Portuguese recommendations for the use of biological therapies in patients with axial spondyloarthritis – 2016 update

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ABSTRACT

Objective: To update the recommendations for the treatment of axial spondyloarthritis (axSpA) 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. At a national meeting, the recommendations included in this document were discussed and updated. A draft of the full text of the recommendations was then circulated and suggestions were incorporated. A final version was again circulated before publication and the level of agreement among Portuguese Rheumatologists was anonymously assessed using an online survey.

Results: A consensus was achieved regarding the initiation, assessment of response and switching of biological therapies in patients with axSpA. In total, seven recommendations were produced. The first recommendation is a general statement indicating that biological therapy is not a first-line drug treatment option and should only be used after conventional treatment has failed. The second recommendation is also a general statement about the broad concept of axSpA adopted by these recommendations that includes both non-radiographic and radiographic axSpA. Recommendations 3 to 7 deal with the definition of active disease (including the recommended threshold of 2.1 for the Ankylosing Spondylitis Disease Activity Score [ASDAS] or the threshold of 4 [0-10 scale] for the Bath Ankylosing Spondylitis Disease Activity Index [BASDAI]), conventional treatment failure (nonsteroidal anti-inflammatory drugs being the first-line drug treatment), assessment of response to treatment (based on an ASDAS improvement of at least 1.1 units or a BASDAI improvement of at least 2 units [0-10 scale] or at least 50%), and strategy in the presence of an ina-

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dequate response (where switching is recommended) or in the presence of long-term remission (where a process of biological therapy optimization can be considered, either a gradual increase in the interval between doses or a decrease of each dose of the biological therapy).

Conclusion: These recommendations may be used for guidance in deciding which patients with axSpA 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: Portugal; axial spondyloarthritis; ankylosing spondylitis; biological therapies; guidelines; recommendations.

INTRODUCTION

In 2005, the first version of the recommendations of the Portuguese Society of Rheumatology (SPR – *Sociedade Portuguesa de Reumatologia*) for the treatment of ankylosing spondylitis (AS) with biological therapies was published in *Acta Reumatológica Portuguesa* (ARP)[1]. These recommendations were updated in 2011[2]. Since then new evidence has been published, the concept of axial spondyloarthritis (axSpA), as comprising the entire spectrum of patients with radiographic sacroiliitis (AS) and without radiographic sacroiliitis (non-radiographic axSpA), has become established, clinical trials with patients covering the entire spectrum of axSpA have been published, and a new class of biological disease modifying anti rheumatic drugs (bDMARDs) has emerged to treat patients with axSpA (IL17-blockers). It was therefore felt timely to update the recommendations for the use of biological therapies in patients with axSpA.

There are currently five registered TNF-blockers for the indication of axSpA: adalimumab, certolizumab, etanercept, golimumab and infliximab (in alphabetical order). These therapies can be used in monotherapy, without the need to combine them with conventional synthetic DMARDS (csDMARDs). All, except infliximab, have European Medicines Agency (EMA) approval for both radiographic and non-radiographic axSpA. Biosimilars of infliximab, etanercept and adalimumab are also approved by the EMA.[3] IL17-blocker therapy (secukinumab) has only been approved by the EMA for axSpA with radiographic sacroiliitis.[4,5]

This article presents the 2016 update of the Portuguese recommendations for the use of biological therapies in patients with axSpA. Although these national recommendations contain some original concepts, their general structure follows the pattern of other international recommendations.[6] They were formulated by Portuguese rheumatologists based on literature evidence and consensus opinion. At a national meeting, the 7 recommendations included in this document were discussed and updated. A draft of the full text of the recommendations was then circulated and suggestions were incorporated. A final version was again circulated before publication and the level of agreement among Portuguese Rheumatologists was anonymously assessed using an online survey. Agreement was measured on a 11-point numerical rating scale (with the anchors 0 = "do not agree at all" and 10 = "fully agree").

These recommendations may be used for guidance on which patients with axSpA should be treated with biological therapies and how to decide regarding continuation of treatment.

