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2017 recommendations of the Brazilian Society of Rheumatology for the pharmacological treatment of rheumatoid arthritis

Licia Maria Henrique da Mota[1,16*], Adriana Maria Kakehasi[2], Ana Paula Monteiro Gomides[1,3], Angela Luzia Branco Pinto Duarte[4], Bóris Afonso Cruz[5], Claiton Viegas Brenol[6], Cleandro Pires de Albuquerque[7], Geraldo da Rocha Castelar Pinheiro[8], Ieda Maria Magalhães Laurindo[9], Ivanio Alves Pereira[10], Manoel Barros Bertolo[11], Mariana Peixoto Guimarães Ubirajara Silva de Souza[12], Max Vitor Carioca de Freitas[13], Paulo Louzada-Júnior[14], Ricardo Machado Xavier[6] and Rina Dalva Neubarth Giorgi[15]

Abstract

The objective of this document is to provide a comprehensive update of the recommendations of Brazilian Society of Rheumatology on drug treatment of rheumatoid arthritis (RA), based on a systematic literature review and on the opinion of a panel of rheumatologists. Four general principles and eleven recommendations were approved. General principles: RA treatment should (1) preferably consist of a multidisciplinary approach coordinated by a rheumatologist, (2) include counseling on lifestyle habits, strict control of comorbidities, and updates of the vaccination record, (3) be based on decisions shared by the patient and the physician after clarification about the disease and the available therapeutic options; (4) the goal is sustained clinical remission or, when this is not feasible, low disease activity. Recommendations: (1) the first line of treatment should be a csDMARD, started as soon as the diagnosis of RA is established; (2) methotrexate (MTX) is the first-choice csDMARD; (3) the combination of two or more csDMARDs, including MTX, may be used as the first line of treatment; (4) after failure of first-line therapy with MTX, the therapeutic strategies include combining MTX with another csDMARD (leflunomide), with two csDMARDs (hydroxychloroquine and sulfasalazine), or switching MTX for another csDMARD (leflunomide or sulfasalazine) alone; (5) after failure of two schemes with csDMARDs, a bDMARD may be preferably used or, alternatively a tsDMARD, preferably combined, in both cases, with a csDMARD; (6) the different bDMARDs in combination with MTX have similar efficacy, and therefore, the therapeutic choice should take into account the peculiarities of each drug in terms of safety and cost; (7) the combination of a bDMARD and MTX is preferred over the use of a bDMARD alone; (8) in case of failure of an initial treatment scheme with a bDMARD, a scheme with another bDMARD can be used; in cases of failure with a TNFi, a second bDMARD of the same class or with another mechanism of action is effective and safe; (9) tofacitinib can be used to treat RA after failure of bDMARD; (10) corticosteroids, preferably at low doses for the shortest possible time, should be considered during periods of disease activity, and the risk-benefit ratio should also be considered; (11) reducing or spacing out bDMARD doses is possible in patients in sustained remission.

* Correspondence: liciamhmota@gmail.com
[1]Programa de Pós-graduação em Ciências Médicas, Faculdade de Medicina-Universidade de Brasília; Serviço de Reumatologia, Hospital Universitário de Brasília, Universidade de Brasília, Brasília, Brazil
[16]Rheos, Centro Médico Lúcio Costa, SGAS 610, bloco 1, salas T50- T51, L2 Sul, Asa Sul, Brasília, DF 70200700, Brazil
Full list of author information is available at the end of the article

Introduction

Rheumatoid arthritis (RA) is a systemic inflammatory autoimmune disease characterized primarily by the involvement of the synovial membrane of peripheral joints. The estimated prevalence of RA in the total population is 0.5–1.0%, and the incidence is higher in the 30–50-year-old age group and among women [1, 2]. In Brazil, a study conducted in Minas Gerais found a prevalence of 0.46% [3]. The past few decades have introduced a substantial increase in the number of RA treatments due to advances in knowledge concerning the pathophysiological mechanisms of the disease and the development of new drugs. Moreover, new monitoring and treatment strategies have been implemented, including comprehensive disease control and early intervention, during the onset of symptoms [4]. In 2012 and 2013, the RA Committee of the Brazilian Society of Rheumatology (Sociedade Brasileira de Reumatologia–SBR) published recommendations on RA diagnosis and treatment in Brazil to provide support to Brazilian rheumatologists, based upon scientific evidence combined with the experience of a panel of specialists, while safeguarding the necessary autonomy of physicians in choosing among the available therapeutic strategies [5–8]. In 2015, the recommendations were updated to include the use of target-specific synthetic disease-modifying antirheumatic drugs [9].

