



## Original article

## Consensus statement of the Spanish Society of Rheumatology on the management of biologic therapies in psoriatic arthritis

Jose Luis Fernández Sueiro,<sup>a</sup> Xavier Juanola Roura,<sup>b</sup> Juan de Dios Cañete Crespillo,<sup>c</sup> Juan Carlos Torre Alonso,<sup>d</sup> Rosario García de Vicuña,<sup>e</sup> Rubén Queiro Silva,<sup>f</sup> Rafael Ariza Ariza,<sup>g</sup> Enrique Batlle Gualda,<sup>h</sup> Estíbaliz Loza Santamaría,<sup>i,\*</sup>

<sup>a</sup>Servicio de Reumatología, Hospital Universitario A Coruña, A Coruña, Spain

<sup>b</sup>Servicio de Reumatología, Hospital Universitari de Bellvitge, IDIBELL, L'Hospitalet de Llobregat, Barcelona, Spain

<sup>c</sup>Servicio de Reumatología, Hospital Universitari Clínic de Barcelona, Barcelona, Spain

<sup>d</sup>Servicio de Reumatología, Hospital Monte Naranco, Oviedo, Asturias, Spain

<sup>e</sup>Servicio de Reumatología, Hospital Universitario de La Princesa, Madrid, Spain

<sup>f</sup>Servicio de Reumatología, Hospital Universitario Central de Asturias, Oviedo, Asturias, Spain

<sup>g</sup>Servicio de Reumatología, Hospital Universitario Virgen Macarena, Sevilla, Spain

<sup>h</sup>Servicio de Reumatología, Hospital General Universitario de Alicante, Alicante, Spain

<sup>i</sup>Unidad de Investigación, Sociedad Española de Reumatología, Madrid, Spain

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## ABSTRACT

**Objective:** Due to the amount and quality variability regarding the use of biologic therapy (BT) in psoriatic arthritis (PsA) patients, the Spanish Society of Rheumatology (SER) has promoted the generation of recommendations based on the best evidence available. These recommendations should serve as reference to rheumatologists and those involved in the treatment of patients with PsA, who are using, or about to use BT.

**Methods:** Recommendations were developed following a nominal group methodology and based on systematic reviews. The level of evidence and degree of recommendation was classified according to the model proposed by the Center for Evidence Based Medicine at Oxford. The level of agreement was established through Delphi technique.

**Results:** We have produced recommendations for the use of TB currently available for PsA in our country. These recommendations include disease assessment, treatment objectives, therapeutic scheme and switching.

**Conclusions:** We present an update on the SER recommendations for the use of BT in patients with PsA.

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### Documento SER de consenso sobre el uso de terapias biológicas en la artritis psoriásica

## RESUMEN

**Objetivo:** Dada la gran cantidad de información actual sobre el uso de terapias biológicas (TB) en la artritis psoriásica (APs), y la variabilidad de la misma en cuanto a su calidad, desde la Sociedad Española de Reumatología (SER) se ha impulsado la generación de recomendaciones basadas en la mejor evidencia posible. Éstas deben servir de referencia para reumatólogos e implicados en el tratamiento de APs que vayan a utilizar o consideren la utilización de TB.

**Métodos:** Las recomendaciones se emitieron siguiendo la metodología de grupos nominales y basadas en revisiones sistemáticas. El nivel de evidencia y el grado de recomendación se clasificaron según el modelo del Center for Evidence Based Medicine de Oxford y el grado de acuerdo se extrajo por técnica Delphi.

## Palabras clave:

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\* Corresponding author.

E-mail address: [estibaliz.loza@ser.es](mailto:estibaliz.loza@ser.es) (E. Loza Santamaría).

**Resultados:** Se realizan recomendaciones sobre el uso de las TB disponibles en la actualidad en nuestro país para el tratamiento de la APs. Estas recomendaciones incluyen la evaluación de la enfermedad, objetivos del tratamiento, esquema terapéutico y cambios en el mismo.

**Conclusiones:** Se presentan las actualizaciones a las recomendaciones SER para el uso de TB en pacientes con APs.

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## Introduction

Psoriatic arthritis (PsA) is a chronic musculoskeletal inflammatory disease that is usually seronegative and associated with the presence of skin psoriasis.<sup>1</sup> Established PsA is classified according to the CASPAR criteria<sup>2</sup> (Table 1), although this use of this criteria is yet to be confirmed for the onset of PsA.<sup>3</sup>

There are five large characteristic areas for PsA manifestation from the clinical point of view: peripheral arthritis, spine, dactylitis, enthesitis and skin-nail.<sup>4</sup> These manifestations can occur separately or merge together in a single patient.

