

PORTUGUESE GUIDELINES FOR THE USE
OF BIOLOGICAL AGENTS IN RHEUMATOID
ARTHRITIS – MARCH 2010 UPDATE

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Resumo

Os autores apresentam a actualização dos Consensos sobre a utilização de terapêuticas biológicas na artrite reumatóide (AR), elaborados por um grupo de trabalho da Sociedade Portuguesa de Reumatologia (SPR). Nestas normas nacionais são discutidos os critérios para início e manutenção de terapêutica biológica, contra-indicações para a sua utilização e actuação se o doente for não respondedor. Para início de terapêutica biológica os doentes com AR devem ter um *disease activity score 28* (DAS 28) superior a 3,2, após pelo menos 3 meses de tratamento com metotrexato (MTX) na dose de 20mg/semana, ou, na impossibilidade de tratamento com MTX nesta dose, após 6 meses de outro fármaco convencional modificador da doença ou associação terapêutica. Está previsto também o início de terapêutica biológica em doentes que, sob terapêuticas convencionais, apresentem um DAS28 entre 2,6 e 3,2 e tenham uma significativa degradação funcional ou radiológica. O objectivo terapêutico deverá ser atingir a remissão ou, pelo menos, uma baixa actividade da doença traduzida por um DAS28 inferior a 3,2, sem degradação funcional ou radiológica significativa.

São considerados critérios de resposta após os primeiros 3 meses de terapêutica a verificação de uma redução do DAS28 superior a 0,6. A partir dos

6 meses de terapêutica considera-se a existência de resposta clínica se os doentes apresentarem uma redução do DAS28 superior a 1,2. Nos doentes considerados não respondedores o Reumatologista assistente poderá optar por mudar para outro agente biológico (antagonista do factor de necrose tumoral, abatacept, rituximab ou tocilizumab).

Palavras-Chave: Artrite Reumatóide; Terapêutica Biológica; Anti-TNF; Rituximab; Abatacept; Tocilizumab.

Abstract

The authors present the revised version of the Portuguese Society of Rheumatology (SPR) guidelines for the treatment of rheumatoid arthritis (RA) with biological therapies. In these guidelines the criteria for introduction and maintenance of biological agents are discussed as well as the contraindications and procedures in the case of non-responders. Biological treatment should be considered in RA patients with a *disease activity score 28* (DAS 28) superior to 3.2 despite treatment with 20mg/week of methotrexate (MTX) for at least 3 months or, if such treatment is not possible, after 6 months of other conventional disease modifying drug or combination therapy. A DAS 28 score between 2.6 and 3.2 with a significant functional or radiological deterioration under treatment with conventional regimens could also constitute an indication for biological treatment.

The treatment goal should be remission or, if that is not achievable, at least a low disease activity, characterized by a DAS28 lower than 3.2, without significant functional or radiological worsening. The response criteria, at the end of the first 3 months of treatment, are a decrease of 0.6 in the DAS28 score. After 6 months of treatment response criteria is defined as a decrease of more than 1.2 in the DAS28 score. Non-responders, in accordance to the Rheumatologist's clinical opinion, should try a switch to another biological agent (tumour necrosis factor antagonist, abatacept, rituximab or tocilizumab).

Keywords: Rheumatoid Arthritis; Biological Therapies; Anti-TNF; Rituximab; Abatacept; Tocilizumab.

Introduction

In 2003, the Rheumatoid Arthritis Study Group (GEAR – Grupo de Estudos de Artrite Reumatóide) of the Portuguese Society of Rheumatology (SPR – Sociedade Portuguesa de Reumatologia) published the first version of the guidelines for the use of biological therapies in rheumatoid arthritis (RA) in Acta Reumatológica Portuguesa (ARP)¹. With the publication of new evidence on the use of these treatments and an increased experience on their use, it was mandatory to revise and update these guidelines.

The monitoring of RA patients in Portugal is performed according to a national protocol of follow-up. The adopted model is based on the systematic use of a RA patient follow-up form, which includes a core set of variables, approved by the GEAR as well as by all national Rheumatology Department Directors. This follow-up protocol includes the data proposed initially in 2001 and reviewed in 2007². This protocol has been included now in a national registry of RA patients (RegistAR) and in a national registry of RA patients treated with biologics (BioRePortAR), which constitute an electronic clinical chart integrated with a database.

The criteria used in these guidelines are based on the standardized use of validated assessment tools: the disease activity score 28 (DAS 28)^{3,4}, the health assessment questionnaire (HAQ)⁵ and the radiology assessment of Sharp score modified by van der Heijde (SvdH)⁶. Although these recommendations contain some original concepts, their general structure follows the pattern of other international recommendations⁷.