The objective of the current document is to provide a comprehensive update of the recommendations of SBR on drug treatment of RA in Brazil considering the advances accrued since the last revision. The scope of this work is limited to adult disease because juvenile idiopathic arthritis requires distinct and specific approaches.

Methods

The present recommendations were based on a Systematic Literature Review (SLR) and on the opinion of a panel of rheumatologists specialized in RA. In September 2016, the RA Committee met to develop questions to guide the SLR based on real-life scenarios, and these questions were improved by multiple subsequent rounds of online discussion. At the end of the interactive process, ten questions considered essential for the preparation of the recommendations were selected (Table 1). Furthermore, four general principles that should guide the entire RA treatment based on concepts widely established in the literature were formulated.

An SLR was undertaken to answer the proposed questions. Randomized clinical trials and systematic reviews of randomized clinical trials were considered eligible primarily, but controlled observational studies were also considered acceptable when interventional studies with those designs were not available. The MEDLINE, EMBASE, and SCOPUS databases were searched using specific search strategies (Table 2). In addition, the references of the selected studies, as well as relevant publications in the area, and the annals of congresses most relevant to the specialty were also searched. The search included the period from 2006 to October 2016 without language restrictions and was updated monthly until March 2017.

The studies were selected using the Covidence system (www.covidence.org). Two independent researchers analyzed the retrieved publications based on the titles and abstracts. Cases of disagreement were resolved by consensus. The risk of bias in clinical trials was assessed using the tool proposed by the Cochrane Collaboration [10]. Systematic reviews were evaluated using the AMSTAR tool [11]. The quality of evidence for each outcome (high, moderate, low, or very low) was evaluated using the GRADE tool (https://gradepro.org) [12]. The risk of publication bias was assessed by consulting the protocols of the clinical trials registered in ClinicalTrials.gov (https://clinicaltrials.gov)

Table 1 Questions based on clinical scenarios, selected by the rheumatoid arthritis committee of the brazilian society of rheumatology to guide the development of the recommendations

Questions about possible clinical scenarios for treating rheumatoid arthritis in Brazil, considering safety, effectiveness, and cost.
Question 1: Should the first line of treatment be csDMARD (methotrexate, hydroxychloroquine, leflunomide, or sulfasalazine), tsDMARD (tofacitinib), or bDMARD (adalimumab, certolizumab, etanercept, infliximab, golimumab, abatacept, rituximab, or tocilizumab)?
Question 2: Is there evidence that a particular csDMARD is more effective than other csDMARDs?
Question 3: Is there evidence that the use of combination therapy with two or more csDMARDs is more effective than csDMARD monotherapy as the first line of treatment?
Question 4: Is there evidence that after failure of a csDMARD monotherapy as the first line of treatment, the best option is to switch to a second monotherapy regimen rather than using combination therapy with two or more csDMARDs?
Question 5: Is there evidence that a particular TNFi (adalimumab, certolizumab, etanercept, golimumab, or infliximab) or non-TNFi (abatacept, rituximab, or tocilizumab) bDMARD is more effective than other biological agents?
Question 6: Is there evidence that bDMARD (adalimumab, certolizumab, etanercept, golimumab, infliximab, abatacept, rituximab, or tocilizumab) combined with methotrexate is more effective than bDMARD monotherapy?
Question 7: In the case of failure of a first bDMARD scheme, is there evidence that a second bDMARD scheme is effective?
Question 8: Is there evidence that tsDMARD (tofacitinib) is more effective than bDMARD (adalimumab, certolizumab, etanercept, golimumab, infliximab, abatacept, rituximab, or tocilizumab)?
Question 9: Is there evidence that oral, parenteral, or intra-articular use of corticosteroids improves prognosis when combined with DMARD?
Question 10: Is there evidence that it is possible to reduce the dose or increase the dose intervals for bDMARD in patients in remission?

