<td>PsA</td>
<td>45%*</td>
<td>22%*</td>
<td>11%*</td>
<td>NE</td>
<td>−5% pts from bsl</td>
<td>−22% from bsl*</td>
<td>NE</td>
<td>52%*</td>
<td>32</td>
</tr>
<tr>
<td><strong>Ustekinumab PHOENIX1 (12 weeks)</strong></td>
<td>Human anti-p40 IL-12/23 monoclonal antibody</td>
<td>45 mg at week 0 and 4, and every 12 weeks</td>
<td>Ps</td>
<td>NE</td>
<td>NE</td>
<td>NE</td>
<td>NE</td>
<td>NE</td>
<td>NE</td>
<td>NE</td>
<td>63.9%*</td>
<td>33</td>
</tr>
<tr>
<td></td>
<td></td>
<td>90 mg at week 0 and 4, and every 12 weeks</td>
<td>Ps</td>
<td>NE</td>
<td>NE</td>
<td>NE</td>
<td>NE</td>
<td>NE</td>
<td>NE</td>
<td>NE</td>
<td>63.3%*</td>
<td></td>
</tr>
<tr>
<td><strong>Ustekinumab PHOENIX2 (12 weeks)</strong></td>
<td>Human anti-p40 IL-12/23 monoclonal antibody</td>
<td>45 mg at week 0 and 4, and every 12 weeks</td>
<td>Ps</td>
<td>NE</td>
<td>NE</td>
<td>NE</td>
<td>NE</td>
<td>NE</td>
<td>NE</td>
<td>NE</td>
<td>67.7*</td>
<td>34</td>
</tr>
<tr>
<td></td>
<td></td>
<td>90 mg at week 0 and 4, and every 12 weeks</td>
<td>Ps</td>
<td>NE</td>
<td>NE</td>
<td>NE</td>
<td>NE</td>
<td>NE</td>
<td>NE</td>
<td>NE</td>
<td>75.7*</td>
<td></td>
</tr>
<tr>
<td><strong>ABT-874 (12 weeks)</strong></td>
<td>Human anti-p40 IL-12/23 monoclonal antibody</td>
<td>200 mg x 1</td>
<td>Ps</td>
<td>NE</td>
<td>NE</td>
<td>NE</td>
<td>NE</td>
<td>NE</td>
<td>NE</td>
<td>NE</td>
<td>63%*</td>
<td>35</td>
</tr>
<tr>
<td></td>
<td></td>
<td>100 mg eow</td>
<td>Ps</td>
<td>NE</td>
<td>NE</td>
<td>NE</td>
<td>NE</td>
<td>NE</td>
<td>NE</td>
<td>NE</td>
<td>93%*</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>200 mg weekly (x4)</td>
<td>Ps</td>
<td>NE</td>
<td>NE</td>
<td>NE</td>
<td>NE</td>
<td>NE</td>
<td>NE</td>
<td>NE</td>
<td>90%*</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>200 mg eow</td>
<td>Ps</td>
<td>NE</td>
<td>NE</td>
<td>NE</td>
<td>NE</td>
<td>NE</td>
<td>NE</td>
<td>NE</td>
<td>93%*</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>200 mg weekly</td>
<td>Ps</td>
<td>NE</td>
<td>NE</td>
<td>NE</td>
<td>NE</td>
<td>NE</td>
<td>NE</td>
<td>NE</td>
<td>90%*</td>
<td></td>
</tr>
<tr>
<td><strong>Alefacept (24 weeks)</strong></td>
<td>Human LFA-3-IgG1 fusion protein</td>
<td>15 mg weekly + methotrexate</td>
<td>PsA</td>
<td>54%*</td>
<td>17%</td>
<td>7%</td>
<td>NE</td>
<td>NE</td>
<td>NE</td>
<td>NE</td>
<td>28%</td>
<td>36</td>
</tr>
<tr>
<td><strong>Alefacept (12 weeks)</strong></td>
<td>Human LFA-3-IgG1 fusion protein</td>
<td>0.025 mg/kg weekly</td>
<td>Ps</td>
<td>NE</td>
<td>NE</td>
<td>NE</td>
<td>NE</td>
<td>NE</td>
<td>NE</td>
<td>NE</td>
<td>21%*</td>
<td>37</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.075 mg/kg weekly</td>
<td>Ps</td>
<td>NE</td>
<td>NE</td>
<td>NE</td>
<td>NE</td>
<td>NE</td>
<td>NE</td>
<td>NE</td>
<td>31%*</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.150 mg/kg weekly</td>
<td>Ps</td>
<td>NE</td>
<td>NE</td>
<td>NE</td>
<td>NE</td>
<td>NE</td>
<td>NE</td>
<td>NE</td>
<td>33%*</td>
<td></td>
</tr>
</tbody>
</table>

*Significantly different from placebo.