Guidelines for the use of biological therapies in RA patients

The guidelines intend to propose national recommendations, approved by SPR members, for the use of biological therapies in RA. The guidelines' aims are:

- To improve the quality of clinical practice in the field of Rheumatology;
- To guarantee a rational use of biological therapies approved for use in RA patients with inadequate response to conventional disease modifying anti-rheumatic drugs (infliximab and anakinra in association with methotrexate (MTX), adalimumab, etanercept and tocilizumab in association with MTX or in monotherapy) or that are inadequate responders to TNF blockers (rituximab and abatacept, in association with MTX, tocilizumab in association with MTX or in monotherapy. (Table I)

Table I. Biological therapies approved for Rheumatoid Arthritis. DMARDs – Disease modifying anti-rheumatic drugs.

	Inadequate response to conventional DMARDs	Inadequate response to TNF blockers
In association with MTX	adalimumab anakinra etanercept infliximab tocilizumab	abatacept rituximab tocilizumab
In monotherapy	adalimumab etanercept tocilizumab	tocilizumab

Selection of patients for treatment with biological agents

Patients who fail or have an inadequate response to conventional disease modifying antirheumatic drugs (DMARDs) are eligible for treatment with biological therapies. «Inadequate response or treatment failure» is defined when a patient, treated with conventional DMARDs over a period of time deemed adequate in these guidelines, present one of the following situations:

- DAS > 3.2 or
- 2.6 < DAS < 3.2 and worsening of HAQ>0.22 (6/6M)⁸ or worsening x-ray scores: Larsen>6/ /SvdH >5 (12/12M)⁹

All patients selected for treatment with biological therapies should be included in the BioRePortAR.

Criteria for introduction of biological agents

1. Biological agents are recommended for patients with an inadequate response to MTX used in a stable dose of at least 20 mg/week (orally or parenterally), for at least 3 months.
2. In case of intolerance, toxicity or refusal (signed statement) to take MTX, the patient may be considered eligible for treatment with a biological agent if there is an inadequate response (according to the above provided definition) after a period of at least 6 months of treatment with a stable dose of another conventional DMARD or an association of conventional DMARDs. In these circumstances, the patient will be eligible for treatment with biological therapies that do not require simultaneous use of MTX.

Treatment Objective

DAS28 < 2.6 or, if that is not achievable, 2.6 < DAS28 < 3.2 in two successive assessments without significant worsening of the HAQ score assessed each 6 months and/or x-ray progression evaluated every 12 months.

Criteria for maintenance of biological therapy

1. The first decision is taken 3 months after the introduction of biological therapy, supported by the opinion of the Rheumatologist:
 - Maintenance of biological treatment if responder, e. g., if there is an improvement of at least 0.6 in the DAS28 score.
2. Subsequent decision after 6 months of treatment with biological therapy, supported by the opinion of the Rheumatologist:
 - Maintenance of biological treatment if there is an improvement of at least 1.2 in the DAS28 score.

Procedure in case of inadequate response to a biological agent

If the patient fails or has an incomplete response to a first-line biological treatment the Rheumatologist, according to the current evidence, may proceed to switch to a second biological agent: TNF antagonist, abatacept, rituximab or tocilizumab.

Tuberculosis screening before introduction of biological therapies

The Portuguese Society of Rheumatology (SPR) and the Portuguese Society of Pneumology

(SPP – Sociedade Portuguesa de Pneumologia) have developed recommendations on the diagnosis and treatment of latent tuberculosis (LTB) and active tuberculosis (ATB) in patients with inflammatory joint diseases (IJD), namely rheumatoid arthritis, psoriatic arthritis and ankylosing spondylitis, treated with TNF antagonists.¹⁰ With the current knowledge and state of evidence, these guidelines should be applied to the other biological therapies available.

The Portuguese Society of Rheumatology (SPR) and the Portuguese Society of Pulmonology (SPP – Sociedade Portuguesa de Pneumologia) have developed recommendations on the diagnosis and treatment of latent tuberculosis (LTB) and active tuberculosis (ATB) in patients with inflammatory joint diseases (IJD), namely rheumatoid arthritis, psoriatic arthritis and ankylosing spondylitis, treated with TNF antagonists, which are periodically updated and available at the SPR, SPP and Direcção-Geral da Saúde websites.

With the current knowledge and state of evidence, these guidelines should be applied to the other biological therapies available.

«Absolute» contraindications

- Active infection;
- Concurrent administration of live vaccines;
- Recent history (<5 years) of malignancy (except in the case of basal cell cancer);
- Congestive heart failure (NYHA class III-IV);
- History of demyelinating disease.

Pregnancy

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

Criteria for temporary suspension/postponement of introduction

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

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