2011 Portuguese recommendations for the use of biological therapies in patients with psoriatic arthritis

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ABSTRACT

Objective: To develop recommendations for the treatment of psoriatic arthritis (PsA) with biological therapies, endorsed by the Portuguese Society of Rheumatology.

Methods: These treatment recommendations were formulated by Portuguese rheumatologists based on literature evidence and consensus opinion. A draft of the recommendations was first circulated to all Portuguese rheumatologists and their suggestions were incorporated in the draft. At a national meeting the recommendations were discussed and all attending rheumatologists voted on the level of agreement for each recommendation. A second draft was again circulated before publication.

Results: A consensus was achieved regarding the initiation, assessment of response and switching biological therapies in patients with PsA. Specific recommendations were developed for several disease domains: peripheral arthritis, axial disease, enthesitis and dactylitis.

Conclusion: These recommendations may be used for guidance in deciding which patients with PsA should be treated with biological therapies. They cover a rapidly evolving area of therapeutic intervention. As more evidence becomes available and more biological therapies are licensed, these recommendations will have to be updated.

Keywords: Spondyloarthritis; Psoriatic arthritis; Biological therapies; Guidelines.

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INTRODUCTION

There are currently four biological therapies licensed for psoriatic arthritis (PsA) and all of them are tumour necrosis factor (TNF) antagonists: adalimumab, etanercept, golimumab and infliximab[1-13]. All these TNF antagonists have demonstrated clinical efficacy in dactylitis, enthesitis and in joint and skin/nail involvement[1-17]. Radiographic/structural efficacy in peripheral disease has also been shown[9,10,18-20]. There is insufficient evidence about the use of TNF antagonists in axial involvement of PsA patients ("psoriatic spondylitis"), with only one observational study specifically reporting on spinal disease associated with PsA[21]. Therefore, the evidence for using TNF antagonists in axial involvement of PsA patients will be extrapolated from trials in patients with ankylosing spondylitis (AS)/axial spondyloarthritis (SpA), for which there is extensive clinical efficacy data[22-33].

Ustekinumab[34,35] and alefacept[36] are potentially useful biological therapies in PsA but not licensed for this disease. Trials with certolizumab, tocilizumab, rituximab, abatacept, briakinumab and secukinumab are also expected in the future but so far have not been performed in PsA[37-39]. The use of biological therapies in PsA (and other rheumatic diseases) is a rapidly evolving field and the list of biologics used in PsA will have to be regularly updated, as new data are published.

These treatment recommendations were formulated by Portuguese rheumatologists based on literature evidence and consensus opinion. For each recommendation (Table I), the group of rheumatologists attending a national rheumatology meeting in October 2011 vo-

ted on the level of agreement, which was measured on a 10-point numerical rating scale (1=no agreement, 10=full agreement). Adalimumab, etanercept, golimumab and infliximab can be used for the treatment of adults with active and progressive PsA according to the recommendations below.

PsA is a heterogeneous and potentially severe disease. It often presents with an overlap of subtypes and the pattern of disease may vary over time. To make clinical and treatment decisions easier, for the purpose of these guidelines, we have differentiated four major clinical patterns: 1) peripheral arthritis, 2) axial disease, 3) enthesitis and 4) dactylitis.

The treatment of cutaneous/nail involvement in patients with PsA is beyond the scope of these recommendations. Currently, there are no national recommendations for the use of biological therapies in psoriasis and the task force involved in developing these recommendations did not include dermatologists, therefore the treatment of cutaneous/nail involvement was not addressed. However, it should be highlighted that the assessment of skin/nail involvement in patients with PsA, in collaboration with a dermatologist, should be taken into account in the overall management of every patient with PsA and in choosing the most adequate therapy.

The aim of these recommendations is to provide a tool that may guide clinicians in managing patients with PsA and contribute to improving their care. These recommendations also aim to increase the knowledge and awareness of PsA. Although these recommendations contain some original concepts, their general structure follows the pattern of other international recommendations[40]. A structured national registry of rheumatic patients (Reuma.pt) incorporating disease assessment tools for inflammatory rheumatic diseases has been created by the Portuguese Society of Rheumatology - all PsA patients selected for treatment with biological therapies should be included in Reuma.pt[41].

RECOMMENDATIONS FOR THE USE OF BIOLOGICAL THERAPIES IN PsA PATIENTS

DIAGNOSIS

The patient should have a definitive diagnosis of PsA made by a rheumatologist or another physician experienced in the management of PsA.

Although several classification criteria have been described, the ClASsification criteria for Psoriatic ARthritis (CASPAR criteria) have been validated, are being used in many studies and are the most widely used criteria in international recommendations[42,43].

