

PORTUGUESE GUIDELINES FOR THE USE
OF BIOLOGICAL AGENTS IN RHEUMATOID
ARTHRITIS – DECEMBER 2007 UPDATERheumatoid Arthritis Study Group (GEAR)
of the Portuguese Society of Rheumatology (SPR)**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 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 follow-up should be performed each 3 months. 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 follows: for those with an initial DAS28 score superior to 5.1, a reduction of the DAS28 score below 4 is required; for those with an initial DAS28 score inferior to 5.1, a decrease of the DAS28 score below 3.2 without a significant functional or radiological worsening is required. Non-responders, in accordance to the Rheumatologist's clinical opinion, should try a switch to other biological agent (tumour necrosis factor alpha antagonist, rituximab or abatacept).

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

sos 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. A monitorização deve ser efectuada trimestralmente. 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 com um DAS28 inicial superior a 5,1 tiverem uma redução do DAS28 para níveis inferiores a 4 ou, se os doentes com um DAS28 inicial inferior a 5,1 apresentarem uma redução para menos de 3,2 desde que não ocorra degradação funcional ou radiológica significativa. Nos doentes considerados não respondedores o Reumatologista assistente poderá optar por mudar para outro agente biológico (antagonista do factor de necrose tumoral alfa, rituximab ou abatacept).

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

Resumo

Os autores apresentam a actualização dos Consen-

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). 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 2007.¹ The criteria used in these guidelines are based on the standardised use of validated assessment tools: the disease activity score 28 (DAS 28),^{2,3} the health assessment questionnaire (HAQ)⁴ and the radiology assessment of Sharp score modified by van der Heijde (SvdH).⁵ Although these recommendations contain some original concepts, their general structure follows the pattern of other international recommendations.⁶

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 (infliximab and anakinra in association with methotrexate (MTX); adalimumab and etanercept in association with MTX or in monotherapy; and rituximab or abatacept in patients who are non-responders to tumour necrosis factor alpha antagonist treatments (TNF-alpha)), avoiding their use in circumstances where they have not demonstrated efficacy and a good cost-effectiveness.

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)⁷ or worsening x-ray scores: Larsen > 6 / SvdH > 5 (12/12M)⁸

For all patients selected for treatment with biological therapies, a RA patient follow-up form should always be filled in. This follow-up form is the assessment tool used for monitoring therapeutic efficacy of biological treatments and constitutes the basis for the SPR database and Registry of RA patients treated with biological therapies.

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.

Criteria for maintenance of biological therapy according to assessment performed every 3 months

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:

2. a) if the initial DAS28 < 5.1, the therapy is maintained if:
 - DAS28 < 2.6 or
 - 2.6 < DAS28 < 3.2 in two successive assessments without significative worsening of the HAQ score assessed each 6 months and/or x-ray progression evaluated every 12 months
2. b) if initial DAS28 > 5.1, the therapy is maintained if:
 - DAS28 < 4 in consecutive assessments

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- α antagonist, rituximab or abatacept.

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- α antagonists.⁹ With the current knowledge and state of evidence, these guidelines should be applied to the other biological therapies available.

Due to the high risk of tuberculosis (TB) in patients with IJD, a screening of ATB and LTB should be held as soon as possible, preferably at the moment of diagnosis of a rheumatic disease. However, and even if the screening has been performed at disease onset, the assessment should be repeated before introduction of biological therapy. Whenever there is an indication for tuberculosis therapy (LTB or ATB), this should preferably be completed before introduction of a biological therapy. In case of high IJD activity, the anti-TNF- α therapy may be introduced after two months of antibacillary therapy for ATB, or after one month, for LTB.

Tuberculosis screening includes chest X-ray and

tuberculin skin test (TST) performed according to SPP recommendations with the use of 2 Units of Tuberculin RT23. If the induration is inferior to 5 mm, the test should be repeated 1 to 2 weeks afterwards on the opposite forearm. The test is considered negative if the second result is equally inferior to 5 mm.

Definition of latent tuberculosis:

- Previous history of tuberculosis inadequately treated
- Gohn complex on chest X-Ray and no previous eradicating treatment
- TST > 5mm without history of ATB
- Negative TST in an immunocompromised patient

The decision to initiate chemoprophylaxis should be assessed by weighing the individual risk of LTB and the fact that isoniazid toxicity is higher in individuals over 50 years of age and/or with previous liver disease and/or alcohol drinking habits.

Whenever an indication for treatment of LTB or ATB is requested, the patient should be referred to a National Pneumology Diagnosis Centre (Centro de Diagnóstico Pneumológico, CDP).

«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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13th International Conference for Behçet's Disease

Austria, Pörschach/Klagenfurt 24-27 de Maio de 2008de

Data limite para envio de resumos: 20 de Janeiro de 2008

35th European Symposium on Calcified Tissues

Espanha, Barcelona, 24-28 de Maio de 2008