1. CRITERIA FOR STARTING BIOLOGICAL THERAPIES AND ASSESSING RESPONSE TO TREATMENT

1.1. General statement

Recommendation 1: In axSpA, biological therapy is recommended for patients with active disease despite optimal conventional treatment (treatment failure).

1.2. Classification of axSpA

Recommendation 2: Patients are classified as having axSpA if they fulfill the Assessment of Spondyloarthritis international Society (ASAS) criteria for axSpA (or the modified New York criteria for AS).

The main aim of this recommendation is to re-emphasise and again acknowledge the fact that radiographic sacroiliitis is often a late finding in the axSpA disease course, that magnetic resonance imaging (MRI) may show evidence of inflammation before structural damage becomes evident on plain radiographs, and that patients with normal imaging results can still be diagnosed as having axSpA based on a typical combination of clinical and laboratory features. Importantly, it has been shown that patients with non-radiographic axSpA have similar disease burden as patients fulfilling the modified New York (mNY) criteria for AS[7,8] and,

overall, studies with TNF-blockers in patients with non-radiographic axSpA have shown at least similar efficacy compared to studies performed in patients fulfilling mNY criteria.[9-21]

Of note, non-radiographic axSpA is not necessarily a pre-radiographic form of the disease, since many patients do not progress to AS. The percentage of patients who shift from non-radiographic axSpA to radiographic axSpA is not easy to determine, mainly due to methodological difficulties, particularly the variability in reading and rating radiographic changes of the sacroiliac joints. The transition rate from non-radiographic axSpA to radiographic axSpA during the early years of the disease seems to happen at a relatively low pace (5–12% during 2 years of follow-up)[22-24]. Among the possible factors associated with this shift, inflammation (elevated serum C-reactive protein [CRP] levels or MRI inflammation of the sacroiliac joints), HLA-B27 positivity and smoking have been identified. We will need to wait for studies with longer follow-up in order to clarify whether these low rates of change remain stable over time, and also to confirm whether the above characteristics are robust prognostic factors of the progression of structural damage of the sacroiliac joints[24].

This recommendation intentionally uses the word "classify" and not the word "diagnose", and it does not dispute the fact that classification criteria differ from diagnostic criteria. There are no diagnostic criteria for axSpA and the diagnosis should always be a decision taken by the rheumatologist based on clinical, laboratory and imaging features, after having considered all the potential differential diagnoses. In this context, the aim of this recommendation is merely to highlight the importance of repeating this diagnostic exercise when the patient is considered for biological treatment, and given that the ASAS criteria for axSpA have a good balance between sensitivity and specificity (sensitivity of 82.9% and specificity of 84.4%, in the original study[25,26]; sensitivity of 82% and specificity of 88%, in a more recent meta-analysis[27]) and excellent positive predictive value (93.3% in the ASAS follow-up study)[28] it was felt that verifying the fulfilment of the ASAS criteria for axSpA (for classification purposes and after a diagnosis has already been made) was a relevant exercise to be made when re-evaluating a patient prior to starting biological treatment.

1.3. Definition of active disease

Recommendation 3: Active axial disease candidate to biological therapy is defined by an Ankylosing Spondylitis Disease Activity Score (ASDAS) ≥2.1 or a Bath Ankylosing Spondylitis Activity Index (BASDAI) ≥4, on two separate occasions, with at least 1 month interval. The decision to treat with biological therapy should be supported by the rheumatologist's opinion.

Historically, the BASDAI[29] has been the most widely used clinical disease activity measure in axSpA, and the BASDAI cut-off ≥4 the most common selection criteria for clinical trials with biological therapies. The ASDAS[26,30-32] is a composite disease activity index more recently developed for axSpA, with validated disease activity cut-offs (an ASDAS ≥2.1 represents high disease activity). An increasing number of clinical trials is now using ASDAS measures as primary or secondary endpoints.

The inclusion of the ASDAS as an alternative (and preferred measure) to the BASDAI to define active axSpA disease is based on the good psychometric properties of this index[32] and its validation among the Outcome Measures in Rheumatology (OMERACT) community[33]. There is also evidence that the ASDAS may better reflect the inflammatory disease processes in patients with axSpA[34] and that ASDAS high disease activity (ASDAS ≥2.1) may be a better cut-off than BASDAI ≥4 to select patients for treatment with TNF-blockers[35-37], namely because it selects a higher number of patients with characteristics predictive of good response to these therapies[37].