It is estimated that cutaneous psoriasis prevalence in the general population is between 0.1% and 2.8%<sup>5</sup> and it is about 7% in patients with arthritis. Inflammatory arthritis occurs in about 2%-3% of the general population, but in patients with psoriasis the prevalence of arthritis varies from 6% to 42%. It is difficult to estimate the exact prevalence of PsA due to the lack of diagnostic criteria and a generalised classification; in addition, many professionals find it difficult to carry out a correct disease diagnosis.<sup>6,7</sup> This varies from 0.04% to 0.1% in the general population,<sup>8</sup> with the incidence being estimated at 3.4-8 cases per 100,000 inhabitants per year.<sup>9-12</sup>

When discussing PsA course and prognosis, although traditionally considered as a less serious form of arthritis than rheumatoid arthritis (RA), all information proceeding from studies in the last few years does not precisely indicate this. Its course generally varies a lot from patient to patient, as with other inflammatory diseases, including SA.

Different studies show that the disease progresses in many patients, even with the use of disease-modifying antirheumatic drugs (DMARDs).<sup>13,14</sup> Finally, there is certain controversy when regarding mortality as to whether this is increased in PsA. Some experts uphold that this is not so, but there are studies where it is confirmed, with the principal causes of death being cardiovascular disease, respiratory disorders and neoplasms.<sup>15,16</sup>

The therapeutic strategy for PsA has been conditioned according to clinical presumptions that are often not based on

objective clinical studies. It has been assumed that, depending on the clinical picture, PsA can be similar to RA and ankylosing spondylitis (AS). That is why there are few quality studies that assess DMARD efficacy in PsA; in fact, none have assessed its efficacy on a structural level.

The treatment used in PsA will also depend on the type of predominant manifestation (peripheral, axial or mixed) and the seriousness of the disease, understanding that seriousness includes PsA activity, its spread and impact on the individual.<sup>17</sup>

### Peripheral forms

Peripheral arthritis treatment is based on non-steroidal anti-inflammatory drugs (NSAIDs), Glucocorticoids (GCs) and DMARDs, which are used either separately or jointly. Non-steroidal anti-inflammatory drugs can be used to control the signs and symptoms of the disease if the joint, enthesitis and dactylitis manifestation is mild.<sup>18</sup> If the joint manifestation is moderate to severe ( $\geq 3$  painful joints (NPJ) or swollen (NSJ) or in cases of refractory enthesitis/dactylitis), a DMARD or a combination of them is used: sulfasalazine (SSZ), leflunomide (LEF), methotrexate (MTX) and cyclosporine A.<sup>19-22</sup>

Oral GCs can be used in low doses with DMARDs for the clinical control of PsA. In cases of monoarthritis, oligoarthritis, polyarthritis with specially symptomatic joints, enthesitis or dactylitis, local GC injections may be useful.<sup>23</sup>

### Axial forms

At present there is no consensus to allow the definition of axial manifestation in PsA patients.<sup>24</sup> However, there are already studies that allow the following considerations to be carried out: axial manifestation should be considered in a patient who presents inflammatory vertebral pain and at least radiological grade II unilateral sacroiliitis.<sup>4,25,26</sup> The NSAIDs are used for the treatment of these manifestations. No efficacy has been seen using DMARDs.<sup>24</sup>

**Table 1**  
CASPAR criteria for psoriatic arthritis classification

<b>Inflammatory joint disease (peripheral, spinal or enthesitic), with 3 or more points obtained from the following categories:</b>	
<i>a) Categories</i>	
Actual psoriasis presence, personal or family history of psoriasis	
Actual presence defined by a rheumatologist or dermatologist as skin or scalp psoriasis	2 points
A personal history is a psoriasis history obtained about the patient by the dermatologist, GP, rheumatologist or other qualified health professional	1 point
Family history is a psoriasis history of a first or second degree family member reported by the patient	1 point
<i>b) Psoriatic nail dystrophy including onycholysis, pitting and hyperkeratosis observed in the current examination</i>	1 point
<i>c) Negative rheumatoid factor, determined by any method except latex, preferably by ELISA or nephelometry. The values will be those of the local reference laboratory</i>	1 point
<i>d) Current history of dactylitis, defined as inflammation of the entire finger or a history of dactylitis recorded by a rheumatologist</i>	1 point
<i>e) Radiographic evidence of bone juxtaarticular formation near the edges of the joint (hands and feet): ill-defined ossification (excluding osteophytes)</i>	1 point

### Mixed musculoskeletal forms (peripheral and axial)

They are based on what has previously been mentioned.

### Dactylitis and enthesitis

They can present themselves separately or in the context of a much more "extended" disease. In isolated dactylitis/enthesitis therapy, NSAIDs and/or local infiltrations with GC can be used to treat them. In the case of refractory dactylitis/enthesitis or a more general disease, DMARDs can be used. In any case, the clinical decision for which DMARD to use would be conditioned by the overall condition of the joint disease.

### Cutaneous and nail affection

The assessment of cutaneous manifestation in PsA patients is outside the environment of these recommendations. However, we must point out that the level of cutaneous psoriasis spread, assessed jointly with the dermatologist, should be taken into account with the overall condition of the patient with PsA when choosing a DMARD for treatment.

