Portuguese recommendations for the use of biological therapies in patients with psoriatic arthritis – 2015 update

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ABSTRACT

Objective: To update recommendations for the treatment of psoriatic arthritis with biological therapies, endorsed by the Portuguese Society of Rheumatology (SPR).
Methods: These treatment recommendations were formulated by Portuguese rheumatologists based on literature evidence and consensus opinion. At a national meeting the 16 recommendations included in this document were discussed and updated. The level of agreement among Portuguese Rheumatologists was assessed using an online survey. A draft of the full text of the recommendations was then circulated and suggestions were incorporated. A final version was again circulated before publication.
Results: A consensus was achieved regarding the initiation, assessment of response and switching biological therapies in patients with psoriatic arthritis (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: Psoriatic Arthritis; Biological therapies; Guidelines.

INTRODUCTION

There are currently six biological therapies licensed in Europe for the treatment of active psoriatic arthritis (PsA) patients: five tumour necrosis factor (TNF) antagonists: adalimumab, etanercept, golimumab, certolizumab and infliximab; and the antagonist of the shared p40 subunit of IL12 and IL23, ustekinumab[1-15]. The oral small molecule inhibitor of phosphodiesterase 4, apremilast, has also been recently approved by the European Medicines Agency and a position paper will follow this recommendations regarding the use of apremilast for the treatment of psoriatic arthritis[16]. All these agents have demonstrated clinical efficacy in peripheral arthritis, enthesitis, dactylitis, and skin/nail involvement[1-13, 17-21]. Radiographic/structural progression inhibition in erosive peripheral disease has also been shown with TNF antagonists and ustekinumab[9, 10, 22-26]. 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[27, 28]. 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[29-37]. Preliminary data on ustekinumab suggests symptomatic improvement of axial disease[38].

Secukinumab is a potentially useful but not yet licensed biological therapy for this disease[21,39,40]. Abatacept has also shown to be superior to placebo[41]. Results from ixekizumab (phase 3), tofacitinib (phase 3) and guselkumab are expected in the near future. The evidence with the use of tocilizumab and rituximab is based in case reports or open label studies, showing limited efficacy[42]. The use of biological therapies in PsA 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. Each recommendation (Table I) was discussed by a group of rheumatologists attending a national rheumatology meeting. The level of agreement for each recommendation was assessed among all Portuguese rheumatologists using an online survey, and measured on a 10-point numerical rating scale (1=no agreement, 10=full agreement).

Adalimumab, etanercept, golimumab, certolizumab, infliximab and ustekinumab 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 recommendations, we have differentiated four major clinical phenotypes: 1) peripheral arthritis, 2) axial disease, 3) enthesitis and 4) dactylitis.

The treatment of skin/nail involvement in patients with PsA is beyond the scope of these recommendations. The task force involved in developing these recommendations did not include dermatologists; therefore, the treatment of skin/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 to achieve remission of both skin and musculoskeletal manifestations.

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. It also aims 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. A structured national registry of patients with rheumatic diseases, the Rheumatic Diseases Portuguese Register (Reuma.pt) incorporating disease assessment tools has been created by the Portuguese Society of Rheumatology[43]. All patients treated with biologic disease modifying anti-rheumatic drugs (DMARDs) should be registered in Reuma.pt.[44]

RECOMMENDATIONS FOR THE USE OF BIOLOGICAL THERAPIES IN PATIENTS WITH PSA

DIAGNOSIS

The patient should have a definitive diagnosis of PsA made by a rheumatologist. Although several classification criteria have been described, the ClASsification criteria for Psoriatic ARthritis (CASPAR) have been validated and are the most widely used criteria in international recommendations and studies in PsA[45,46].

The five subgroups proposed by Moll and Wright are still frequently used in clinical practice, although considerable overlap between these groups is now recognized[47].

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 a positive result does 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, and for disease monitoring[47,48].