It has also been shown that higher ASDAS levels may contribute to syndesmophyte formation, while this has not been shown for BASDAI alone (only for BASDAI in combination with CRP)[38,39]. Furthermore, while a high ASDAS was shown to be a predictor for continuation of TNF-blockers, a high BASDAI appeared to be a predictor for stopping TNF-blockers. It should also be highlighted that the ASDAS cut-offs for disease activity states and response criteria were based on a robust validation process, while the BASDAI cut-offs were arbitrarily chosen[31].

Importantly, the decision to consider the disease as active should be supported by the rheumatologist's opinion, who should base his judgment on clinical, laboratorial (eg. CRP) and imaging (eg. MRI) features of the disease. Of note, increased CRP levels and inflammation on MRI have been shown to be predictors of a good response to TNF-blockers[10,12,14,35,40,41] and, whenever possible, the decision to treat with biological therapies should take these factors into account.

It should be noted that the EMA approval for the treatment of patients with radiographic axSpA (AS)

with TNF-blockers is not dependent on any other patients' characteristics (ie. fulfilment of mNY criteria for AS suffices), while in patients with non-radiographic axSpA this approval only applies to patients with an elevated CRP and/or inflammation on MRI. However, given that MRI is still not widely available in a timely fashion across all Portuguese Centres, and given the limited availability of radiologists with an interest in musculoskeletal diseases, rheumatologists opted not to restrict the use of biologics in patients with non-radiographic axSpA. Furthermore, data about the efficacy of the IL17-blocker secukinumab and of the TNF-blocker infliximab in patients with non-radiographic axSpA are still lacking and therefore these drugs lack EMA approval for non-radiographic axSpA.

Finally, the group of rheumatologists decided that none of the drugs should be prioritised over the other, since efficacy with regard to musculoskeletal manifestations seems comparable (although no solid head-to-head comparisons are available)[9-14,42]. However, it was acknowledged that given the more extensive experience (in particular to what concerns long-term safety) with TNF-blockers these are more likely to be prescribed as first biologic compared to IL17-blockers. Moreover, patients' preferences/lifestyle and patients' clinical characteristics should be taken into account when prescribing a biologic drug, namely in the presence of certain extra-articular features: monoclonal antibodies (adalimumab, infliximab and certolizumab; no data on golimumab) are efficacious in preventing the recurrence of uveitis and in the treatment of inflammatory bowel disease (IBD), whereas etanercept has shown contradictory results for uveitis, less efficacy in psoriasis (no head-to-head comparisons though), and is not efficacious in IBD[43-52]. On the other hand, etanercept seems to have a lower tuberculosis risk compared to monoclonal antibody TNF-blockers[53]. Secukinumab should be avoided in patients with active IBD, as secukinumab in comparison to placebo was not efficacious in Crohn's disease and resulted in more adverse events.[54]

1.4. Definition of conventional treatment failure:
Recommendation 4: Conventional treatment failure 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 anti-inflammatory doses, unless contraindicated or if the patient develops intolerance or side-effects. For axial disease, no additional treatment with csDMARDs is required before the initiation of biological therapy.
Patients with peripheral arthritis should have an adequate trial (at least three months of full dose treatment) with a csDMARD (preferably sulfasalazine), unless contraindicated or if the patient develops intolerance or side-effects.
In the case of monoarthritis or oligoarthritis (≤4 active joints) at least 1 intra-articular injection with corticosteroids should also have been tried, as long as there is no contraindication.
For symptomatic enthesitis, at least one local steroid injection is required, as long as there is no contraindication.
NSAIDs (classical or COX-2 inhibitors) have demonstrated clinical efficacy in axial disease[55-60], contrary to csDMARDs, for which there is no evidence of clinical efficacy[61-63].