For more information on conventional PsA treatment, we recommend consulting the ESPOGUIA.<sup>27</sup>

The objective of these recommendations is to give rheumatology specialists and all the other specialists (such as primary care doctors, intern doctors, etc.) or health professionals who look after patients with PsA an instrument that can provide guidance for therapeutic management of biological therapies (BT) in these patients. We should emphasise that references for BT monitoring will be shown in another consensus document. All these recommendations should contribute to improving the care of patients with PsA. They should also contribute to an understanding and greater diffusion of the importance of this disease.

### Methods

To carry out this consensus we used a modification of the RAND/UCLA methodology.<sup>28</sup> This document is based on reviews and recommendations of the ESPOGUIA<sup>27</sup> together with a critical review of the previous consensus.<sup>29</sup> A panel of 19 rheumatology experts was created from those who belonged to the Ankylosing Spondylitis Group of the Spanish Society of Rheumatology (SER) (GRESSER), who had taken part in creating the ESPOGUIA<sup>27</sup> or who participated in a previous ankylosing spondylitis (AS) consensus.<sup>29</sup> They were sent a dossier with all the previous consensus and the ESPOGUIA. The whole document was prepared by distributing tasks and commentaries to all parties. Two expert epidemiologists were in charge of the Consensus methodology. No patients participated in this Consensus.

Firstly, one or several consensus sections were assigned to each panellist for the sections to be written up. Once completed, they were sent to all panel members for their comments. After that, SER Investigation Unit (IU) members unified, categorised, classified and summarised all comments prior to assessment by the meeting panel.

A nominal group meeting was held, chaired by SER IU members. The proposed document modifications regarding format and contents, including recommendations, were discussed at this meeting.

Later on, through the Delphi survey (carried out anonymously online), the consensus recommendations were voted on. The aggregated results were shown to all panellists (modified Delphi). Recommendations with an agreement level (AL) less than 70% were re-edited and voted on in a second round. It is understood that there is agreement if a panel member votes with 7 or more points on a scale from 1 (totally disagree) to 10 (totally agree).

The levels of evidence (LE) and grades of recommendation (GR) were classified by SER IU members according to the model from the Oxford Centre for Evidence-Based Medicine.<sup>30</sup>

The final document was written up with all this information.

### Preliminary considerations

#### Available biological therapy

The expansion of the therapeutic repertoire of PsA with BT has meant a radical change in the treatment paradigm of this unit (Table 2). Currently, 4 of these treatments have an indication approved by regulatory bodies for treatment of symptoms and signs of active PsA refractory to conventional treatment. These agents are: etanercept (ETN), infliximab (IFX), adalimumab (ADA) y golimumab. Other drugs that could potentially be useful, but that are not currently approved are ustekinumab and certolizumab.

Biological therapy has been shown to be effective in PsA treatment for joint and cutaneous manifestations even in patients with a serious or very serious disease,<sup>31-37</sup> not only in the short term,<sup>36,38-40</sup> but also after 1 or 2 years of treatment,<sup>33,41-45</sup> and even after 5 years.<sup>46</sup> However, there is currently insufficient evidence available on the general use of many drugs (including anti-TNF $\alpha$ ) for the treatment of axial affection in patients with PsA. We extrapolate from AS evidence to PsA due to this. On the other hand, they also improve function, quality of life and laboratory parameters such as ESR and CRP.<sup>36,44,47-53</sup>

In studies with simple x-rays, it has been proved that they slow down disease progress in the peripheral joints.<sup>43,54,55</sup>

In patients with PsA, the effect of BT on other types of manifestations such as amyloidosis,<sup>56</sup> osteoporosis<sup>57</sup> or cardiovascular risk<sup>58,59</sup> is yet to be determined.

There is no data supporting one TNF $\alpha$  antagonist as better than another.<sup>60</sup> That is why the specific choice will depend on the doctor's criteria and the particular circumstances of each patient.

Finally, given their different structures, antigenicity and mechanisms of action, the lack of response to one antagonist does not necessarily mean the inefficacy of another, as we have seen that a patient can respond to a change of BT.<sup>61-63</sup>

**The panel members consider that anti-TNF $\alpha$  should be available for PsA therapeutic practice, without any priority or hierarchy outside scientific evidence itself (LE 5; GR D; AL 93%).**

#### Characteristics of available biological therapy

**Etanercept.** This is a fusion protein with the TNF soluble receptor p75 linked to the Fc of a IgG (Table 2.) In studies carried out on patients with cutaneous psoriasis, ETN presented a dependent efficacy dose; the dose of 50 mg twice a week (subcutaneously), double that normally used in PsA, was much more effective.<sup>64</sup>

Etanercept has been shown to be more effective than the placebo in active PsA cases refractory to conventional therapies (joint and cutaneous clinical picture),<sup>45,55</sup> which has been made objective in parameters such as joint counts, ACR20, Psoriatic Arthritis Response Criteria (PsARC), Psoriasis Area and Severity Index (PASI), PASI 50. Likewise, it improves function (HAQ), quality of life (SF-36), ESR and CRP and decreased NSAID use and radiological progression.<sup>44,47,51,55</sup>

Etanercept has shown to be effective for the treatment of manifestations such as enthesitis and dactylitis in PsA.<sup>64</sup>