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

PERIPHERAL ARTHRITIS

In PsA, treatment with TNF antagonists or ustekinumab is recommended for patients with active peripheral disease despite optimal treatment with conventional synthetic (cs) DMARDs (treatment failure), and if 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 peripheral arthritis, including PsA. The American College of Rheumatology (ACR) joint count of 68 tender and 66 swollen (68/66) and the modified 78/76 joint count are the most widely used methods. The 28-joint count included in Disease Activity Score (DAS28) used for the assessment of RA may not be appropriate for all PsA patients, particularly in the oligoarticular subtype and in patients with disease predominantly affecting lower limb joints or the distal interphalangeal joints[49-53]. Dedicated screens for joint counts as well as DAS28 are available in Reuma.pt. The presence of at least one tender and/or swollen joint is generally accepted as active peripheral disease[1-13,17,53-55]. Some poor prognosis factors have been identified in PsA, namely the number of actively inflamed joints (defined by some authors as 5 or more), elevated acute phase reactants, progressing radiographic damage, loss of physical func-

tion and impairment of quality of life[18,56].

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 biological therapies should be made on a case-by-case basis, according to the rheumatologist opinion, and taking into account disease severity and the presence of poor prognostic factors.

DEFINITION OF TREATMENT FAILURE

Several good systematic literature reviews on the different disease-modifying therapies used for peripheral PsA have been published[18-20,57]. In general, few randomized controlled trials (RCTs) assessed the efficacy of csDMARDs 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, sulphasalazine, leflunomide, cyclosporine and even injected gold salts are effective in peripheral arthritis[18-20]. The use of intramuscular gold salts is however not usually recommended because other less toxic treatments are available. Although the level of evidence is limited, methotrexate has been considered as first choice csDMARD based on experts' opinion[58,59]. Regarding prevention of radiographic progression, csDMARD studies have either failed to document it, had inconclusive results, or have not reported it. To date, there is also no data showing that combination therapy with TNF antagonists and csDMARDs is more efficacious than TNF antagonists' monotherapy. Furthermore it was not possible to conclude of an additional benefit in adding MTX to TNF antagonists in what concerns inhibition of radiographic progression[26]. However, data from registers suggests that the association of MTX and TNF antagonists increases TNF antagonists' drug survival and that this effect is more evident for infliximab[60,61].

Two RCTs showed efficacy of non-steroidal anti-inflammatory drugs (NSAIDs), including classic and cyclo-oxygenase-2 selective inhibitors, in reducing the symptoms and signs of PsA. No difference in efficacy between different NSAIDs was identified in comparative studies[18,59].

Although no evidence exists to support the use of systemic corticosteroids in peripheral PsA, and despite concerns over their safety in patients with psoriasis, they are widely prescribed[18-20,59]. 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[59,62,63].

Recommendation 3: Biological therapy is recommended for treatment of active peripheral arthritis in patients who have failed to respond to at least one csDMARD (methotrexate or leflunomide) for at least 3 months on a standard (full) target dose, unless intolerance, toxicity or contraindication. In the absence of poor prognostic factors, a second csDMARD (methotrexate, sulfasalazine, leflunomide, cyclosporine) or an association of csDMARDs can be considered, with reassessment after 3 additional months of therapy. In case of mono/oligoarthritis intra-articular corticosteroids should also be considered.

ASSESSMENT OF RESPONSE TO TREATMENT OF ACTIVE PERIPHERAL ARTHRITIS

Unlike for RA, there are no validated and unequivocally reliable instruments to evaluate response to therapy in PsA[23,50,55,64-67].

By analogy to clinical trials and previously published recommendations, the definition of response to treatment can be based in the psoriatic arthritis response criteria (PsARC) or in the ACR response criteria[8,65-67]. To obtain a PSARC response, a patient has to achieve tender[68] or swollen joint[66] count improvement of 30% and 1 of the following: patient global or physician global improvement of at least 1 point on a 5-point Likert scale. No worsening of any measure should occur[66]. To achieve an ACR 20, 50, or 70 response, at least 20%, 50%, or 70% improvement in tender and swollen joint counts and three of five scores of individual elements [visual analog scale (VAS) scores of patient pain, physician and patient global assessment, a disability measure (Health Assessment Questionnaire - HAQ) and an acute phase reactant (erythrocyte sedimentation rate - ESR or C-reactive protein - CRP)] must be obtained without worsening of the other two[68]. Furthermore, the physician should base his decision on clinical, laboratory and radiological parameters of the disease[66].