The five subgroups proposed by Moll and Wright[44] are still frequently used in clinical practice, although considerable overlap between these groups is now recognized[45].

Despite no biological markers for PsA being available, assays of rheumatoid factor and anti-citrullinated protein antibodies (ACPA) may help in some cases in the differential diagnosis with rheumatoid arthritis (RA), although they do not exclude a PsA diagnosis. Power Doppler Ultrasound (PDUS) and/or magnetic resonance imaging (MRI) may be useful to help establishing the diagnosis, particularly in early PsA[45].

RECOMMENDATION 1: A definitive diagnosis of PsA requires the presence of validated criteria such as the Moll and Wright or CASPAR criteria.

RECOMMENDATIONS FOR TREATING PERIPHERAL INVOLVEMENT WITH TNF ANTAGONISTS IN PATIENTS WITH PsA

In PsA, treatment with TNF antagonists is recommended for patients with active peripheral disease despite optimal conventional treatment (treatment failure), and supported by the rheumatologist opinion.

DEFINITION OF ACTIVE PERIPHERAL ARTHRITIS

Published evidence has used tender and swollen joint counts as a marker of disease activity. Counting the number of tender and swollen joints is the key assessment for chronic arthritis, including PsA. Several systems of joint count have been applied to PsA, with the American College of Rheumatology (ACR) joint count of 68 tender and 66 swollen and the modified 78/76 count being the most widely methods used. The 28-joint count included in DAS28 used for the assessment of RA may not be appropriate for all PsA patients, as it does not include some of the joints that are frequently involved in this disease[46-49]. Different definitions of active peripheral arthritis have been used in published clinical trials and in other treatment recommendations[1-14,40,50]. Some poor prognosis factors have been identified in PsA, namely the number of actively inflamed joints (defined by some authors as 5 or more[40,50]), elevated acute phase reactants, progressing radiographic damage, loss of physical function and impairment of quality of life[15,51].

TABLE I. RECOMMENDATIONS FOR THE USE OF BIOLOGICAL THERAPIES IN PATIENTS WITH PSORIATIC ARTHRITIS

Domain	Recommendation	Agreement mean (SD)
PsA Definition	A definitive diagnosis of PsA requires the presence of validated criteria such as the Moll and Wright or CASPAR criteria.	9.5 (0.6)
Peripheral arthritis	Active peripheral arthritis candidate to biological therapy should be considered when 5 or more swollen joints (in a 66 joint count) are present on two separate occasions at least 1 month apart. In patients with mono/oligoarthritis (1-4 swollen joints), the decision to treat patients with TNF antagonists should be made on a case-by-case basis according to the rheumatologist opinion, and taking into account factors such as the severity and progression of structural damage, the presence of elevated acute phase reactants and the impact of the disease in activities of daily life, physical function and quality of life.	8.0 (1.6)
	Biological therapy is recommended for treatment of active peripheral arthritis in patients who have failed to respond to at least one synthetic DMARD (methotrexate, sulfasalazine, leflunomide, cyclosporine) for at least 3 months on a standard (full) target dose, unless intolerance, toxicity or contra-indication. In case of mono/oligoarthritis intra-articular corticosteroids should also be considered.	9.0 (0.8)
	For peripheral arthritis, response should be defined by PsARC criteria. The rheumatologist opinion and other clinical, laboratory and radiological parameters should be considered in the decision to maintain or stop the treatment. In patients with "RA-like" PsA response may be also assessed according to changes in the DAS28: response criteria correspond to improvement of at least 0.6 at 3 months and greater than 1.2 at 6 months. The first evaluation should be done 3 months after the introduction of biological therapy. Subsequent decision should be done at 6 months.	7.6 (1.9)
Axial involvement	Patients with PsA are classified as having axial involvement if they also fulfill the ASAS criteria for axial SpA or the modified New York criteria for AS.	9.3 (0.8)
	Active axial disease candidate to biological therapy is defined by a BASDAI ≥4 or ASDAS ≥2.1, in two separate occasions with at least 1 month interval.	9.5 (0.6)
	Treatment failure in axial disease is defined as active disease despite a continuous therapeutic trial with at least two NSAIDs over at least a 2-week period each, at maximum recommended or tolerated anti-inflammatory doses, unless contraindicated or if the patient develops intolerance or side-effects.	8.9 (1.2)
	Response to treatment should be assessed after at least 3 months of continuous treatment with a biological therapy. Response criteria are: 1) a decrease in BASDAI ≥50% or ≥2 units (0-10) or 2) a decrease in ASDAS ≥1.1 units.	9.3 (1.0)
Enthesitis	In patients with PsA, the diagnosis of enthesitis should be established on clinical grounds and, in case of doubt, with the aid of Power Doppler Ultrasound or MRI.	9.0 (1.2)
	Active enthesitis should be defined on a case-by-case basis according to the rheumatologist opinion, and taking into account the impact of enthesitis in activities of daily life, physical function and quality of life. Power Doppler Ultrasound or MRI, whenever feasible, should be used to support the rheumatologist opinion.	8.3 (1.7)