csDMARD conventional synthetic disease-modifying drugs – methotrexate, leflunomide, sulfasalazine and antimalarials (hydroxychloroquine and chloroquine)
tsDMARD: synthetic target-specific disease-modifying drugs – tofacitinib
bDMARD: biological disease-modifying drugs – tumor necrosis factor inhibitors/TNFi (adalimumab, certolizumab, etanercept, golimumab, infliximab), T-lymphocyte costimulation modulator (abatacept), anti-CD20 (rituximab), and IL-6 receptor blocker (tocilizumab)

Table 2 Search strategies used in the MEDLINE, EMBASE and SCOPUS databases for obtaining evidence on drug therapies for rheumatoid arthritis

Database	Strategy
MEDLINE (via PubMed)	((((meta analysis[ptyp] OR meta-analysis[tiab] OR meta-analysis[mh] OR (systematic[tiab] AND review[tiab]) NOT ((case[ti] AND report[ti]) OR editorial[ptyp] OR comment[ptyp] OR letter[ptyp] OR newspaper article [ptyp])) OR (randomized controlled trial[Publication Type] OR (randomized[Title/Abstract] AND controlled[Title/Abstract] AND trial[Title/Abstract])))))) AND ((arthritis, rheumatoid[mh:noexp]) or (rheumatoid arthriti*[text word])) Filters: Publication date from 2006/01/01
EMBASE	'rheumatoid arthritis'/mj AND ([cochrane review]/lim OR [systematic review]/lim OR [controlled clinical trial]/lim OR [randomized controlled trial]/lim OR [meta analysis]/lim) AND [2006–2016]/py NOT [medline]/lim
SCOPUS	TITLE-ABS-KEY(rheumatoid arthritis) AND((TITLE-ABS-KEY(randomized) AND TITLE-ABS-KEY(controlled) AND TITLE-ABS-KEY(trial)) OR (TITLE-ABS-KEY(meta-analysis) OR (TITLE-ABS-KEY(systematic) AND TITLE-ABS-KEY(review)))) AND (PUBYEAR > 2006) AND NOT (INDEX(medline) or INDEX(embase))

and WHO International Clinical Trials Registry Platform (http://www.who.int/ictrp/en) when available and by asymmetry analysis of funnel plots.

The methodological details of the SLR that supported the present recommendations and the expanded results, together with the rationale of the answers to the formulated questions, will be available as Additional file 1. In the present document, a predominantly clinical approach was adopted, in which the SLR findings were summarized in a technically accessible language as the basis for the recommendations.

Based on the results of the SLR, the RA Committee met in June and August 2017 in São Paulo and Belo Horizonte to establish the level of agreement with each general principle and recommendation according to the methodology described below. After presenting each statement, a secret ballot was held, in which the participants could agree or disagree with the general proposition of each statement. In cases of agreement by at least 70% of the participants present, a new vote was conducted to assess the level of agreement with the text using a numerical scale from 0 ("completely disagree") to 10 ("completely agree"). The general principles and recommendations that did not reach a minimum rate of agreement of 70% initially were subjected to repeated steps of reformulation and voting until this rate was reached, and the level of agreement was then determined.

This process resulted in the approval of four general principles and eleven recommendations for drug treatment of RA in Brazil, which are presented in Table 3 and discussed below. This document also includes a section on therapeutic strategies, and this section serves as the basis for the understanding and practical application of the recommendations. The therapeutic strategies were graphically summarized into the new flowchart for drug treatment of RA in Brazil (Fig. 1).

