

PORTUGUESE GUIDELINES FOR THE USE OF
BIOLOGICAL AGENTS IN RHEUMATOID ARTHRITIS –
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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 (with a tumour necrosis factor antagonist, abatacept or tocilizumab) should be considered in RA patients with a disease activity score 28 (DAS 28) equal to or greater than 3.2 despite treatment with at least 20mg-weekly-dose of methotrexate (MTX) for at least 3 months or, if such treatment is not possible, after 3 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, defined by a DAS28 lower than 3.2,

without significative functional or radiological worsening.

The response criteria, at the end of the first 3 months of treatment, are a decrease of at least 0.6 in the DAS28 score. After 6 months of treatment response criteria is defined as a decrease greater 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; Guidelines.

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.

These guidelines have been regularly updated as new evidence is published and the experience on their use increases.

Grupo de Estudos de Artrite Reumatóide da Sociedade Portuguesa de Reumatologia

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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 rheumatic patients (Reuma.pt)³. The criteria used in these guidelines are based on the standardized use of validated assessment tools: the disease activity score 28 (DAS 28)^{4,5}, the health assessment questionnaire (HAQ)⁶ and the radiological assessment of Sharp score modified by van der Heijde (SvdH)⁷. Although these recommendations contain some original concepts, their general structure follows the pattern of other international recommendations⁸.

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 (DMARDs) or that are inadequate responders to at least one TNF antagonist, in accordance with the indications approved by the European Medicines Agency (Table I).

Criteria for introduction of biological agents

1. 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
- $2.6 \leq \text{DAS} < 3.2$ and worsening of HAQ ≥ 0.22 (6/6M)⁹ or worsening x-ray scores: Larsen ≥ 6 / SvdH ≥ 5 (12/12M)¹⁰

All patients selected for treatment with biological therapies should be included in Reuma.pt³.

2. 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. In this situation, the rheumatologist may either proceed directly to biological therapy (particularly in patients with severe prognostic markers) or may consider further treatment with another con-

Table I. Biological therapies approved for Rheumatoid Arthritis

	Inadequate response to conventional DMARDs	Inadequate response to at least one TNF antagonist
In association with MTX	abatacept adalimumab anakinra certolizumab etanercept golimumab infliximab tocilizumab	abatacept rituximab tocilizumab
In monotherapy	adalimumab etanercept certolizumab tocilizumab	tocilizumab

DMARD – Disease Modifying Antirheumatic Drugs.

ventional DMARD or association of conventional DMARDs during at least 3 months before starting a biological agent (chiefly in patients without a severe prognosis).

3. 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 3 months of treatment with a stable dose of another conventional DMARD or an association of conventional DMARDs. If MTX cannot be included in the treatment regime, the patient will be eligible for treatment with biological therapies that do not require simultaneous use of MTX.

Treatment Objective

Remission is a realistic goal and a major therapeutic target in RA patients under treatment with biologicals. In clinical practice, remission can be defined in two distinct levels:

1. Remission based on a DAS28 < 2.6.
2. A more stringent goal for remission can be considered: a tender joint count (in 28), swollen joint count (in 28), CRP (in mg/dl) and patient global assessment (0-10 scale) scoring all ≤1 or Simplified Disease Activity Index (SDAI) ≤ 3.3¹¹.

If DAS28 < 2.6 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 is considered acceptable.

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 6 months after the introduction of biological therapy, supported by the opinion of the Rheumatologist:
 - Maintenance of biological treatment if there is an improvement greater than 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.

Failure to respond to one TNF antagonist does not preclude response to another. Patients have been switched successfully from one TNF antagonist to another. Observational studies suggest that non-responding patients are less likely to respond to a second TNF antagonist. Patients who have not tolerated one TNF antagonist may respond to a second one but are also less likely to tolerate a second TNF antagonist. Globally, after a second TNF antagonist failure the probability of response to a third TNF antagonist is low¹².

Procedure in case of sustained long-term remission under a biological agent

If the patient experiences remission for at least 12 months, the Rheumatologist can consider tapering biological DMARDs (expanding the interval between doses or reducing the dose), especially if this treatment is combined with a conventional DMARD¹³.

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 RA, psoriatic arthritis and ankylosing spondylitis, treated with biologicals, which are periodically updated and available at the SPR, SPP and Direção-Geral da Saúde websites¹⁴.

«Absolute» contraindications for the use of biologicals

- Active infection (some exceptions can be considered and this issue is detailed in the practical guide for prescribing biological published by SPR¹⁵);

- 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 and the use of biologicals

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 published by SPR¹⁵ and reviewed in a recently published systematic literature review¹⁶.

Criteria for temporary suspension / postponement of introduction of biologicals

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 published by SPR¹⁵ and in a recent review¹⁷.

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