Response to treatment of "RA-like" PsA (i.e. PsA with a pattern of joint involvement similar to RA) may be assessed using criteria developed for RA, such as the DAS28 and the European League Against Rheumatism

(EULAR) response criteria, shown to be reliable and discriminative in this subtype of PsA[67,69,70]. Patients with distal interphalangeal joint or oligoarticular involvement should not be considered as "RA-like" PsA and the DAS28 should not be used in this subgroup of patients[53].

Composite measures evaluating the different domains of psoriatic disease have been developed such as the psoriatic arthritis disease activity score (PASDAS), the composite psoriatic arthritis disease activity score (CPDAI), the arithmetic mean of the desirable function (AMDF), the psoriatic arthritis joint activity index (PsAJAI) and the disease activity index for psoriatic arthritis (DAPSA), but their validity and discriminative capacity are still being assessed[71]. An effort for the definition of cut-offs for low, moderate and high disease activity for PASDAS, CPDAI, DAPSA and DAS28-CRP has been undertaken[72]. Finally, minimal disease activity (MDA) has been defined, and tender and swollen joint counts ≤1 based on 68 tender/66 swollen joint counts have been included as two of the domains. An MDA is attained if 5/7 of the following are achieved: tender joint count ≤1, swollen joint count ≤1; psoriasis activity and severity index (PASI) ≤1 or body surface area (BSA) ≤3 patient pain VAS score of ≤15; patient global disease activity VAS score of ≤20; HAQ score ≤0.5 and tender entheseal points ≤1[73].

Recommendation 4: For peripheral arthritis, response should be defined by PsARC / ACR criteria. The rheumatologist opinion and other clinical, laboratorial and radiological parameters should be considered in the decision to maintain or stop treatment. Response should be assessed at 3 and then 6 months after starting biological therapy. In patients with "RA-like" disease, response may also be determined according to changes in the DAS28: response defined by an improvement of at least 0.6 units at 3 months, and greater than 1.2 units at 6 months. The maintenance of treatment beyond that period, despite failure to achieve response, should be done according to the rheumatologist opinion.

AXIAL DISEASE

In PsA, treatment with TNF antagonists is recommended for patients with active axial disease despite optimal conventional treatment (treatment failure), and if supported by the rheumatologist opinion. Ustekinumab and secukinumab have shown promising results in AS/axial SpA but have not been approved for this disease yet. Since the evidence for treating "psoriatic spondylitis" is extrapolated from AS/axial SpA trials, other drugs than TNF antagonists should only be considered to specifically treat the axial component of PsA once they have been approved by regulatory agencies to treat AS/axial SpA. Specific trials in "psoriatic spondylitis" are unlikely to be performed.

DEFINITION OF AXIAL INVOLVEMENT

There is currently no consensus about the definition of "axial involvement" of patients with PsA ("psoriatic spondylitis")[74]. The combination of inflammatory back pain and at least bilateral grade II or unilateral grade III sacroiliitis has been often used to define axial involvement is PsA, reflecting an adaptation of the modified New York (mNY) criteria for AS[23, 75-77]. The more recently developed Assessment of Spondyloarthritis International Society (ASAS) classification criteria for axial SpA allow classifying patients with early disease, in the absence of radiographic sacroiliitis[78, 79]. The overlap of classification criteria between AS/axial SpA and "psoriatic spondylitis" has been supported by studies that found no differences in disease activity, function and quality of life between AS patients with and without psoriasis[80, 81].

Recommendation 5: Patients with PsA are classified as having axial disease if they also fulfill the ASAS classification criteria for axial SpA or the mNY criteria for AS.