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TABLE I. RECOMMENDATIONS FOR THE USE OF BIOLOGICAL THERAPIES IN PATIENTS WITH PSORIATIC ARTHRITIS *(continuation)*

Domain	Recommendation	Agreement mean (SD)
	Biological therapy is recommended for patients with persistent (at least 3 months) active enthesitis, who have failed to respond to physical therapy, NSAIDs (in full therapeutic or tolerated doses, unless contraindicated) and at least two corticosteroids injections (unless the procedure is contra-indicated).	8.6 (1.2)
	Assessment of response should be performed at three months. Patients are considered as responders to treatment if there is a reduction in the number of active enthesitis sites and a reduction in functional impairment. The decision to continue treatment should be supported by the rheumatologist opinion. Power Doppler Ultrasound or MRI, whenever feasible, should be used to support the decision.	8.4 (1.1)
Dactilytis	In patients with PsA, the diagnosis of dactylitis should be established on clinical grounds and, in case of doubt, with the aid of Power Doppler Ultrasound or MRI.	8.9 (1.1)
	Active dactylitis should be defined on a case-by-case basis according to the rheumatologist opinion, and taking into account the impact of dactylitis in activities of daily life, physical function and quality of life. Power Doppler Ultrasound or MRI, whenever feasible, should be used to support the rheumatologist opinion.	6.8 (2.1)
	Biological therapy is recommended for patients with persistent (at least 3 months) active dactylitis who have failed to respond to NSAIDs (in full therapeutic or tolerated doses, unless contra-indicated), DMARD therapy and at least two corticosteroids injections (unless the procedure is contra-indicated).	7.6 (1.7)
	Assessment of response should be performed at three months. Patients are considered as responders to treatment if there is a reduction in the number of digits with dactylitis and a reduction in functional impairment. The decision to continue treatment should be supported by the rheumatologist opinion. Power Doppler Ultrasound or MRI, whenever feasible, should be used to support the decision.	8.1 (1.7)

Agreement was voted on a scale from 1 to 10 (fully disagree to fully agree) by 36 voting rheumatologists.
AS, ankylosing spondylitis. **ASAS**, Assessment of Spondyloarthritis international Society. **ASDAS**, Ankylosing Spondylitis Disease Activity Score. **BASDAI**, Bath Ankylosing Spondylitis Disease Activity Index. **CASPAR,** ClASsification criteria for Psoriatic ARthritis. **DAS,** disease activity score. **DMARD,** disease-modifying anti-rheumatic drug. **MRI,** magnetic resonance imaging. **NSAID,** non-steroidal anti-inflammatory drug. **PsA,** psoriatic arthritis. **PsARC,** Psoriatic Arthritis Response Criteria. **RA,** rheumatoid arthritis. **SD**, standard deviation. **TNF,** tumour necrosis factor.

RECOMMENDATION 2: Active peripheral arthritis candidate to biological therapy should be considered when 5 or more swollen joints (in a 66 joint count) are present on two separate occasions at least 1 month apart. In patients with mono/ /oligoarthritis (1-4 swollen joints), the decision to treat patients with TNF antagonists should be made on a case-by-case basis according to the rheumatologist opinion, and taking into account factors such as the severity and progression of structural damage, the presence of elevated acute phase reactants and the impact of the disease in activities of daily life, physical function and quality of life.

DEFINITION OF TREATMENT FAILURE IN ACTIVE PERIPHERAL ARTHRITIS

Several good systematic literature reviews on the different disease-modifying therapies used for peripheral PsA were identified[15-17,52]. These reviews cover mostly the same studies. In general, few randomised controlled trials (RCTs) were found studying the use of synthetic disease-modifying antirheumatic drugs (DMARDs)

in PsA and many of the studies were of poor quality. Although limited, some evidence exists, based on some RCTs and observational studies, that methotrexate, sulfasalazine, leflunomide, cyclosporine and even injected gold salts are effective in peripheral arthritis[15-17]. However, the use of intramuscular gold salts is not usually recommended because other less toxic treatments are available. Regarding prevention of radiographic progression, synthetic DMARD studies have either failed to document it or had inconclusive results. No studies were identified that addressed the comparative efficacy of methotrexate, sulfasalazine, leflunomide and cyclosporine, or that addressed the optimal strategy for the sequential or combined use of synthetic DMARDs. To date, there is also no data showing that combination therapy with TNF antagonists and synthetic DMARDs is superior to TNF antagonists' monotherapy[4,7,15,53].