We have seen that ETN produces a quick fall in the precursor levels of osteoclasts and a general improvement of bone marrow oedema (objectified with MRI), which accounts for its (possible) antiresorptive effect on PsA.<sup>57</sup>

The possible beneficial effect of intra-articular infiltrations of ETN have also been described.<sup>51</sup>

**Infliximab.** Infliximab is a monoclonal antibody of chimerical origin against TNF $\alpha$  approved for PsA treatment (Table 2). The recommended

**Table 2**  
Biological agents for psoriatic arthritis treatment according to the technical file (updated December 2010)<sup>a</sup>

Active ingredient	Dosage and administration	Indications	Contraindications	Adverse events <sup>b</sup>
Adalimumab	- Dose: 40 mg	- Active and progressive PsA with insufficient response to DMARD	- Allergy to the active ingredient or excipients	- Very frequent: reaction at the injection site (pain, reddening)
	- Route: subcutaneous		- Active TB, serious infections	- Frequent: headache, respiratory or urinary infection, herpes, diarrhoea
	- Frequency: every 2 weeks		- Moderate/serious HF (NYHA classes III/IV)	- Uncommon: SLE, arrhythmia, TB, sepsis, cytopenia
Etanercept	- Dose: 25 or 50 mg	- Active and progressive PsA with insufficient response to DMARD	- Allergy to the active ingredient or excipients	- Very frequent: reaction at the injection site, respiratory, urinary, cutaneous infection
	- Route: subcutaneous		- Sepsis or risk of sepsis	- Frequent: allergy, auto-antibodies
	- Frequency: 25 mg/twice a week (interval of 72-96 hrs); 50 mg once a week		- Active infections	- Uncommon: serious infections, thrombocytopenia, psoriasis
Golimumab	- Dose: 50 mg	- On its own or combined with MTX, for active or progressive PsA with inadequate response to DMARD	- Allergy to the active ingredient or excipients	- Rare: pancytopenia, TB, SLE
	- Route: subcutaneous		- Active TB or other serious infections such as sepsis or opportunist infections	- Very frequent: upper tract respiratory infection
	- Frequency: 1/month, the same day of each month		- Moderate/serious HF (NYHA classes III/IV)	- Frequent: cellulitis, herpes, bronchitis, sinusitis, hypertension, superficial fungal infections, anaemia, antibodies, allergic reactions, depression, insomnia, headache
Infliximab	- Dose (according to weight): 5 mg/kg	- Active and progressive PsA with insufficient response to DMARD	- Allergy to the main ingredient, excipients or other murine proteins	- Uncommon: TB, sepsis, malignancy, ↑ glucose, lipids, CHF, thrombosis, arrhythmia, eye disorders
	- Route: intravenous perfusion during 2 hrs		- Active TB, serious infections	- Rare: reactivation of hepatitis B, lymphoma, pancytopenia
	- Frequency: after the first dose, another at 2 and 6 weeks later. Then 1 every 6-8 weeks		- It will be administered combined with MTX, or in monotherapy if MTX is contraindicated/not tolerated	- Moderate/serious HF (NYHA classes III/IV)
				- Frequent: headache, respiratory infection, herpes, diarrhoea
				- Uncommon: SLE, TB, sepsis, cytopenia
				- Rare: CHF, multiple sclerosis, lymphoma

AS indicates ankylosing spondylitis; CHF, congestive heart failure; DMARD, disease modifying anti-rheumatic drugs; HF, heart failure; HTA, hypertension; MTX, methotrexate; NYHA, New York Heart Association; PsA, psoriatic arthritis; SLE, systemic lupus erythematosus; TB, tuberculosis; TNF, tumour necrosis factor.

<sup>a</sup>The data for this table have been obtained from the technical file from the Spanish Medicines Agency and the European Medicines Agency.

<sup>b</sup>Adverse events: very frequent (at least 1 in each 10 patients); frequent (at least 1 in each 100 patients); uncommon (at least 1 in each 1,000 and less than 1 in each 100); rare (at least 1 in each 10,000 and less than 1 in each 1,000 patients).

dose is 5 mg/kg every 6-8 weeks administered intravenously. Some studies have shown that with lower doses at the same intervals, a similar efficacy is obtained.<sup>65-67</sup> However, these data come from studies carried out on AS, which makes it currently impossible to extrapolate these results to PsA.

It has been seen that using IFX in the usual manner in PsA, it is effective not only for joint but also for cutaneous affectation in active patients who are refractory to at least one DMARD, efficacy that has been measured in joint count, ACR20/50/70, DAS28, PsARC or PASI response.<sup>32,41,54,68-70</sup>

Infliximab has similarly been shown to be effective for manifestations such as enthesitis and dactylitis in PsA,<sup>54</sup> together

with intestinal manifestations<sup>71</sup> and uveitis (decrease in the number of outbreaks).<sup>72</sup>

With infliximab, quality of life (SF-36), physical function (HAQ),<sup>48</sup> ESR and CRP improved,<sup>70,73</sup> and there was also a reduction in radiological progression.<sup>68,74</sup>

When IFX treatment was interrupted, its beneficial effect was seen to be maintained for between 2 to 6 months.<sup>75</sup>

*Adalimumab*. This is the first totally humanised monoclonal antibody with a high affinity for human TNF $\alpha$  (Table 2). The recommended dose is 40 mg once every 2 weeks administered subcutaneously.