DEFINITION OF ACTIVE AXIAL DISEASE

There is no specific tool to assess disease activity of the axial involvement in PsA[82-84]. Therefore, assuming similar responses to therapy, the use of the same instruments of AS has been recommended for axial PsA: the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) and the Ankylosing Spondylitis Disease Activity Score (ASDAS), including ASDAS validated cut-offs (an ASDAS ≥2.1 represents high disease activity)[83-88]. Importantly, in a study of PsA patients with axial involvement, the ASDAS performed equally well as the BASDAI[82].

There is also recent evidence that the ASDAS may better reflect the inflammatory disease processes in patients with axial SpA 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, namely because it selects a higher number of patients with characteristics predictive of good response to these therapies[89-91].

Dedicated screens to register axial disease activity are available in Reuma.pt.[44]

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

Recommendation 6: Active axial disease candidate to biological treatment is defined by a BASDAI ≥4 or ASDAS ≥2.1, in two separate occasions, with at least 1 month interval and a positive opinion from the rheumatologist.

DEFINITION OF TREATMENT FAILURE OF ACTIVE AXIAL DISEASE

NSAIDs (classical or COX-2 inhibitors) have demonstrated clinical efficacy in axial disease, contrary to csDMARDs[92]. All patients should have an adequate therapeutic trial of at least two NSAIDs before starting biologic therapies. 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 suggest that the maximum effect is achieved after 2 weeks in AS patients[93, 94]. For clinical purposes most guidelines have considered a period of 1 to 3 months of NSAIDs for the definition of treatment failure[95-98].

Recommendation 7: Treatment failure in axial disease is defined as active disease despite a continuous therapeutic trial with at least two NSAIDs over 1-3 months, at maximum recommended or tolerated doses, unless contraindicated.

ASSESSMENT OF RESPONSE TO TREATMENT

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 metric properties of the ASDAS compared to the BASDAI and its wide acceptance[86,88,91,99]. Specific measures of treatment response for axial PsA are being studied but until their full validation, BASDAI and ASDAS response criteria were selected as adequate tools.

The initial RCTs of infliximab, adalimumab, etanercept and golimumab did not assess specifically axial disease in PsA. The more recently studies of certolizumab efficacy in axial SpA showed significant improvement of ASAS20 but patients with psoriasis were not defined as a group[100]. Ustekinumab showed numerical improvements of BASDAI in PsA patients with axial disease but this was a sub-analysis in a small subset of patients, as the trial was not designed to assess efficacy in this subpopulation of PsA patients[37,40,101].

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.

ENTHESITIS

In PsA, treatment with TNF antagonists or ustekinumab 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 one has gained widespread acceptance[50,65,66,102]. Clinical examination is based on pain, tenderness and swelling at tendons, ligaments or capsules bone insertion. Although the term enthesitis presupposes inflammation of the entheseal site, differential diagnosis with non-inflammatory enthesopathy can be difficult. To support the rheumatologist' opinion, both PDUS and MRI can be used and several studies have documented a good correlation with the current "gold standard", which is the clinical examination[103-107].

Recommendation 9: In patients with PsA, the diagnosis of enthesitis should be established on clinical grounds. PDUS or MRI can be used to support the diagnosis.

DEFINITION OF ACTIVE ENTHESITIS

There are several tools to assess enthesitis namely the Modified Mander Enthesitis Index, the Maastricht AS enthesitis score (MASES) and its PsA modified version, including the plantar fascia, the Leeds Enthesitis Index (LEI) and the SpA research consortium of Canada (SPARCC) score[108-113]. Up to now there is still no consensus on

the preferable index to use in clinical practice, although the LEI has been the only developed and validated specifically for PsA[113]. In TNF antagonists and ustekinumab RCTs, several of these tools have been used to assess the burden of enthesitis: the number of patients with enthesitis[3-6,13,17,114], severity scores[5,6,13,37,101,115] and an MRI score[116].