Some RCTs showed efficacy of non-steroidal anti-inflammatory drugs (NSAIDs), including classic and cyclo-oxygenase-2 selective inhibitors, in reducing symptoms and signs of PsA. No difference in efficacy between different NSAIDs was identified in comparative studies[15].

Although no evidence exists to support the use of systemic corticosteroids in peripheral PsA and despite previous concerns over their safety in patients with psoriasis, they appear to be widely used[15-17]. Intra-articular corticosteroids are also extensively used in clinical practice, supported by few observational studies. A wise use of intra-articular corticosteroids to treat persistent synovitis of a given joint is recommended, particularly for mono or oligoarthritis, or for bridging therapy whilst waiting for other therapies to become effective[54].

RECOMMENDATION 3: Biological therapy is recommended for treatment of active peripheral arthritis in patients who have failed to respond to at least one synthetic DMARD (methotrexate, sulfasalazine, leflunomide, cyclosporine) for at least 3 months on a standard (full) target dose, unless intolerance, toxicity or contra-indication. In case of mono/oligoarthritis intra-articular corticosteroids should also be considered.

ASSESSMENT OF RESPONSE TO TREATMENT

Unlike for RA, there are no validated and unequivocally reliable instruments to evaluate response to therapy in PsA[47,50,55-59].

By analogy to clinical trials and previously published recommendations, the definition of response to treatment can be based on the decrease in at least 30% of the tender and swollen joint counts and in patient and physician global improvement, as in the psoriatic arthritis response criteria (PsARC)[8,59-61]. PsARC response is defined as an improvement in at least 2 of the 4 following measures, one of which must be joint swelling or tenderness, and no worsening in any of the 4 measures:

a) Joint tenderness and joint swelling count: improvement is defined as at least 30% decrease in the joint count and worsening is defined as at least 30% increase in the joint count.
b) Physician and patient global assessment of articular disease: improvement is defined as a decrease by at least one Likert category and worsening is defined as an increase by at least one Likert category (in a 0-5 or 1-5 Likert scale). The original article describing the PsARC used a 1-5 Likert scale,[61] while subsequent trials have used either a 0-5 Likert scale[8,9] or a 0-100 (or 0-10) visual analogue scale (VAS)[4,7]. In a 0-100 (or 0-10) scale improvement/worsening would correspond to at least 20mm (or 2 units) decrease/increase in the scale. Data from clinical trials using either a Likert or VAS scale were recently pooled in an exercise assessing response criteria in PsA[62,63].

Several domains may be affected in PsA[58], therefore the physician global assessment may be an important evaluation parameter in the decision to maintain or stop the treatment. The physician should base his decision on clinical, laboratory and radiological parameters of the disease[58].

Response to treatment of "RA-like" PsA (i.e. PsA with a joint involvement pattern similar to RA) may be assessed using criteria developed for RA as DAS28 and the EULAR response criteria, shown to be reliable and discriminative in this type of PsA[59,64,65]. Patients with distal interphalangeal joint involvement should not be considered as "RA like" PsA, and the DAS28 should not be used in this subgroup of patients.

In the near future, following appropriate validation, composite measures evaluating all aspects of psoriatic disease might be used to assess eligibility and response to treatment of PsA patients[66-69].

RECOMMENDATION 4: For peripheral arthritis, response should be defined by PsARC criteria. The rheumatologist opinion and other clinical, laboratory and radiological parameters should be considered in the decision to maintain or stop the treatment. In patients with "RA-like" PsA response may be also assessed according to changes in the

DAS28: response criteria correspond to improvement of at least 0.6 at 3 months and greater than 1.2 at 6 months. The first evaluation should be done 3 months after the introduction of biological therapy. Subsequent decision should be done at 6 months.

RECOMMENDATIONS FOR TREATING AXIAL INVOLVEMENT WITH BIOLOGICAL THERAPIES IN PATIENTS WITH PsA

In PsA, treatment with TNF antagonists is recommended for patients with active axial involvement despite optimal conventional treatment (treatment failure), and supported by the rheumatologist opinion.