In the same way as with other anti-TNF $\alpha$  agents, ADA has been shown to be effective in patients with active PsA refractory to normal treatments, not only from point of view of joints but also cutaneous: in ACR20/50/70, PsARC, PASI, PASI/50/75/90/100 response, pain and fatigue.<sup>34,35,42,49,76</sup>

It has also been shown to be effective for the treatment of manifestations such as enthesitis and dactylitis in PsA, function (HAQ) and quality of life (SF-36, DLQI),<sup>42,43,49</sup> or in laboratory parameters.<sup>50,53</sup> This is also true of intestinal manifestations<sup>71</sup> and uveitis (decrease in the number of outbreaks).<sup>72</sup>

In studies with simple x-rays, it has been seen that progression of the disease decreases.<sup>37,42</sup> On the other hand, in an open study with a 6 month follow up, a significant improvement in bone marrow oedema was observed, without the erosion assessment worsening in the peripheral joint MRI scan. However, the parameters that assessed synovitis had not improved.<sup>77</sup>

**Golimumab.** This (see Table 2) is a new totally human monoclonal antibody directed against TNF $\alpha$ . Its recommended dose is 50 mg subcutaneously every 4 weeks. Golimumab has been shown to have higher efficacy than the placebo in a recent phase III study with patients with active PsA.<sup>36,78</sup> This study tested the efficacy at 14 weeks on ACR20 and PASI75 responses. Significant improvements were also confirmed in HAQ, SF-36, Nail Psoriasis Severity Index and enthesitis scores. This effect was maintained until week 24 of the study.

We have yet to see whether this new anti-TNF $\alpha$  agent has the capacity demonstrated by its predecessors to slow down or detain the progression of the structural damage.

## Results

### Therapeutic aim

**The aim of PsA treatment is for the disease to remit or, if it does not, to reduce its inflammatory activity to the minimum (MAE) so as to attain significant improvement in symptoms and signs, preserve functional capacity, maintain a good quality of life and control structural damage (LE 5; GR D; AL 100%).**

To attain an MAE, PsA patients should fulfil at least 5 of the following 7 criteria:

- NPJ $\leq$ 1.
- NSJ $\leq$ 1.
- PASI $\leq$ 1 or body surface area $\leq$ 3%.
- VNS patient pain $\leq$ 15.
- VNS patient activity $\leq$ 20.
- HAQ $\leq$ 0.5.
- Number of painful entheses $\leq$ 1.

In predominantly peripheral forms, the panel considers it acceptable to achieve -if damage is polyarticular- a DAS28 $<$ 2.6 (nearly remission) or, alternatively, a DAS28 $<$ 3.2 (low activity) and/or a MAE. In oligoarticular forms, complete disappearance of inflammation is acceptable or, alternatively, reaching a MAE.

However, if despite correct treatment there is still radiological progression and/or monoarthritis and/or isolated arthritis in IFD, dactylitis and/or enthesitis, which cause a marked functional impotency or significantly alter a patient's working activities or quality of life, it is considered as therapeutic failure. Likewise, the existence of non-controlled extra-articular manifestations (previous repeated uveitis, extensive cutaneous affectation, gastrointestinal manifestations, etc.) is considered as treatment failure.

The therapeutic aim for predominantly axial PsA is to achieve the minimum clinical activity possible, which will ideally correspond to a BASDAI index and an overall doctor's assessment of  $\leq$ 2, with a general disease assessment by the patient of  $\leq$ 2 and axial pain at night of

$\leq$ 2 in the VNS.<sup>79</sup> However, a BASDAI, overall doctor's assessment and a general disease assessment by the patient and axial pain at night of  $\leq$ 4 in the VNS is considered acceptable. Persistent activity after the patient has been submitted to proper conventional treatment indicates therapeutic failure.<sup>80</sup>

The therapeutic aim for mixed forms will depend on the predominant pattern.

### Indications for biological therapy for patients with psoriatic arthritis

**Biological therapy is indicated for active patients refractory to conventional treatment (NSAIDs, infiltrations, DMARD), except in specific circumstances when the seriousness of PsA (spread of psoriasis, dactylitis, enthesitis, monoarthritis, uveitis, etc.) clearly limit the individual's quality of life and capabilities for leisure and work, making it possible to indicate BT without the need for exhausting conventional treatment possibilities (LE 5; GR D; AL 93.3%).**

For more information on conventional PsA treatment, we recommend consulting the ESPOGUIA.<sup>27</sup>

#### A) Peripheral forms

Before starting BT in these patients, and similarly to conventional therapy, we must establish the prognosis in agreement with severity parameters (number of joints with active synovitis, HAQ, erosive disease, etc.) as well as assessing PsA activity.