The number of enthesitis sites, pain intensity (VAS or NRS) and the repercussion on function (HAQ) have been used to quantify disease severity. Olivieri *et al* used the criteria of a patient global assessment greater than 40 mm (0-100 VAS) and entheseal pain greater than 2 in a 0-4 Likert scale to define active enthesitis. In the more comprehensive GRAPPA guidelines, severe disease was defined as pain on palpation of >2 entheses and/or functional impairment according to the physician, while in the CPDAI the criteria for severe disease was pain on palpation of >3 entheses and functional disability according to the patient (HAQ≥0.5)[41,113,116]. However, these criteria still require further validation in RCTs and longitudinal observational studies. To define activity, in case of diagnostic doubt, either PDUS or MRI can also be helpful.(48) Most published guidelines state that enthesitis should be treated as a separate entity and, until further trial data become available, TNF antagonists and ustekinumab therapy for PsA entheseal disease should be decided on an individual basis[117].

Recommendation 10: Active enthesitis should be defined on a clinical basis, using a validated enthesitis index and the rheumatologist opinion, taking into account the impact of enthesitis in activities of daily life, physical function and quality of life. PDUS or MRI can be used to assist the rheumatologist opinion.

DEFINITION OF TREATMENT FAILURE

Traditionally the conventional treatment for enthesitis includes NSAIDs, glucocorticoid injections and physical therapy, although, in fact, their efficacy has not been properly studied[55,58,116,118-120]. There is also a substantial lack of evidence on the use of csDMARDs and up to now they have shown little effect on enthesitis[58,119-121]. TNF antagonists, as a class, and ustekinumab are therefore considered effective therapies for the treatment of enthesitis in PsA[3-7,13,17,27,37,101,114,115,120]. Several limitations preclude conclusions regarding differences of efficacy between TNF antagonists or in comparison with ustekinumab: 1) different outcome measures used in RCTs, 2) lack of head-to-head studies, 3) limitations of study design, 4) absence of adequately powered studies for this endpoint.

There is no consensus for the definition of treatment failure in PsA enthesitis. Olivieri *et al* defined treatment 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[27]. In the HEEL study (etanercept), treatment failure was defined as lack of response to full dose NSAIDs for at least 3 months[116]. Furthermore, in the main TNF antagonist trials there were no specific references to criteria for failure to standard therapy in enthesitis. Therefore, in the absence of evidence for the use of csDMARDs, both TNF antagonists and ustekinumab can be considered for the treatment of persistent, active, refractory enthesitis, if there is significant impact on physical function and quality of life based on the rheumatologist opinion[55, 122, 123].

Recommendation 11: Biological therapy is recommended for patients with persistent (at least 3 months) active enthesitis, who have failed to respond to NSAIDs (in full therapeutic or tolerated doses, unless contraindicated) and local corticosteroids injections (if applicable and not contra-indicated).

ASSESSMENT OF RESPONSE TO TREATMENT FOR PATIENTS WITH PERSISTENT (AT LEAST 3 MONTHS) ACTIVE ENTHESITIS

There are no validated thresholds for the commonly used enthesitis indexes in PsA to evaluate treatment response in PsA enthesitis. For the new composite indexes that include enthesitis assessment, such as the PASDAS and CPDAI, the defined cutoffs are considered for the whole score[72]. Minimal disease activity considers that the enthesitis domain has ≤ 1 tender entheses from a maximum of 13, allowing any of the available enthesitis outcome measures to be used[73].

Based in these limitations, 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[124]. 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[116,125].

By analogy to data from RCTs, although not specifically for enthesitis, at least 3 to 6 months should be proposed for initial evaluation of TNF antagonist or ustekinumab efficacy for the treatment of enthesitis.

Recommendation 12: Assessment of response should be a continuous process. Patients are considered as responders to treatment if, within 3 to 6 months, there is a reduction in the number of active enthesitis sites or a reduction in functional impairment. The decision to continue treatment should be supported by the rheumatologist opinion. PDUS or MRI can be used to assist the decision.

DACTYLITIS

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

DEFINITION OF DACTYLITIS

There are several definitions of dactylitis that integrate the concept of swelling of a digit, usually due to a combination of synovitis, tenosynovitis and enthesitis together with soft-tissue oedema[55,126,127].