All patients should have an adequate therapeutic trial of at least two NSAIDs over at least a 2-week period each, corresponding to a total of at least 4 weeks of full-dose continuous NSAID treatment, 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 a 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.[56,57] However, the evidence for recommending this treatment period is limited and there are patients that may still respond after 2 weeks of treatment. Therefore, on a shared decision with the patient, the rheumatologist may choose to reasonably expand this treatment period for each NSAID.

There are studies suggesting some efficacy of sulfasalazine in peripheral disease and to a lesser degree in the prevention of anterior uveitis.[61-63] Regarding methotrexate and leflunomide, data are very limited and there is no evidence of efficacy in peripheral disease[64,65]. Although it was recognized that methotrexate in often prescribed in axSpA patients with peripheral arthritis, no evidence based recommendation can presently support this treatment. Therefore, slight preference was still given to sulfasalazine for axSpA patients with concomitant peripheral disease, despite limited evidence. This preference is reflected in the wording of the recommendation 4.

It should be noted that when we speak about peripheral involvement in the context of the current

recommendations, it is assumed that the patients have both axial and peripheral involvement, and that the peripheral disease is contributing to the overall level of disease activity. Currently, biological therapies are not licensed for patients with pure peripheral involvement (peripheral SpA), unless they have been diagnosed with psoriatic arthritis, for which SPR has recently published specific recommendations[66].

1.5. Assessment of response to treatment

Recommendation 5: 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 ASDAS ≥1.1 units or 2) a decrease in BASDAI ≥50% or ≥2 units (0-10 scale).

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 with biologics, where response rates generally stabilized from 3 months onwards[67]. The inclusion of the ASDAS response as an alternative (and preferred measure) 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[26,30-32,35,68] and its validation among the OMERACT community[33]. Furthermore, the ASDAS may better reflect the inflammatory disease processes in patients with axSpA than the BASDAI[34]. Beyond that, post-hoc analyses of the ASCEND trial demonstrated that ASDAS response has better discriminatory capacity than BASDAI and ASAS response[69]. In other studies, using data from other TNF-blocker trials, ASDAS showed better correlation with improvement in MRI scores than BASDAI[70,71]. Thus, and consistent with recommendation 2, preference is given to ASDAS for assessing response to treatment, while BASDAI is a possible alternative.

2. PROCEDURE IN CASE OF INADEQUATE RESPONSE TO A BIOLOGICAL AGENT

Recommendation 6: After 3-6 months of an adequate dose of continuous treatment with a biologic, we recommend switching the biological therapy in non-respondent patients.

Patients have been switched successfully from one TNF-blocker to another. There are several studies confirming a significant response to a second or third TNF-blocker[72-78]. A reduced response is seen more frequently in patients who switched because of inefficacy when compared with patients who switched due to adverse events[74]. Furthermore, patients with secondary loss of response seem to have a higher potential for response to a second TNF-blocker switch than patients who are primary non-responders[79,80]. There is no evidence that a dose increase or a decrease in dose interval enhances response. Secukinumab has shown efficacy both in TNF-blocker-naive and TNF-blocker-experienced subjects with active AS, though a better response was seen for the former[5]. No specific recommendation was made regarding the prescription order of biologic drugs when switching.

3. PROCEDURE IN CASE OF SUSTAINED LONG-TERM REMISSION UNDER A BIOLOGICAL AGENT

Recommendation 7: In case of sustained inactive disease (ASDAS<1.3) for more than 12 months under biological therapy, a process of biological therapy optimization can be initiated (gradual increase in the interval between doses or decrease of each dose) on an individual basis and according to the judgement of the rheumatologist.

Taking into account the potentially serious adverse effects and costs associated with biological therapies, it seems reasonable to consider tapering these drugs in axSpA patients in a sustained, inactive/remission state. The same procedure is recommended for other drugs with important side effects in rheumatology, such as NSAIDs or csDMARDs, as well as for biological therapies in patients with rheumatoid arthritis[81]. One randomized controlled trial has shown that reduced doses of TNF-blockers can be as effective as the standard dose in a large proportion of AS patients (up to 52% of responders as defined by the BASDAI)[82]. Several observational studies have shown similar results in the clinical setting, using pre-defined dose reduction schedules or tailored approaches to reduce dose on an individual basis, with equivalent control of disease activity, in even larger proportions of patients[83-92]. Reduced doses were also shown to be effective on spinal inflammation on MRI[93].