DEFINITION OF AXIAL INVOLVEMENT

There is currently no consensus about the definition of "axial involvement" of patients with PsA[70]. The combination of inflammatory back pain and at least bilateral grade II sacroiliitis has been often used to define axial involvement is PsA, reflecting an adaptation of the modified New York (mNY) criteria for AS to patients with PsA[55,71-73]. However, this adaptation is restrictive because the presence of definite sacroiliitis on plain radiographs is a late finding in the majority of patients[74-76]. Thus, the mNY criteria perform well in established disease but lack sensitivity in early spinal disease. Furthermore, the mNY criteria ignore the role of MRI in assessing patients suspected of having axial SpA: MRI can visualize sacroiliitis in patients with normal radiographs of the sacroiliac joints, and has evolved as the most important diagnostic imaging tool in early axial disease, also referred to as non-radiographic axial SpA[77,78]. This new paradigm has led the ASAS group to develop new criteria for axial SpA, published in 2009[79,80] .The new criteria allow classifying patients as having axial SpA in the absence of radiographic sacroiliitis and therefore in earlier disease stages. Importantly, it has also been shown that patients with non-radiographic axial SpA have similar disease burden as patients fulfilling the mNY criteria[81]. Furthermore, studies with TNF antagonists in patients with early/non-radiographic axial SpA[22-25] have shown at least similar efficacy to, and, in part, better efficacy than, studies in patients fulfilling mNY criteria[26-33].

RECOMMENDATION 5: Patients with PsA are classified as having axial involvement if they also fulfill the Assessment of Spondyloarthritis international Society (ASAS) criteria for axial SpA or the modified New York criteria for AS.

DEFINITION OF ACTIVE AXIAL DISEASE

There is no specific tool to assess disease activity of the PsA axial component[82-84]. Therefore, in the absence of specific alternatives, the use of the same instruments used for AS have been recommended: the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI)[83-85], historically the most widely used clinical disease activity measure, and the Ankylosing Spondylitis Disease Activity Score (ASDAS)[86-88], a new composite disease activity index developed for AS/axial SpA, which already has validated cut-offs (an ASDAS ≥2.1 represents high disease activity). Importantly, in a study of PsA patients with axial involvement, the ASDAS performed equally well as the BASDAI[82].

The inclusion of the ASDAS as an alternative to the BASDAI to define active axial disease was based on the good psychometric properties of this new index[89] and its recent validation among the Outcome Measures in Rheumatology (OMERACT) community[90]. There is also recent evidence that the ASDAS may better reflect the inflammatory disease processes in patients with axial SpA[91] and that ASDAS high disease activity (ASDAS ≥ 2.1) may be a better cut-off than BASDAI elevation (BASDAI ≥ 4) to select patients for treatment with TNF antagonists[92-94], namely because it selects a higher number of patients with characteristics predictive of good response to these therapies[92,95].

The decision to consider the disease as active should be supported by the rheumatologist's opinion, who should base is judgment on clinical, laboratorial (acute phase reactants) and imaging (radiographs, MRI) features of the disease.

RECOMMENDATION 6: Active axial disease candidate to biological therapy is defined by a BASDAI ≥4 or ASDAS ≥2.1, in two separate occasions with at least 1 month interval.

DEFINITION OF TREATMENT FAILURE IN ACTIVE AXIAL DISEASE

NSAIDs (classical or COX-2 inhibitors) have demonstrated clinical efficacy in axial disease[96-99], contrary to synthetic DMARDs, for which there is no evidence of clinical efficacy[97]. All patients should have an adequate therapeutic trial of at least two NSAIDs (a total of at least 4 weeks of full-dose continuous NSAID treatment, at least 2 weeks for each NSAID, unless contraindicated

or if the patient develops intolerance or side-effects). The literature about the length of time beyond which it would be unlikely that an NSAID would be effective is scarce. Only a few trials provided detailed information on the time course of efficacy and these trials suggest that the maximum effect is achieved after 2 weeks[96,99]. However, the evidence for recommending this period is limited and there are patients that may still respond after 2 weeks of treatment. Therefore, the rheumatologist may choose to expand this treatment period for each NSAID.

RECOMMENDATION 7: Treatment failure in axial disease is defined as active disease despite a continuous therapeutic trial with at least two NSAIDs over at least a 2-week period each, at maximum recommended or tolerated anti-inflammatory doses, unless contraindicated or if the patient develops intolerance or side-effects.

ASSESSMENT OF RESPONSE TO TREATMENT IN ACTIVE AXIAL DISEASE

The choice of at least a 3-month interval as the time for evaluation of response to a biological agent was based on observations from phase III trials of TNF antagonists, where response rates stabilized from 12 weeks onwards. The inclusion of the ASDAS response as an alternative to the BASDAI response in assessing efficacy of the biological therapy was based on the improved psychometric properties of the ASDAS compared to the BASDAI[86,88,89] and its recent validation among the OMERACT community[90]. Furthermore, there is recent evidence that the ASDAS may better reflect the inflammatory disease processes in patients with axial SpA than the BASDAI[91].

RECOMMENDATION 8: Response to treatment should be assessed after at least 3 months of continuous treatment with a biological therapy. Response criteria are: 1) a decrease in BASDAI ≥50% or ≥2 units (0-10) or 2) a decrease in ASDAS ≥1.1 units.