Although there is no uniformity in the methods used for diagnosing dactylitis, clinical assessment based on inspection and palpation constitutes, up to now, the "gold standard". Based on the two scores developed to define dactylitis activity, the dactylitis severity score (DSS) and the Leeds dactylitis index (LDI), dactylitis can be defined as a DSS score higher than 1 or a digital circumference >10% compared to the contra lateral finger for the LDI, respectively[5,128]. Furthermore, imaging methods such as PDUS and MRI may improve diagnostic accuracy and severity evaluation[129,130].

Recommendation 13: In patients with PsA, the diagnosis of dactylitis should be established on clinical grounds based on the swelling of a whole digit. PDUS or MRI can be used to support the diagnosis.

DEFINITION OF ACTIVE DACTYLITIS

Active dactylitis is defined based on physical examination as a swollen digit, although PDUS/MRI can be used for confirmation.

Most guidelines assess dactylitis as an "active" joint. The distinction between "active or tender" and "inactive or non-tender" has prognostic impact as active dactylitis is associated with a higher risk of developing local erosions[131]. Some clinical trials used a simple count of fingers with dactylitis[21, 121], while others used severity scores such as the DSS[2,3,5,17,37,101,132] and the LDI[115]. The DSS grades severity from 0 to 3[5]. The LDI assesses severity based on two parameters: digital circumference in the proximal phalange (tumefaction) and a 0-3 tenderness score resembling the Ritchie Index[128]. In the CPDAI composite index, dactylitis was assessed by using a simple digit count and 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, defined as an HAQ score >0.5)[133]. In the PASDAS the number of tender dactylitis was also included[72]. For routine clinical practice, simple tender dactylitic fingers count is possibly the most feasible tool to define active disease and monitor patients.

Recommendation 14: Active dactylitis should be defined on a clinical basis, according to the rheumatologist opinion, taking into account swelling and tenderness, and the impact of dactylitis in daily life activities, physical function and quality of life. PDUS or MRI can be used to assist the decision.

DEFINITION OF TREATMENT FAILURE OF ACTIVE DACTYLITIS

The treatment of dactylitis is largely empirical. Treatment strategies include NSAIDs, steroid injections, csDMARDs, TNF antagonists and ustekinumab. NSAIDs and steroids injections have not been properly studied but are often used as first line treatment. There is also a substantial lack of evidence of efficacy of csDMARDs and there is no evidence that any of these drugs actually prevent disease progression.

Conversely, TNF antagonists, including etanercept, infliximab, adalimumab, certolizumab and golimumab, and the IL-12 and IL-23 blocker ustekinumab, have shown promising results in dactylitis, although dactylitis has not been assessed as a primary endpoint in these trials[3-7,13,17,115].

There is no international consensus on the definition of treatment failure even if many authors consider refractoriness to NSAIDs and corticoids injections[54,55,123,134]. Olivieri *et al* defined treatment failure as the lack of response to at least 2 NSAIDs for >3 months and at least two steroid injections[27]. In the main TNF antagonists' trials, there was no reference to criteria defining treatment failure in dactylitis. Further, in most guidelines, dactylitis is not separately addressed and is usually analyzed together with peripheral arthritis[134-136].

Although there is scarce evidence to support the use of csDMARDs in dactylitis, they are commonly used,

namely in the context of concomitant peripheral active disease[137]. Considering the component of joint synovitis, often observed in dactylitis, most rheumatologists still feel that patients should have an adequate trial of csDMARDs, before progressing to treatment with biological therapy, until further evidence is available. In selected cases, namely when severe and erosive disease is observed, biologic therapies can be considered before csDMARDs.

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), csDMARD therapy and at least two local corticosteroids injections, when applicable.

ASSESSMENT OF RESPONSE TO TREATMENT OF ACTIVE DACTYLITIS

In the absence of validated measures, the reduction in the number of digits with dactylitis, the reduction on dactylitis scores and the improvement in functional scores or in composite scores are some of the outcome measures that have been proposed and can be considered to assess response. MDA includes the dactylitis domain requiring ≤ 1 dactylitis as a criterion[73]. By analogy with the assessment of response of 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[4-7,13,17,114]. It is important to keep in mind that, in both TNF antagonist and ustekinumab long-term follow-up trials, a progressive improvement of dactylitis scores up to 52 weeks was depicted. Therefore, for responders, further improvement beyond 24 weeks can be expected[101,132].