Ps, psoriasis; PsA, psoriatic arthritis; ACR20, 50, 70: 20, 50, 70% improvement according to American College of Rheumatology response criteria; PASI, Psoriasis Activity and Severity Index; NE, not evaluated.
increased up to week 24 and was still present at week 40. Another human anti-p40 IL-12/23 monoclonal antibody, called ABT 784, at the doses of 100 or 200 mg given with different time regimens, was shown to be significantly more effective than placebo in improving plaque Ps.55 Alefacept, a human fusion protein of the lymphocyte function associated with antigen 3 and with the Fc of IgG1, given intravenously at 0.025, 0.075, and 0.150 mg/kg weekly, induced a significantly greater reduction in psoriatic skin lesions than placebo36 (level 1B, grade A). This drug administered at the dose of 15 mg weekly intramuscularly, in association with methotrexate, was also significantly more effective than placebo in decreasing the number of inflamed joints in PsA37 (level 1B grade A). In both the studies, the rate and type of adverse events were similar to that of placebo. Finally, two other drugs, abatacept, a co-stimulation blocker, and certolizumab pegol, a novel anti-TNF-α inhibitor, already used in rheumatoid arthritis, are currently being studied in PD. Abatacept has already shown significant efficacy in Ps.38

Emerging issues

Uveitis. Anterior uveitis is relatively common feature of PD, but there are no published studies dealing with this specific issue. Both infliximab and adalimumab have demonstrated significant efficacy in controlling uveitis associated with seronegative spondyloarthopathies39 (level 1B, grade A), but etanercept does not seem to prevent uveitis flares and recent data showed that this drug was associated with a significantly greater number of reported uveitis cases than infliximab and adalimumab.40–42

Cardiovascular risk. It is well known that PsA is associated with a higher risk of cardiovascular disease. The chronic inflammatory response typical of the autoimmune diseases is likely to accelerate the atherogenic process, which, in PD patients, is also enhanced by a higher rate of metabolic syndrome. Whether TNF-α blockers can reduce this risk in PD is yet to be proved.43

Induction or exacerbation of psoriasis by TNF-α blockers. Numerous reports on the induction or worsening of Ps in patients treated with TNF-α inhibitors have been published.44,45 A recently published literature review clearly shows that all of the three anti-TNF-α drugs can be responsible for this side-effect and that it can occur in virtually all of the conditions usually treated with these agents.46 Pustular and guttate lesions seem to be the most frequent type of anti-TNF-α-induced psoriatic manifestations.

Anti-TNF-α agent switching. The published RCTs showed that about 30–40% of the PsA patients and about 15–30% of the Ps patients did not respond to anti-TNF-α therapy (primary inefficacy). In addition, in the patients who respond to this therapy, both loss of efficacy (secondary inefficacy) and adverse events can occur and lead to drug discontinuation. Dose escalation (especially when using infliximab) and switching to another biological agent could be possible options for these patients. The observational studies dealing with this topic showed that switching to a second, and sometimes even to a third, TNF-α inhibitor was a successful strategy in the majority of the cases.77–80 However, no proper RCT on this topic has been published and the available data only provide weak evidence (level 3, grade C).

Moreover, in Ps patients, dose escalation and switching of biological agents may be a rescue treatment for difficult cases,51–54 but the level of evidence supporting this strategy is low (level 3, grade C).

