Portuguese recommendations for the use of biological therapies in patients with axial spondyloarthritis – December 2011 update

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ABSTRACT

Objective: To develop recommendations for the treatment of axial spondyloarthritis 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 and supporting evidence was first circulated to all Portuguese rheumatologists and their suggestions were incorporated in the draft. Secondly, at a national meeting the recommendations were presented, discussed and revised. Finally, the document resulting from this meeting was again circulated to all Portuguese rheumatologists, who anonymously voted online on the level of agreement with the recommendations.
Results: A consensus was achieved regarding the initiation, assessment of response and switching biological therapies in patients with axial spondyloarthritis.
Conclusion: These recommendations may be used for guidance in deciding which patients with axial spondyloarthritis 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.

INTRODUCTION

In 2005, the first version of the Portuguese Society of Rheumatology guidelines for the treatment of ankylosing spondylitis (AS) with biological therapies was published in Acta Reumatológica Portuguesa (ARP)[1]. Since then new evidence has been published, the concept of axial spondyloarthritis (SpA)/AS has changed and the knowledge about the use of tumour necrosis factor (TNF) antagonists has grown substantially, urging the need to revise these recommendations.

There are currently four approved biological therapies for AS and all of them are TNF antagonists: adalimumab, etanercept, golimumab and infliximab[2-13]. These therapies can be used in monotherapy, without the need to combine them with synthetic disease modifying anti-rheumatic drugs (DMARDs). Importantly, there is now evidence that patients with non-radiographic axial SpA also benefit from biological therapies, and that this benefit may even be greater compared to patients with radiographic axial SpA[10-13].

This article presents the 2011 update of the Portuguese recommendations for the use of biological therapies in patients with axial SpA. Although these national recommendations contain some original concepts, their general structure follows the pattern of other international recommendations[14]. They were formulated by Portuguese rheumatologists based on literature evidence and consensus opinion. A draft of the recommendations and supporting evidence was first circulated to all Portuguese rheumatologists and their suggestions were incorporated in the draft. Secondly, at a national meeting the recommendations were presented, discussed and revised. Finally, the document resulting from this meeting was again circulated to all Portuguese rheumatologists, who anonymously voted online on the level of agreement with the recommendations. Agreement was measured on a 10-point nu-

merical rating scale (1=no agreement, 10=full agreement).

These recommendations may be used for guidance in deciding which patients with axial SpA should be treated with biological therapies. The use of biological therapies in axial SpA (and other rheumatic diseases) is a rapidly evolving field and as more evidence becomes available and more biological therapies are licensed, these recommendations will have to be updated.

CRITERIA FOR STARTING BIOLOGICAL THERAPIES AND ASSESSING RESPONSE TO TREATMENT

GENERAL STATEMENT

RECOMMENDATION 1: In axial SpA, biological therapies are recommended for patients with active disease despite optimal conventional treatment (treatment failure).

DIAGNOSIS OF AXIAL SPA

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

In the 2005 consensus statement, it had already been recognized that the modified New York (mNY) criteria for AS were restrictive and did not cover the whole spectrum of patients with axial SpA. At that time, a modification of the mNY criteria was proposed, allowing the definition of sacroiliitis not only according to the findings observed on plain radiographs but also according to other imaging methods, namely magnetic resonance imaging (MRI) or computed tomography (CT)[1].

It is now widely recognized that the mNY criteria perform well in established disease but lack sensitivity in early spinal disease. Furthermore, over the last years MRI has become the preferred imaging method in assessing patients with suspected early disease who do not yet have definite sacroiliitis on plain radiographs as required by the mNY criteria[15].

On MRI, active inflammation of the sacroiliac joints with or without signs of structural damage can be anatomically accurately visualized. Importantly, MRI performs better than radioisotope scintigraphy (which has limited diagnostic value)[16] and CT (which is associated with higher radiation exposure and cannot visualize active inflammation, although it can better detect structural lesions of the sacroiliac joints such as erosions)[17]. Active sacroiliitis on MRI has also been shown to predict the later appearance of sacroiliitis on radiographs[18,19], thereby adding validity to the identification of inflammation of the sacroiliac joints on MRI as an important finding in early axial SpA[15,20].