Recommendation 16: Assessment of response of active dactylitis should be performed at three months. Patients are considered responders to treatment if there is a reduction in the number of digits with active dactylitis and a reduction in functional impairment. The decision to continue treatment should be supported by the rheumatologist opinion. PDUS or MRI can be used to assist the decision.

SWITCHING AND TAPERING BIOLOGICAL THERAPIES

After an adequate dose and length of treatment, non-responders are recommended to switch to another biological therapy. The evidence in this area is still scarce and mainly based on registry data. Even though responses might be slightly lower, there are sustained and good response rates to a second or third TNF antagonist, supporting switching recommendations[138-143]. Drug survival is also reduced with the number of switches[139,140,142]. Dose increase of biological treatments, in case of treatment failure, is not advised.

In case of a good response to biological therapy there is also still little evidence for recommending a dose reduction or the interruption of the treatment, with the latest being associated with high rates of flare[144]. 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 or regular NSAID treatment), according to the rheumatologist opinion (and potentially supported by imaging methods), and especially if the treatment is being combined with a csDMARD[144].

FINAL REMARKS

PsA is a multidomain disease characterized by involvement of peripheral joints, spine, enthesis, dactylitis, skin/nails and other extra-articular sites. 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 for 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. Diagnosing, as early as 6 months after symptoms onset, is recognized as fundamental to improve radiographic and functional outcomes and should be aimed in routine clinical practice[145].

MDA criteria for patients with PsA have been defined and validated and constitute a relevant outcome measure to assess effectiveness[64,146,147]. Treat to target recommendations in spondyloarthritis including PsA aiming at maximising long-term health related quality of life and social participation through rapid control of signs and symptoms, prevention of structural damage, normalisation or preservation of function, avoidance of toxicities and minimisation of comorbidities have been recently developed and should be taken into account in the global management of PsA patients. Similarly, recommendations for the use of imaging in the diagnosis of spondyloarthritis in clinical practice were established[148,149].

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

Domain	Recommendations	Agreement mean (SD)
Diagnosis	**Recommendation 1** A definitive diagnosis of PsA requires the presence of validated criteria such as the CASPAR or Moll and Wright criteria.	7.9 (2.0)
Peripheral arthritis	**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 biological therapies should be made on a case-by-case basis, according to the rheumatologist opinion, and taking into account disease severity and the presence of poor prognostic factors.	8.5 (1.6)
	Recommendation 3 Biological therapy is recommended for treatment of active peripheral arthritis in patients who have failed to respond to at least one csDMARD (methotrexate or leflunomide) for at least 3 months on a standard (full) target dose, unless intolerance, toxicity or contraindication. In the absence of poor prognostic factors, a second csDMARD (methotrexate, sulfasalazine, leflunomide, cyclosporine) or an association of csDMARDs can be considered, with reassessment after 3 additional months of therapy. In case of mono/oligoarthritis intra-articular corticosteroids should also be considered.	8.8 (1.5)
	Recommendation 4 For peripheral arthritis, response should be defined by PsARC / ACR criteria. The rheumatologist opinion and other clinical, laboratorial and radiological parameters should be considered in the decision to maintain or stop treatment. Response should be assessed at 3 and then 6 months after starting biological therapy. In patients with "RA-like" disease, response may also be determined according to changes in the DAS28: response defined by an improvement of at least 0.6 units at 3 months, and greater than 1.2 units at 6 months. The maintenance of treatment beyond that period, despite failure to achieve response, should be done according to the rheumatologist opinion.	8.6 (1.3)
Axial disease	**Recommendation 5** Patients with PsA are classified as having axial disease if they also fulfill the ASAS classification criteria for axial SpA or the mNY criteria for AS.	8.9 (1.7)
	Recommendation 6 Active axial disease candidate to biological treatment is defined by a BASDAI ≥4 or ASDAS ≥2.1, in two separate occasions, with at least 1 month interval and a positive opinion from the rheumatologist.	8.9 (1.5)
	Recommendation 7 Treatment failure in axial disease is defined as active disease despite a continuous therapeutic trial with at least two NSAIDs over 1-3 months, at maximum recommended or tolerated doses, unless contraindicated.	8.7 (1.4)
	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.	8.9 (1.3)