Assessment measures for PD

Assessment of PsA. Both the Disease Activity Score and the ACR response criteria have been successfully used in RCTs to measure peripheral joint involvement of PsA.51 The core set of measures to be collected is as follows: number of tender (68 count) and swollen (66 count) joint, pain evaluation on a 100-mm Visual Analogue Scale (VAS), patient global evaluation of arthritis activity (10 cm-VAS), physician global evaluation of arthritis activity (10 cm-VAS), physical function as measured by the Disability Index of the Health Assessment Questionnaire, Quality of Life (QoL) as measured by a specific instrument such as the PsAQoL or generic instruments such as the Short Form-36, erythrocyte sedimentation rate and C-reactive protein.55,56 Number of joints with irreversible deformity and radiography of hands and feet and other involved joints should be used to assess joint damage.

To measure axial involvement, at least two subjective instruments should be used: the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) and the Bath Ankylosing Spondylitis Functional Index (BASFI).57 The Bath Ankylosing Spondylitis Metrology Index (BASMI), an objective measure of spine function, should only be used by physician familiar with it. The Ankylosing Spondylitis Quality of Life (ASQol) questionnaire can be reliably used to assess QoL in patients with AS-like involvement.58 Radiography of the spine should be taken to evaluate disease progression.

Several indices have been suggested for the evaluation of enthesal involvement and dactylitis, but they are mainly used in RCTs.59 At present, for daily practice, it is more practical to use a simple count of number of enthesic sites and digits with acute inflammation, the latter defined by the presence of both swelling and pain.

Assessment of Ps. A number of instruments are available to score Ps severity. For plaque-psoriasis, the most used are the PASI,60 the percentage of affected Body Surface Area (BSA),61 and the Psoriasis Global Assessment (PGA)70 (7-point scale from clear to severe). PASI and PGA are not useful in guttate and pustular psoriasis. Psoiatric palmoplantar pustular lesions should be scored using the Palmoplantar Pustular Psoriasis Area and Severity Index
(PPASAI)\(^62\) (score range 0–72) and nail involvement using the Nail Psoriasis Severity Index (NAPSI)\(^63\) (score range 0–80, finger nails only) or a modified version (mNAPSI)\(^64\) (score range 0–140, finger nails only) validated in PsA.

Quality of life in Ps patients can be measured by a number of different self-administered questionnaires. Although not specific for this condition, the Dermatology Life Quality Index (DLQI)\(^65\) is the most used; the Skindex-29\(^66\) and the Psoriasis Disability Index (PDI)\(^67\) are other reliable instruments to measure QoL in Ps patients.

### Table 3 Dermatological and rheumatological proposal for the use of anti-TNF-\(\alpha\) agents in moderate to severe PD