These new developments led to the concept of "axial SpA" that serves as an umbrella for patients with definite radiographic sacroiliitis, that is AS, and for patients without definite radiographic sacroiliitis, referred to as non-radiographic axial SpA[15]. This new paradigm has led the ASAS group to develop new criteria for axial SpA, published in 2009[21,22]. 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[23]. Furthermore, studies with TNF antagonists in patients with early/non-radiographic axial SpA[10-13] have shown at least similar efficacy to, and, in part, better efficacy than, studies in patients fulfilling mNY criteria[2-9].

DEFINITION OF ACTIVE DISEASE

RECOMMENDATION 3: 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. The decision to treat with biological therapy should be supported by the rheumatologist's opinion.

Historically, the Bath AS Disease Activity Index (BASDAI)[24] has been the most widely used clinical disease activity measure in axial SpA, and the BASDAI cut-off ≥4 the most common selection criteria for clinical trials with TNF antagonists. The AS Disease Activity Score (ASDAS)[25-28] is a new composite index recently developed for axial SpA, with validated disease activity cut-offs (an ASDAS ≥2.1 represents high disease activity).

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[28] and its recent validation among the Outcome Measures in Rheumatology (OMERACT) community[29]. There is also recent evidence that the ASDAS may better reflect the inflammatory disease processes in patients with axial SpA[30] 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[31-33], namely because it selects a higher number of patients with characteristics predictive of good response to these therapies[31,34].

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

DEFINITION OF TREATMENT FAILURE:

RECOMMENDATION 4: 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 synthetic DMARDs is required before initiation of therapy with a TNF antagonist.

Patients with peripheral arthritis should have an adequate trial (at least three months of full dose treatment) with a synthetic DMARD (preferably sulfasalazine), unless contraindicated or if the patient develops intolerance or side-effects. In the case of monoarthritis or oligoarthritis (≤ 4 joints) at least one 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[35-40], contrary to synthetic DMARDs, for which there is no evidence of clinical efficacy[41-43].

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[36,37]. However, the evidence for recommending this treatment 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.

There are studies suggesting some efficacy of sulfasalazine in peripheral disease and in the prevention of anterior uveitis[41-43]. Regarding methotrexate and leflunomide, data are very limited and there is no evidence of efficacy in peripheral disease[44,45]. However, it was recognized that methotrexate in often prescribed in SpA patients with peripheral arthritis, but no evidence based recommendation can presently support this treatment.

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

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 TNF antagonists, where response rates stabilized from 3 months onwards[14]. 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[25-28,33] and its recent validation among the OMERACT community[29]. Furthermore, there is recent evidence that the ASDAS may better reflect the inflammatory disease processes in patients with axial SpA than the BASDAI[30].

PROCEDURE IN CASE OF INADEQUATE RESPONSE TO A BIOLOGICAL AGENT

RECOMMENDATION 6: After an adequate dose and length of treatment, we recommend switching the biological therapy in non-respondent patients.

Patients have been switched successfully from one TNF antagonist to another. There are several studies confirming a significant response to a second or third TNF antagonist[46-52]. A reduced response is seen more frequently in patients who switched because of inefficacy when compared with patients who switched due to adverse events[48]. Furthermore, patients with secondary loss of response (in which antibody formation may be involved) seem to have a higher potential for response to a TNF antagonist switch than patients who are primary non-responders[53,54]. There is no evidence that a dose increase or a decrease in dose interval enhances response.

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

RECOMMENDATION 7: 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 this can be considered in selected patients in a remission-like state for more than 12 months.

There is no evidence for recommending a dose reduction or the interruption of the biological treatment[55-62]. However, tapering biological therapy (expanding the interval between doses or reducing the dose, and eventually discontinuing treatment) may be considered in individualized cases, namely patients with ASDAS inactive disease[27] and/or ASAS partial remission criteria[63] for at least 12 months[57,58,61,64-66]. 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 reintroduction should be planed. It should be noted that most patients flare after discontinuation of treatment but the reintroduction of treatment seems safe and effective[55-62].