It is essential to give patients with peripheral forms of PsA proper treatment with at least one DMARD, which has documented evidence of its efficacy before using BT.<sup>17,19,20</sup> For polyarticular forms, NSAIDs and low doses of oral GCs can be useful. In monoarticular or oligoarticular forms, dactylitis or enthesopathy, the use of local GC infiltrations is also recommended. In refractory monoarthritis, intra-articular therapy with radioisotopes can be used.

**In patients with PsA and peripheral manifestations, the DMARDs recommended, due to their benefit-risk ratio, are MTX and LEF (LE 2b; GR B; AL 93.3%).**

Among DMARDs with documented efficacy are SSZ, MTX, LEF or cyclosporin A. The recommended instructions are as follows:

- MTX on a rapid dose scale: 7.5 mg/week for the first month. If the arthritis persists in any location, the dose should be increased to 15 mg/week. If the arthritis still persists after a month, it should be increased to 20-25 mg/week. If, after 1 month (or in the case of intolerance), the therapeutic aim has not been achieved, this indicates a change of treatment. If oral MTX is not effective, the clinician could consider the possibility of administering it intravenously due to its greater bioavailability.
- LEF: 20 mg/day for 3 months (or a 10 mg dose in case of intolerance). The load dose of 100 mg/day for the first 3 days is not necessary.
- SSZ: 2-3 g daily for 3 months.
- Cyclosporin A: 3-5 mg/kg/day for 3 months or, in the case of adverse effects, the maximum tolerated dose.

Although there is no solid evidence for the use of combined DMARD therapy in PsA, this could be a valid option in patients who are not controlled with monotherapy or who have structural damage progression despite treatment.

**Biological therapy use should be considered in peripheral predominance PsA when there is no proper response to a DMARD or a combination of them, over a period of at least 3 months, of which at least 2 months must have been at full dose (except if tolerance or toxicity problems limit the dose) (LE 5; GR D; AL 100%).**

Even the isolated presence of monoarthritis, enthesitis, dactylitis or cutaneous psoriasis, which is sufficiently serious to condition the individual's quality of life (in this case, according to the dermatologist) or working or leisure capability, could be an indication for BT if conventional treatment fails.

If there are activity criteria, the fact that the patient has extensive radiological affection or absolute mobility limitation does not exclude BT use.

In any case, when establishing definitive BT indication, the opinion of the rheumatologist or any other medical expert in PsA and BT should be considered of maximum relevance.

Previously treated patients should be checked to see if they received proper treatment before BT is considered and then the action should be according to what is set out below:

- If they have been correctly treated and there are still activity criteria, we recommend adding BT as previously specified.
- If the patient has not been correctly treated, before considering BT we recommend completing or restarting the treatment following the recommended instructions.
- In the specific case of patients where PsA fulfils the response criteria for a specific DMARD, and this has been stopped and the disease has been reactivated, we recommend a new cycle of treatment with the DMARD to which the patient previously responded before considering BT.

### B) Axial forms

**In predominantly axial PsA, BT should be considered if at least two NSAIDs with demonstrated anti-inflammatory potency have failed during a period of 4 weeks, with each NSAID at the maximum recommended or tolerated dose, except if there is evidence of toxicity or contraindication to NSAIDs (LE 5; GR D; AL 100%).**

Although NSAIDs have shown their efficacy,<sup>81</sup> specific inhibitors of cyclooxygenase-2 (coxibs) are an alternative therapy to conventional NSAIDs and in some cases have been shown to be highly effective.<sup>82,83</sup>

In previously treated patients, we should check that they had received proper treatment before considering BT and act according to what has been pointed out in the previous point.

### C) Mixed forms

The indication for BT will be carried out if any of the aforementioned criteria are fulfilled.

*Assessment: tools, criteria and definition of active disease*

The assessment of PsA activity is complex due to its clinical heterogeneity. In addition, there is still no clear and agreed definition of "active disease" as in RA.

*Assessment tools*

**The panel recommends assessing PsA activity together with a minimum number of parameters adapted to predominantly clinical type, peripheral joint, axial or enthesitic manifestation (LE 5; GR D; AL 100%).**

As there is a lack of a current, validated and widely-accepted specific index to assess PsA activity, we must take into account that for the decision to use BT in PsA, we have to assess not only activity parameters but also disease severity and impact. As stated below, we describe the variables to assess, which in turn depend on the predominant clinical pattern.<sup>17,27,84</sup>

#### A) Clinical pattern with peripheral manifestations:

**We recommend assessing patients with peripheral joint manifestations (LE 5; GR D; AL 80%):**

- Swollen joint count (out of 66) and painful (out of 68).
- Dactylitis count.
- Overall disease assessment of the patient on a visual numerical scale (VNS 0-10 in the last week) or a visual analogue scale (VAS 0-10 in the last week).
- Overall disease assessment by the doctor with VNS or VAS (0-10).
- Overall pain assessment with VNS or VAS (0-10 in the last week).