RECOMMENDATIONS FOR TREATING ENTHESITIS WITH TNF ANTAGONISTS IN PATIENTS WITH PsA

In PsA, treatment with TNF antagonists is recommended for patients with active enthesitis despite optimal conventional treatment (treatment failure), and supported by the rheumatologist opinion.

DEFINITION OF ENTHESITIS

The diagnosis of enthesitis is challenging and several instruments proposed for clinical assessment have been tested but no single instrument has gained widespread acceptance[47,55,57,58]. Although the term enthesitis presupposes inflammation of the entheseal site differential diagnostic difficulty can arise from lesions encompassed in the concept of enthesopathy, especially if they occur as an isolated phenomenon and without a history of psoriasis. There are several studies that document the good correlation between PDUS findings, MRI and the current "gold standard" which is the clinical opinion of the expert[100-104].

Currently two approaches have been described: clinical examination (pain, tenderness, swelling at tendon, ligament or capsule insertion site by palpation and pressure) or imaging methods (PDUS and MRI demonstrating enthesitis that may be clinically undetectable or doubtful).

RECOMMENDATION 9: In patients with PsA, the diagnosis of enthesitis should be established on clinical grounds and, in case of doubt, with the aid of Power Doppler Ultrasound or MRI.

DEFINITION OF ACTIVE ENTHESITIS

Most published guidelines state that enthesitis should be treated as a separate entity and until further trial data become available, TNF antagonists' therapy for PsA entheseal disease will have to be decided on an individual basis[105]. In this context, the rheumatologist opinion is essential on this decision.

There are several tools to assess enthesitis but no consensus regarding the best instrument for its evaluation[106-109]. The enthesitis count is used in the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) guidelines[50]. In TNF antagonists RCTs, several tools have been used to assess the burden of enthesitis: an MRI score[110], the number of patients with enthesitis[3-6,13,14,34] and a severity score[13]. Although implicit in most of the guidelines, the rheumatologist opinion is referred in some of them as a disease assessment tool.

Pain intensity, the number of enthesitis sites and the repercussion on function [Health Assessment Questionaire (HAQ)] have been used to quantify disease severity but are not generally accepted. Olivieri et al used the criteria of a patient global assessment greater than 40 mm (0-100 VAS scale) and entheseal pain greater than 2 in a 0-4 Likert scale to define active enthesitis.

In the more comprehensive GRAPPA guidelines[50], severe disease was defined as pain on palpation of >2 entheses and/or functional impairment according to the physician, while in the Composite Psoriatic Disease Activity Index (CPDAI)[67] the criteria for severe disease was pain on palpation of >3 entheses and functional disability according to the patient (HAQ≥0.5). However, these criteria still require further validation in RCTs and longitudinal observational studies.

RECOMMENDATION 10: Active enthesitis should be defined on a case-by-case basis according to the rheumatologist opinion, and taking into account the impact of enthesitis in activities of daily life, physical function and quality of life. Power Doppler Ultrasound or MRI, whenever feasible, should be used to support the rheumatologist opinion.

DEFINITION OF TREATMENT FAILURE IN ACTIVE ENTHESITIS

Traditionally the standard treatment for enthesitis includes physical therapy, NSAIDs, glucocorticoid injections and synthetic DMARDs[50,110-112]. However, there is a substantial lack of evidence on which synthetic DMARDs to use because they have shown little effect on enthesitis and there is no evidence that any of these drugs actually prevent disease progression[112]. More recently, the introduction of TNF antagonists including etanercept, infliximab, adalimumab and golimumab for the treatment of PsA have shown remarkable results. However different outcome measures were used to assess efficacy in clinical trials[3-7,13,14,21,34].

Given the absence of international consensus, the various guidelines adopted different criteria[50,113,114]. In the main TNF antagonist trials there were no specific reference to criteria for failure to standard therapy in enthesitis. Olivieri *et al* defined failure as lack of response to at least 2 NSAIDs for at least 3 months and lack of response to at least two steroid injections[21]. In the HEEL study (etanercept), treatment failure was defined as lack of response to full dose NSAIDs for at least 3 months[110].

RECOMMENDATION 11: Biological therapy is recommended for patients with persistent (at least 3 months) active enthesitis, who have failed to respond to physical therapy, NSAIDs (in full therapeutic or tolerated doses, unless contraindicated) and at least two corticosteroids injections (unless the procedure is contra-indicated).

ASSESSMENT OF RESPONSE TO TREATMENT IN ACTIVE ENTHESITIS

Unlike RA, in PsA there are no validated and universally accepted scores to evaluate response to therapy. Also there is no validated treatment duration threshold for assessment of treatment response.