CLINICAL ASSESSMENT

The following should be considered for clinical assessment of patients with axial SpA:

a) Disease activity: BASDAI[24,67], ASDAS (preferably ASDAS with C-reactive protein [CRP], alternatively ASDAS with erythrocyte sedimentation rate [ESR])[25-27], patient global assessment (visual analogue scale [VAS] or 0-10 numeric rating scale [NRS]), physician global assessment (VAS or 0-10 NRS), spinal pain in the last week (VAS or 0-10 NRS), spinal night pain in the last week (VAS or 0-10 NRS) and CRP or ESR. Where there is peripheral arthritis or enthesitis, appropriate joint counts and number of symptomatic entheses should be recorded.
b) Physical function should be assessed by the Bath Ankylosing Spondylitis Functional Index (BASFI)[67,68]. Where there is peripheral arthritis or enthesitis, the Health Assessment Questionnaire (HAQ) disability questionnaire may provide additional useful information[69]. A modification of the Health Assessment Questionnaire for the spondyloarthritis (HAQ-S) may be used as an alternative to the BASFI[70] .
c) Spinal mobility should be assessed by the Bath Ankylosing Spondylitis Metrology Index (BASMI)[71-73], occiput to wall distance and chest expansion.
d) Health related quality of life should be assessed by specific (Ankylosing Spondylitis Quality of Life [ASQoL])[74] or generic questionnaires (Short Form 36 [SF-36] or Short Form 12 [SF-12])[75-77].

A register of patients with rheumatic diseases (Reuma.pt) has been established in Portugal since 2008[78]. This registry includes standardized disease assessment tools for inflammatory rheumatic diseases, including axial SpA. All patients selected for treatment with biological therapies should be included in Reuma.pt[78].

TUBERCULOSIS SCREENING BEFORE INTRODUCTION OF BIOLOGICAL THERAPIES

The Portuguese Society of Rheumatology (SPR) and the Portuguese Society of Pneumology (SPP) have developed recommendations on the diagnosis and treatment of latent tuberculosis and active tuberculosis in patients with inflammatory joint diseases treated with biologic therapies, which are periodically updated and available at the SPR, SPP and *Direcção-Geral da Saúde* websites[79].

"ABSOLUTE" CONTRAINDICATIONS FOR THE USE OF BIOLOGICAL THERAPIES

1. Active infection (some exceptions can be considered and this issue is detailed in the practical guide for prescribing biological therapies published by SPR[80]).
2. Concurrent administration of live vaccines.
3. Recent history (<5 years) of malignancy (except in the case of basal cell carcinoma).
4. Congestive heart failure (NYHA class III-IV).
5. History of demyelinating disease.

PREGNANCY AND THE USE OF BIOLOGICAL THERAPIES

1. Biological therapy should not be started in pregnant or breastfeeding women.
2. If pregnancy occurs under treatment, biological therapy should be stopped.

This issue is detailed in the practical guide for prescribing biological therapies published by SPR[80] and in a recently published systematic literature review[81].

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

Domain	Recommendation	Agreement mean (SD)
General recommendation	In axial SpA, biological therapies are recommended for patients with active disease despite optimal conventional treatment (treatment failure)	9.5 (0.8)
Classification of patients	Patients are classified as having axial SpA if they fulfill the ASAS criteria for axial SpA or the modified New York criteria for AS	9.0 (1.5)
Active disease	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. The decision to treat with biological therapy should be supported by the rheumatologist's opinion	8.9 (1.8)
Treatment failure	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 synthetic DMARDs is required before initiation of therapy with a TNF antagonist. Patients with peripheral arthritis should have an adequate trial (at least three months of full dose treatment) with a synthetic DMARD (preferably sulfasalazine), unless contraindicated or if the patient develops intolerance or side-effects. In the case of monoarthritis or oligoarthritis (≤ 4 joints)at least one 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	8.0 (2.2)
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	9.0 (1.3)
Inadequate response	After an adequate dose and length of treatment, we recommend switching the biological therapy in non-respondent patients	9.2 (1.0)
Long-term "remission"	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 this can be considered in selected patients in a remission-like state for more than 12 months	8.8 (1.4)

Agreement was voted on a scale from 1 to 10 (fully disagree to fully agree) by 38 voting rheumatologists.
AS, ankylosing spondylitis. **ASAS,** Assessment of Spondyloarthritis international Society. **ASDAS,** Ankylosing Spondylitis Disease Activity Score. **BASDAI,** Bath Ankylosing Spondylitis Disease Activity Index. **DMARD,** disease-modifying antirheumatic drug. **NSAID,** non-steroidal anti-inflammatory drug. **SD,** standard deviation. **TNF,** tumour necrosis factor.

CRITERIA FOR TEMPORARY SUSPENSION/ /POSTPONEMENT OF INTRODUCTION OF BIOLOGICAL THERAPIES

1. Active infection.
2. Recurrent infection or high risk for infections.
3. Major surgery planned.

This issue is detailed in the practical guide for prescribing biological therapies published by SPR[80] and in a recent review[82].

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