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TABLE I. ***(continuation)***

Domain	Recommendations	Agreement mean (SD)
Enthesitis	**Recommendation 9** In patients with PsA, the diagnosis of enthesitis should be established on clinical grounds. PDUS or MRI can be used to support the diagnosis.	9.0 (1.1)
	Recommendation 10 Active enthesitis should be defined on a clinical basis, using a validated enthesitis index and the rheumatologist opinion, taking into account the impact of enthesitis in activities of daily life, physical function and quality of life. PDUS or MRI can be used to assist the rheumatologist opinion.	8.8 (1.3)
	Recommendation 11 Biological therapy is recommended for patients with persistent (at least 3 months) active enthesitis, who have failed to respond to NSAIDs (in full therapeutic or tolerated doses, unless contraindicated) and local corticosteroids injections (if applicable and not contra-indicated).	8.2 (1.7)
	Recommendation 12 Assessment of response should be a continuous process. Patients are considered as responders to treatment if, within 3 to 6 months, there is a reduction in the number of active enthesitis sites or a reduction in functional impairment. The decision to continue treatment should be supported by the rheumatologist opinion. PDUS or MRI can be used to assist the decision.	8.7 (1.3)
Dactylitis	**Recommendation 13** In patients with PsA, the diagnosis of dactylitis should be established on clinical grounds based on the swelling of a whole digit. PDUS or MRI can be used to support the diagnosis.	9.4 (0.8)
	Recommendation 14 Active dactylitis should be defined on a clinical basis, according to the rheumatologist opinion, taking into account swelling and tenderness, and the impact of dactylitis in daily life activities, physical function and quality of life. PDUS or MRI can be used to assist the decision.	9.1 (1.1)
	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), csDMARD therapy and at least two local corticosteroids injections, when applicable.	8.4 (1.7)
	Recommendation 16 Assessment of response of active dactylitis should be performed at three months. Patients are considered responders to treatment if there is a reduction in the number of digits with active dactylitis and a reduction in functional impairment. The decision to continue treatment should be supported by the rheumatologist opinion. PDUS or MRI can be used to assist the decision.	8.7 (1.3)

Agreement was voted on a scale from 1 to 10 (fully disagree to fully agree) by 73 voting rheumatologists through an online survey. **PsA**, Psoriatic Arthritis. **CASPAR**, ClASsification criteria for Psoriatic ARthritis. **csDMARD**, conventional synthetic disease modifying antirheumatic drug. **PsARC**, Psoriatic Arthritis Response Criteria. **ASAS**, Assessment of Spondyloarthritis international Society. **BASDAI**, Bath Ankylosing Spondylitis Disease Activity Index. **ASDAS**, Ankylosing Spondylitis Disease Activity Score. **MRI**, magnetic resonance imaging. **SD**, standard deviation. **PDUS**, power Doppler ultrasound. **DAS28**, Disease Activity Score 28-joint count.

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. Importantly, safety should not be underestimated. The preliminary workup to initiate treatment with TNF antagonists and ustekinumab in PsA patients should follow the same principles and recommendations as for RA[150,151]. Patients with latent tuberculosis should receive appropriate prophylactic therapy as recommended[152,153]. 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. Several composites indexes have been recently developed (CPDAI, PASDAS and AMDF) and for some their respective cut-offs were defined but its broad use and implementation in treatment guidelines is not yet established[133,154-156]. In the absence of a validated composite tool to select patients for biological treatment, the rheumatologist opinion is of utmost importance to identify patients in which the overall disease burden justifies this treatment.

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