In the absence of universally accepted scores applicable to the whole PsA disease spectrum, response to treatment can be judged on the basis of the decrease in either the number of active enthesitis sites and/or in the degree of impairment (which could be defined by a reduction of HAQ score)[13]. Some investigators have suggested that the minimal clinically important difference in the HAQ score is 0.22[115]. However, such cut-off has never been validated in PsA. Besides clinical methods, PDUS and MRI have shown to be reproducible methods for monitoring therapeutic response in enthesitis of SpA[110,116].

By analogy to data from RCTs, although not specifically for enthesitis, at least 3 months should be proposed for initial evaluation of TNF antagonist efficacy for the treatment of enthesitis.

RECOMMENDATION 12: Assessment of response should be performed at three months. Patients are considered as responders to treatment if there is a reduction in the number of active enthesitis sites and a reduction in functional impairment. The decision to continue treatment should be supported by the rheumatologist opinion. Power Doppler Ultrasound or MRI, whenever feasible, should be used to support the decision.

RECOMMENDATIONS FOR TREATING DACTYLITIS WITH TNF ANTAGONISTS IN PATIENTS WITH PsA

In PsA, treatment with TNF antagonists is recommended for patients with active dactylitis despite optimal conventional treatment (treatment failure), and supported by the rheumatologist opinion.

DEFINITION OF DACTYLITIS

There is no uniformity in the methods used for diagnosing dactylitis. The clinical method (inspection and palpation) is important and constitutes the "gold standard; however, imaging methods such as PDUS and MRI may improve diagnostic accuracy and severity evaluation[117,118].

RECOMMENDATION 13: In patients with PsA, the diagnosis of dactylitis should be established on clinical grounds and, in case of doubt, with the aid of Power Doppler Ultrasound or MRI.

DEFINITION OF ACTIVE DACTYLITIS

Regarding disease activity, similarly to previous domains, there is no consensus regarding the best instruments to use for evaluation[118].

Most guidelines assess dactylitis as an "active" joint. Some clinical trials used a simple count of fingers with dactylitis, and others classified its severity in a scale[4,6,7,61,119,120]. Studies with TNF antagonists in PsA have used the number of fingers (n=20) with dactylitis and also the degree of severity as a measure of effectiveness. Healy *et al*, developed the Leeds Dactylitis Index (LDI) based on two parameters: digital circumference in the proximal phalange (tumefaction) and 0-3 tenderness score resembling the Ritchie Index[118]. In the CPDAI composite index, dactylitis was assessed by using a simple digit count with the examining physician recording the presence of swelling and/or tenderness in the involved digits[67]. This index classifies dactylitis activity in 3 grades: mild (≤3 Digits; normal function), moderate (≤3 digits but function impaired; or >3 digits but normal function) and severe (>3 digits and function impaired). In the CPDAI function impairment was defined as an HAQ score >0.5[67]. However these cut-offs still require further scrutiny in order to be applied as selection criteria for treatment with biological therapies. Therefore, the group recommended that TNF antagonists' therapy for dactylitis will have to be decided on an individual basis. In this context, the rheumatologist opinion is essential on this decision.

RECOMMENDATION 14: Active dactylitis should be defined on a case-by-case basis according to the rheumatologist opinion, and taking into account the impact of dactylitis in activities of daily life, physical function and quality of life. Power Doppler Ultrasound or MRI, whenever feasible, should be used to support the rheumatologist opinion.

DEFINITION OF TREATMENT FAILURE IN ACTIVE DACTYLITIS

As for enthesitis, treatment of dactylitis is largely empirical. Treatment recommendations for dactylitis include NSAIDs, steroid injections, synthetic DMARDs and TNF antagonists. However, there is a substantial lack of evidence on which synthetic DMARDs to use. Synthetic DMARDs have shown little effect and there is no evidence that any of these drugs actually prevent disease progression[121].

More recently the introduction of TNF antagonists including etanercept, infliximab, adalimumab and golimumab for the treatment of PsA has shown remarkable results in dactylitis[3-7,13,14].

In most guidelines, dactylitis is not separately addressed and is usually analyzed together with peripheral arthritis. Given the absence of international consensus, previously published guidelines adopted different criteria for treatment failure[50,105,111,122]. In the main TNF antagonists' trials, there was no reference to criteria defining treatment failure in dactylitis. Olivieri *et al* defined treatment failure as the lack of response to at least 2 NSAIDs> 3 months and at least two steroid injections[21].

Although there is no evidence to support the use of synthetic DMARDs in dactylitis, they are often used in this type of involvement. Furthermore, in dactylitis there is usually a joint synovitis component, associated with tenosynovitis and soft tissue swelling. Therefore, when discussing the recommendation for treatment failure in dactylitis, most rheumatologists felt that patients should have an adequate trial of all conventional treatment modalities, including a synthetic DMARD, before progressing to treatment with biological therapy.