- **Fatigue assessment with VNS or VAS (0-10 in the last week), through BASDAI (question no. 1) or specific validated questionnaires such as Functional Assessment of Chronic Illness Therapy (FACIT).<sup>85,86</sup>**
- **CRP and/or ESR.**
- **HAQ or similar questionnaires.**
- **Generic type validated quality of life questionnaires such as SF-12, SF-36 or EQ-5D, or specific type such as PsAQoL.<sup>87,88</sup>**
- **X-rays of the hands and feet and other affected joints.**

More joints are assessed that include IFD<sup>17,27,84</sup> when compared to RA. However, a recent study has shown a good performance of more reduced counts (36 and 28 joints), even without including IFD, and without taking in differences in the final ACR20.<sup>89</sup>

X-rays of the hands and feet and other affected joints should be carried out once a year for the first 3 or 4 years of the PsA evolution. In order to be able to quantify the manifestation level, we recommend some of the validated indices, preferring the Sharp-van der Heijde index modified for PsA.<sup>90</sup>

The variables listed also allow for the calculation of indices composed of activity assessment and response such as ACR, DAS, DAS28 or PsARC. Although this last one is specific to PsA, it lacks special complexity. The simple addition of these combined variables in an composed index similar to the Simplified Disease Activity Index (SDAI) or Clinical Disease Activity Index (CDAI) in RA is seen as an interesting alternative.<sup>91,92</sup>

For more information on conventional PsA treatment, we recommend consulting the ESPOGUIA.<sup>27</sup>

#### B) Clinical pattern for axial manifestation:

**We recommend assessing patients with axial manifestations (LE 5; GR D; AL 100%) with:**

- **BASDAI questionnaire<sup>93</sup> in VNS or VAS (0-10) (questionnaires available on the SER website: <http://www.ser.es/catalina/?cat=13>).**
- **Overall disease assessment of the patient in VNS or VAS (0-10 in the last week).**
- **Axial pain at night due to SA in VNS or VAS (0-10 in the last week).**
- **CRP and ESR**
- **Overall disease assessment by the doctor (VAS or VNS 0-10).**

Although the validity of using BASDAI in patients with PsA and its axial manifestation is disputed, at the moment we continue with the recommendation due to a lack of better alternatives.<sup>94-96</sup>

As axial manifestation in PsA can be silent,<sup>97</sup> we recommend a sacroiliac x-ray in the first assessment of patients with PsA to classify them.

The validity of metrological measures used in the AS has been demonstrated in assessing the limitation of spinal mobility. Therefore, if there are axial manifestations, these should be systematically used in patient follow up (available on the SER website: <http://www.ser.es/catalina/?cat=13>).<sup>25,98</sup>

#### C) Enthesitic manifestation

**We recommend collecting the number and location of symptomatic entheses, preferably through a validated index (EL5; GR D; AL 93.3%).**

For more information on conventional PsA treatment, we recommend consulting the ESPOGUIA.<sup>27</sup>

#### D) Skin and nails

**No specific tool is recommended to assess cutaneous and nail affection in daily practice, but we recommend noting the presence or absence of onicopathy, and consulting a dermatologist if there is doubt (LE 5; GR D; AL 100%).**

*Criteria and definition of active disease*

**There is no consensus agreement on what "active disease" is in PsA, but we understand that there is disease activity if there**

**are swollen joints and at least moderate activity in the disease according to the PsA activity assessment scale (DAS, ACR, PsACR, etc.) (LE 5; GR D; AL 93.3%).**

Activity criteria are proposed for each of the clinical patterns (axial, peripheral and mixed forms).<sup>24,86,99</sup>

#### **A) Peripheral forms**

**Active disease is defined in patients with polyarticular pattern if the DAS28 $\geq$ 3.2; with oligoarticular pattern ( $\leq$ 4 joints), if there is arthritis/enthesitis/dactylitis and the overall doctor's assessment is (VNS)  $\geq$ 4 and there is at least one of the following: overall patient assessment (VNS)  $\geq$ 4 or the acute phase reactants are raised (LE 5; GR D; AL 93.3%).**

#### **B) Axial forms**

**Active disease is defined in patients with axial affection if the BASDAI and the overall doctor's assessment (VNS) are  $\geq$ 4 and there is at least one of the following criteria: overall patient assessment (VNS)  $\geq$  4, axial pain at night (VAS)  $\geq$ 4 or raised acute phase reactants (ESR and/or CRP) (LE 5; GR D; AL 100%).**

#### **C) Mixed forms**

**The definition of active disease in patients with mixed forms will be marked by the dominant/relevant clinical pattern (LE 5; GR D; AL 100%).**

It is also important to take into account the spread and location of the cutaneous disease, as well as its impact on quality of life, so as to carry out an overall PsA activity assessment.<sup>17,20-22,100</sup>

#### *Assessment of therapeutic response*

**We recommend that BT response for PsA should be assessed every 3-4 months using the proper criteria for each clinical pattern (LE 5; GR D; AL 100%).**

In polyarticular affection, PsA patients respond to BT if they achieve clinical remission (DAS28 $<$ 2.6) or at least reduce their inflammatory activity to below the therapeutic target (DAS28 $<$ 3.2). In the cases where this is not reached, we would accept a DAS decrease of 1.2 (from the previous level) as sufficient to maintain BT treatment which the clinician considered of choice, except if some of the non-biological treatments previously used had been more effective, in which case we would recommend assessing their reinstatement.<sup>17,29</sup>

In oligoarticular forms, there are no clear response criteria to anti-TNF $\alpha$ . Consequently, the clinician must individually assess the patient and take into account the type of joint affected and the impact that this produces on the subject to make decisions.