<table>
<thead>
<tr>
<th>Clinical manifestation</th>
<th>Definition of moderate/severe disease</th>
<th>Recommended therapy prior to anti-TNF use</th>
<th>Minimal acceptable response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plaque-psoriasis</td>
<td>PASI (\geq) 10 or BSA (\geq) 10 or DLQI (\geq) 10 or other validated instruments (PGA, LS-PGA, Skindex, PDI or others) reliably used by the individual physician</td>
<td>At least two systemic therapies (MTX, CyA, acitretin, phototherapy) alone or in combination</td>
<td>PASI75 (PASI50 in selected cases) or DLQI (&lt;) 5 if PASI not applicable: BSA or other validated instruments (LS-PGA, PGA, Skindex, PDI or others) reliably used by the individual physician (threshold of improvement not available for all)</td>
</tr>
<tr>
<td>Other cutaneous psoriatic changes</td>
<td>BSA (\geq) 10 or DLQI (\geq) 10 or other validated instruments (PPASAI in PPP, PGA, LS-PGA, Skindex, PDI or others) reliably used by the individual physician</td>
<td>At least two systemic therapies (MTX, CyA, acitretin, phototherapy) alone or in combination</td>
<td>BSA (&lt;) 3 or DLQI (&lt;) 5 or other validated instruments (PPASAI in PPP, PGA, LS-PGA, Skindex, PDI or others) reliably used by the individual physician (threshold of improvement not available for all)</td>
</tr>
<tr>
<td>Nail psoriatic involvement</td>
<td>NAPSI (threshold of severity not available but (\geq) 12 is acceptable), or mNAPSI (threshold of severity not available) or DLQI (\geq) 10 or other validated instruments reliably used by the individual physician</td>
<td>Topical treatment. At least two systemic therapies (MTX, CyA, acitretin)</td>
<td>NAPSI or mNAPSI or DLQI other validated instruments reliably used by the individual physician (threshold of improvement not available)</td>
</tr>
<tr>
<td>Peripheral arthritis</td>
<td>(\geq) 1 inflamed joint + patient global VAS (\geq) 4 (or PsAQoL if available) + physician’s judgement or arthritic joint deformities or radiographic joint damage plus (\geq) 5 inflamed small joints or (\geq) 1 large joints</td>
<td>Oligoarthritis: intrarticular corticosteroids, NSAIDs, (\geq) 2 traditional DMARDs (MTX, LEF, SSZ, CyA) alone or combo</td>
<td>ACR50 (ACR20 in selected cases) No development of new arthritic joint deformities and no radiographic evolution</td>
</tr>
<tr>
<td>Dactylitis</td>
<td>(\geq) 1 digit with acute involvement (pain and swelling) + patient global VAS (\geq) 4 (or PsAQoL if available) + physician’s judgement</td>
<td>At least two corticosteroid injections, NSAIDs, MTX, LEF</td>
<td>Improvement in number of involved digits and/or severity of inflammation (physician’s judgement) Leeds dactylosmeter if available</td>
</tr>
<tr>
<td>Enthesitis</td>
<td>(\geq) 1 involved site + patient global VAS (\geq) 4 or (or PsAQoL if available) + physician’s judgement</td>
<td>At least two corticosteroid injections, NSAIDs, MTX, LEF</td>
<td>Improvement in number of involved sites and/or severity of inflammation (physician’s judgement)</td>
</tr>
<tr>
<td>Spondylitis</td>
<td>BASDAI (\geq) 4 + physician’s judgement; ASQoL advisable</td>
<td>At least two full-dose NSAIDs for 3 months</td>
<td>BASDAI50 + physician’s judgement</td>
</tr>
<tr>
<td>Uveitis</td>
<td>Recurrent flares or risk of developing irreversible damage</td>
<td>Local anti-inflammatory therapy (including corticosteroids), at least one DMARDs (CyA, MTX LEF)</td>
<td>No or less frequent flares (physician’s judgement)</td>
</tr>
</tbody>
</table>

PASI, Psoriasis Activity and Severity Index; BSA, body surface area; DLQI, Dermatology Life Quality Index; PGA, Psoriasis Global Assessment; LS-PGA, Lattice System-PGA; PDI, Psoriasis Disability Index; PPASAI, Palmpoplantar Pustular Psoriasis Area and Severity Index; PPP, Palmpoplantar Pustular Psoriasis; NAPSI, Nail Psoriasis Severity Index; DI-HAQ, Disability Index of the Health Assessment Questionnaire; PS-AQoL, Psoriatic Arthritis Quality of Life; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; ASAQol, Ankylosing Spondylitis Quality of Life; MTX, methotrexate; CyA, cyclosporin A; NSAIDs, non-steroidal anti-inflammatory drugs; DMARDs, disease modifying anti-rheumatic drugs; LEF, leflunomide; SSZ, sulphasalazine; ACR, American College of Rheumatology.

### Proposal for the use of biologicals in PD

Our proposal for the use of biologicals in PD is shown in Table 3. Basically, a treatment with biologicals is indicated if, after a traditional therapy, a single clinical feature can be classified as moderate/severe.

#### Skin and nail involvement

Tumour necrosis factor-\(\alpha\) blockers can improve all of the psoriatic skin changes and their use is indicated in all cases of moderate to severe Ps refractory to topical treatment and at least to two non-biological systemic
drugs. The PASI is the most popular instrument to measure plaque-psoriasis and a score of 10 or greater is considered indicative of moderate/severe Ps. Other scoring methods such as the BSA, the PGA, and the PPPASI can be used if the PASI is not applicable or if the physician is more comfortable with them. QoL should always be assessed using at least one instrument. The DLQI is the most popular method and a value of this index of 10 or greater is considered indicative of moderate/severe Ps. As there are no RCTs comparing the three TNF-α inhibitors, the choice of the first to be used is only based on patient’s and physician’s preference and local access to infusion facilities.

A good response to biologics is defined by at least a 75% reduction in the PASI from its baseline value. To define a patient as responder to the therapy, a meaningful improvement (physician’s judgement) in the score of the QoL evaluation should also occur.