RECOMMENDATION 15: Biological therapy is recommended for patients with persistent (at least 3 months) active dactylitis who have failed to respond to NSAIDs (in full therapeutic or tolerated doses, unless contra-indicated), DMARD therapy and at least two corticosteroids injections (unless the procedure is contra-indicated).

ASSESSMENT OF RESPONSE TO TREATMENT IN ACTIVE DACTYLITIS

As in enthesitis, there is no validated minimum interval for response to treatment assessment, or for assessment intervals. This issue was not approached in any of the existing guidelines. Reduction in the number of digits with dactylitis, reduction on dactylitis scores, improvement in functional scores and improvement in composite scores are some of the outcome measures that have been proposed, but there are no consensual response criteria. Thus, the decrease in either the number of digits with dactylitis or in the degree of im-

pairment could be considered as response to treatment parameters. In the absence of specific data and by analogy with the response assessment for peripheral arthritis used in TNF antagonists' trials, the time for assessment of response should be at least 3 months, with the possibility of a 3 month extension[4-7,13,14,34].

RECOMMENDATION 16: Assessment of response should be performed at three months. Patients are considered as responders to treatment if there is a reduction in the number of digits with dactylitis and a reduction in functional impairment. The decision to continue treatment should be supported by the rheumatologist opinion. Power Doppler Ultrasound or MRI, whenever feasible, should be used to support the decision.

CHANGING THE DOSE AND SWITCHING BIOLOGICAL THERAPIES

After an adequate dose and length of treatment, we recommend switching the biological therapy in non-respondent patients. The evidence in this area is scarce - a recent observational study showed good efficacy[123]. There is no evidence to support dose increases of the biological treatments in case of treatment failure. In case of a good response to biological therapy there is no evidence for recommending a dose reduction or the interruption of the treatment. However, tapering biological DMARDs (expanding the interval between doses or reducing the dose) may be considered in individualized cases (eg. remission for at least 12 months in the absence of steroid treatment), according to the rheumatologist opinion and especially if the treatment is being combined with a synthetic DMARD.

FINAL REMARKS

PsA is a multidomain disease characterized by involvement of peripheral joints, skin/nails, spine, entheseal sites and dactylitis. However, even the isolated presence of monoarthritis, enthesitis or dactylitis may be severe enough to seriously limit the patient's quality of life, working or leisure capability. In this context, if conventional treatment fails, the rheumatologist opinion is essential in the decision to start biological therapy, as highlighted in the above recommendations. A key aspect of treatment is accurate diagnosis and assessment, which facilitates the institution of appropriate treatment in a timely fashion. Factors such as patient preference for the type and frequency of treatment administration, treatment compliance and potential adverse events should also be taken into account when treating a patient with PsA.

Recently *Coates et al* led an exercise among GRAPPA members, based on reviewing hypothetical cases, which led to the definition of "minimal disease activity" (MDA) criteria for patients with PsA[124]. Patients were classified as achieving MDA if they fulfilled 5 of 7 outcome measures: tender joint count ≤1; swollen joint count ≤1; psoriasis activity and severity index ≤1 or body surface area ≤3; patient pain VAS score ≤15 (0--100 scale); patient global disease activity VAS score of ≤ 20; HAQ score ≤ 0.5; and tender entheseal points ≤1. These criteria were validated in a Canadian cohort[125] and interventional trial datasets[124]. The development of this instrument is a step toward "treatment to target" in PsA[56,126].

Importantly, safety should not be underestimated. The preliminary workup to initiate treatment with TNF antagonists in PsA patients should follow the same principles and recommendations as for RA[127,128]. Patients with latent tuberculosis should receive appropriate prophylactic therapy as recommended[129]. In addition, immunization records should be checked for compliance with recommended vaccinations.

Given the complex array of clinical features in PsA, treatment guidelines based in individual domains may result in an underestimation of the extent of disease. When assessing a patient with PsA the overall burden of disease should also be taken into account. It is therefore of great importance to consider the impact of the disease as a whole on an individual's physical function, work disability, health and quality of life. Optimal treatment of PsA involves the use of drugs that have the ability to improve multiple clinical domains or the use of combinations of treatments that can beneficially affect multiple domains and can be used safely together. The CPDAI was recently developed by GRAPPA as a composite measure for PsA but still requires further validation and the development of composite cut-offs to enable it to be used for treatment guidelines[67-69]. In the absence of a validated composite tool to select patients for biological treatment, expert opinion is of utmost importance in selecting patients that do not fulfill individual criteria to start a biological therapy based on single disease features but in which the overall disease burden may justify that treatment.

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