In axial PsA manifestation, while there is no more solid data, we should consider the same response criteria to BT recommended for AS: response to anti-TNF $\alpha$  if after 4 months treatment there is at least a BASDAI decrease and overall doctor's assessment of 50% (or a total decrease of more than 2 points with respect to the previous values) and a relative decrease of 50% in at least one of the following: overall patient assessment, axial pain at night (if both were  $\geq$  4 before treatment) or the decrease of ESR and/or CRP, if they were previously raised.

Biological therapy treatment can be considered a failure if monoarthritis, enthesopathy or dactylitis are persistent or incapacitating, or if the relevant extra-articular manifestations are not controlled or are recurrent.

**Switches in dosage. If after 3-4 months of starting BT there is no response or the initially reached response is lost, there is no evidence that can vouch for a switch in the biological agent dose and a change of therapeutic treatment should be considered (LE 5; GR D; AL 100%).**

We can generally confirm that there is no solid evidence regarding the use of switching biological doses.

**Switching biological agents. When the therapeutic aim has not been achieved or has been lost, we recommend switching to another anti-TNF $\alpha$  (LE 2c; GR B; AL 100%).**

In a recently published study on PsA, the switch to another anti-TNF $\alpha$  obtained a good clinical response.<sup>101</sup> However, further studies are needed to confirm these findings.

On the other hand, as there are no other approved PsA therapeutic targets, it seems reasonable to switch to another anti-TNF $\alpha$  when the therapeutic aim has not been achieved or has been lost.

**Reduction in dosage. There is no current evidence for PsA patients in remission with BT that allows the recommendation of decreasing the dose and lengthening the period between doses (LE 5; GR D; AL 81%).**

There is not sufficient evidence at present to recommend the practice of possibly reducing the dose in PsA patients in clinical remission when using BT. In an open study, good results were obtained with low ETN doses (25 mg/week),<sup>102</sup> but this study did not respond to the research question that had been asked. A reduction in treatment could be considered individually.

#### **Discussion**

This document forms part of the second consensus SER update on BT use in SA. It is based on reviews and recommendations of ESPOGUIA<sup>27</sup> together with a critical review of the previous consensus,<sup>29</sup> following a scientific methodology through the Delphi survey. In relation to previous consensuses, PsA appears as an individual entity for which a specific consensus has been carried out. This decision has been taken by a panel of experts due to the differential PsA characteristics, scientific evidence and actual trends in literature that support this differentiation.

Given the relevance and current scale of evidence on safety with the use of biological therapies in our environment, we have decided to carry out a specific consensus that will be published shortly.

Interest in PsA has been growing over the last few years, and this is seen through the creation of an international group (GRAPPA) devoted to PsA and cutaneous psoriasis study. In addition, there are currently PsA research groups in Spain that have notable international relevance.

Although there is certain discussion on whether AS and PsA should be studied "jointly", the reality is that except in certain aspects, these diseases are very different from a clinical point of view. In PsA, peripheral joint affection is a characteristic problem, and today it is not possible to assimilate axial PsA affection as a process similar to AS. Consequently, we are talking about different diseases with different clinical assessments. In fact, there is currently a discussion on the possibility of developing a compound index to encapsulate all aspects necessary to assess PsA.

It is therefore necessary to separate these two entities, which has been carried out by the great majority of scientific societies. There are also no current recommendations developed in the same way as those undertaken in this manuscript; the GRAPPA group recommendations are perhaps the most similar to these. The manuscript provides a new approach when confronting PsA therapy in a different way to that set out in previous consensuses; the clinician will not be confused with another disease such as SA when consulting these recommendations.

The TNF $\alpha$  antagonist agents are a reality in the treatment of PsA patients. This consensus has updated the recommendations on BT use in patients with PsA. It is clear that TNF $\alpha$  antagonist agents are notably changing the prognosis of these patients, improving their quality of life. In fact, there are even data indicating that these treatments change the natural history of the disease. In addition, new BTs are appearing that could be useful in patients who do not tolerate anti-TNF $\alpha$  due to different circumstances.

This is why the present consensus has tried to issue recommendations in relation to the use of these trial drugs covering all the spectrum of our daily activity with PsA patients. We would

also like to point out that, although there is not sufficient scientific evidence for many of the recommendations at present, the agreement level of the panel members when assessing them has been very high. This means that these recommendations have great value in daily practice.

Finally, the great quantity of evidence published in this context and the future entry of new biological drugs make it necessary to update this document regularly.

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