**Articular involvement.** The TNF-α inhibitors are the most effective drugs for controlling virtually all of the inflammatory manifestations of PsA and for preventing or retarding irreversible anatomical damage and disability.

Patients with severe disease, defined by both disease activity and anatomical osteo-articular damage, not responsive to non-biological DMARDs are candidates for anti-TNF-α therapy. The cut-off limits of severity of the various rheumatic manifestations are showed in Table 1. Basically, in cases of peripheral arthritis, enthesitis and dactylitis, the inflammation of a single site can be considered severe enough to warrant anti-TNF-α therapy if the value of the global patient evaluation (VAS) of arthritis activity is four or greater or if a meaningful reduction of QoL is present. Anatomical irreversible damage (clinically or radiographically detectable) is always indicative of severe disease and should be treated with anti-TNF-α therapy if signs of active inflammation are present. In psoriatic spondylitis, we suggest to adopt the same recommendations for anti-TNF-α use as in AS.

The target of anti-TNF-α therapy for PsA should always be complete remission, defined by absence of signs of disease activity and no evolution of the articular damage or, at least, minimal disease activity. In our opinion, anti-TNF therapy can be considered successful if at least the criteria reported in Table 1 are met.

Despite the low level of evidence (level 3, grade C) in PsA patients already taking MTX, or another DMARD, it is recommended to maintain this drug when an anti-TNF-α is given. As there are no comparative RCTs, the choice of the first anti-TNF-α agent to be used should be based on the same principles described for Ps.

**Safety issues concerning the TNF-α blockers**

Tumour necrosis factor-α blockers are contraindicated in any of the following conditions:

- severe active infections
- active or latent tuberculosis (TB) not adequately treated
- neoplasm over the last 10 years (with the exception of the basal cell carcinoma)
- heart failure class III or IV according to the NYHA
- demyelinating disorders
- infection with hepatitis B virus (HBV)
- pregnancy
- major surgery planned over the next 3 months.

Patients with HBV infection, who absolutely need anti-TNF-α therapy, can receive this treatment in association with specific prophylactic antiviral therapy and close liver monitoring. In patients treated with PUVA with a cumulative dosage of more than 1000 J, anti-TNF-α therapy requires careful monitoring for non-melanoma skin cancer.

Before starting anti-TNF-α therapy, patients must be screened for latent TB (personal history, chest radiography, tuberculin skin test) and treated with prophylactic anti-TB agents for 9 months if positive at the screening. The more specific and sensitive TB test based on the release of γ-interferon by T cell should be used if available.

The available data seem to indicate that the outcome of the pregnancies in women taking TNF-α inhibitors is not different from that of non-treated women70–72 (level 3 evidence). There are no or little data on the safety of a pregnancy if the male partner is taking TNF-α and on lactation and no data on breastfeeding.

**Conclusive remarks**

The unifying concept of PD strongly encourages both dermatologists and rheumatologists to have a global approach to the treatment of their patients. Dermatologists should always be aware that a Ps patient might have arthritis, even if he/she has no apparent musculoskeletal complaints. As in most cases, PsA develops many years after the skin manifestations, and they are in the best position to detect this rheumatic condition at an early stage. Dermatologists uncomfortable and untrained in diagnosing and treating PsA should refer all patients with suspected articular involvement to the rheumatologist. On the other hand, rheumatologists should refer their PsA patients to the dermatologist to confirm the diagnosis and to treat the cases with moderate/severe skin changes or a meaningful impact on QoL.

Tumour necrosis factor-α blockers are effective in treating all of the clinical manifestations of PD. However, their use should be limited to the patients in whom the benefit can outweigh risks and expenses.

In our proposal for the use of biological therapy in PD, we have tried to provide a simple and flexible framework for classifying the patients in daily practice. However, although treatment guidelines and recommendations are of help in the therapy decision-making process, they should always be seen as general framework where the individual patient can be fitted on the basis of the physician’s judgement. A similar approach has been recently proposed in the GRAPPA treatment recommendations for PD.3 These recommendations suggest to stratify the patient’s manifestations into three categories of severity (mild, moderate and severe) and to treat them accordingly. In addition, they are suitable to create composite indices of disease activity/severity.
Finally, we would like to underline that our proposal only has clinical purposes and that it is not meant to establish any legal standard of care.

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References