This approach should be thoroughly discussed with the patient and supported by the rheumatologist opinion. In such cases, a short-term reassessment of the need of treatment readjustments should be planed. It should be noted that although dose optimization seems possible for many patients, most patients flare after full discontinuation of treatment and only exceptionally remission is maintained after discontinuation[94]. Nevertheless, the reintroduction of treatment seems safe and effective[95,96].

CONCLUSION

An updated consensus was achieved regarding the initiation, assessment of response and switching biological therapies in patients with axSpA (Table 1). These recommendations may be used for guidance in deciding which patients with axSpA should be treated with biological therapies. The benefit/risk profile of the patient should always be taken into account when prescribing a biologic drug and the decision to treat with a biological drug should be a process shared between the patient and the physician. The description of contra-indications to biological treatment are outside the scope of this article and there are already position papers or

TABLE I. RECOMMENDATIONS FOR THE USE OF BIOLOGICAL THERAPIES IN PATIENTS WITH AXIAL SPONDYLOARTHRITIS

Domain	Recommendation	Agreement mean (SD) % scores ≥8
General recommendation	In axSpA, biological therapy is recommended for patients with active disease despite optimal conventional treatment (treatment failure).	9.6 (0.8) 97.4%
Classification of patients	Patients are classified as having axSpA if they fulfill the ASAS criteria for axSpA (or the modified New York criteria for AS).	9.5 (0.8) 97.4%
Active disease	Active axial disease candidate to biological therapy is defined by an ASDAS ≥2.1 or a BASDAI ≥4, on two separate occasions with at least 1 month interval. The decision to treat with biological therapy should be supported by the rheumatologist's opinion.	9.4 (1.0) 97.4%
Conventional treatment failure	Conventional treatment failure 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 anti-inflammatory doses, unless contraindicated or if the patient develops intolerance or side-effects. For axial disease, no additional treatment with conventional synthetic DMARDs is required before the initiation of biological therapy. Patients with peripheral arthritis should have an adequate trial (at least three months of full dose treatment) with a conventional synthetic DMARD (preferably sulfasalazine), unless contraindicated or if the patient develops intolerance or side-effects. In the case of monoarthritis or oligoarthritis (≤ 4 active joints) at least 1 intra-articular injection with corticosteroids should also have been tried, as long as there is no contraindication. For symptomatic enthesitis, at least one local steroid injection is required, as long as there is no contraindication.	9.0 (1.5) 87.2%
Assessment of response	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 scale) or 2) a decrease in ASDAS ≥1.1 units.	9.3 (0.9) 94.7%
Inadequate response	After 3-6 months of an adequate dose of continuous treatment with a biologic, we recommend switching the biological therapy in non-respondent patients.	9.3 (1.2) 89.5%
Long-term "remission"	In case of sustained inactive disease (ASDAS<1.3) for more than 12 months under biological therapy, a process of biological therapy optimization can be initiated (gradual increase in the interval between doses or decrease of each dose) on an individual basis and according to the judgement of the rheumatologist.	9.4 (0.9) 97.4%

Agreement was voted on a scale from 0 to 10 (fully disagree to fully agree) by 39 voting rheumatologists.
AS – Ankylosing Spondylitis; ASAS – Assessment of Spondyloarthritis international Society; ASDAS – Ankylosing Spondylitis Disease Activity Score; axSpA – axial spondyloarthritis; BASDAI – Bath Ankylosing Spondylitis Disease Activity Index; csDMARD – conventional synthetic disease modifying anti-rheumatic drug; NSAIDs – nonsteroidal anti-inflammatory drugs; SD, standard deviation.

recommendations issued by SPR regarding the use of biosimilars, vaccination strategy and tuberculosis screening in patients with immune mediated inflammatory diseases, including patients that are candidates for treatment or already treated with biological therapies[3,97,98]. The use of biological therapies in axSpA is a rapidly evolving field. As more evidence becomes available and more biological therapies are licensed, these recommendations will have to be updated.

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