The following abbreviations and nomenclature for disease-modifying antirheumatic drugs (DMARDs) were used in this document:

csDMARD: conventional synthetic disease-modifying antirheumatic drugs – methotrexate, leflunomide, sulfasalazine, and antimalarial drugs (hydroxychloroquine and chloroquine).

tsDMARD: synthetic target-specific disease-modifying antirheumatic drug – tofacitinib.

bDMARD: biological disease-modifying antirheumatic drugs – tumor necrosis factor inhibitors/TNFi (adalimumab, certolizumab, etanercept, golimumab, infliximab), T-lymphocyte co-stimulation modulator (abatacept) , anti-CD20 (rituximab), and IL-6 receptor blocker (tocilizumab).

boDMARD: original biological disease-modifying antirheumatic drugs.

bsDMARD: biosimilar biological disease-modifying antirheumatic drugs.

General principles

General principle 1: Treatment of patients with RA should preferably consist of a multidisciplinary approach coordinated by a rheumatologist. (level of agreement: 9.87)

Patients with RA should be preferably monitored by a multidisciplinary team, including a physician, physiotherapist, occupational therapist, psychologist, and nutritionist, among others. The rheumatologist, as a specialist in RA, should be responsible for coordinating the treatment.

General principle 2: Treatment of patients with RA should include counseling on lifestyle habits, strict control of comorbidities, and updates of the vaccination record. (level of agreement: 10)

Smoking, excessive intake of alcoholic beverages, obesity, and a sedentary lifestyle should be strongly discouraged. The active search and appropriate management of comorbidities, particularly systemic arterial hypertension, diabetes mellitus, dyslipidemia, and osteoporosis, are part of the care of patients with RA. The patient's vaccination record should be updated

Table 3 General principles and recommendations of the Brazilian Society of Rheumatology for pharmacological treatment of rheumatoid arthritis in Brazil

General principles
General principle 1: Treatment of patients with RA should preferably consist of a multidisciplinary approach coordinated by a rheumatologist. Level of agreement: 9.87
General principle 2: RA treatment should include counseling on lifestyle habits, strict control of comorbidities, and updates of the vaccination record. Level of agreement: 10
General principle 3: RA treatment should be based on decisions shared by the patient and physician after clarification about the disease and the available therapeutic options. Level of agreement: 9.93
General Principle 4: The goal of RA treatment is sustained clinical remission or, when this is not feasible, low disease activity. Level of agreement: 9.87
Recommendations for drug treatment of RA
Recommendation 1: The first line of treatment should be a csDMARD, started as soon as the diagnosis of RA is established. Level of agreement: 9.93
Recommendation 2: Methotrexate is the first-choice csDMARD. Level of agreement: 10
Recommendation 3: Combination of two or more csDMARDs, including methotrexate, may be used as the first line of treatment. Level of agreement: 9.62
Recommendation 4: After failure of first-line therapy with MTX, the therapeutic strategies include combining MTX with another csDMARD (leflunomide), with two csDMARDs (hydroxychloroquine and sulfasalazine), or switching MTX for another csDMARD (leflunomide or sulfasalazine) alone. Level of agreement: 9.12
Recommendation 5: After failure of two schemes with csDMARD, a bDMARD may be preferably used or, alternatively, a tsDMARD, preferably combined, in both cases, with a csDMARD. Level of agreement: 9.5
Recommendation 6: The different bDMARDs in combination with MTX have similar efficacy, and therefore, the therapeutic choice should take into account the peculiarities of each drug in terms of safety and cost. Level of agreement: 9.31
Recommendation 7: The combination of bDMARD and methotrexate is preferred over the use of bDMARD alone. Level of agreement: 9.87
Recommendation 8: In case of failure of an initial treatment scheme with bDMARD, a scheme with another bDMARD can be used. In cases of failure with a TNFi, a second bDMARD of the same class or with another mechanism of action is effective and safe. Level of agreement: 9.37
Recommendation 9: Tofacitinib can be used to treat RA after failure of bDMARD. Level of agreement: 9.81
Recommendation 10: Corticosteroids, preferably at low doses for the shortest possible time, should be considered during periods of disease activity, and the risk-benefit ratio should also be considered. Level of agreement: 9.81
Recommendation 11: Reducing or spacing out bDMARD doses is possible in patients in sustained remission. Level of agreement: 9.31

csDMARD: Conventional synthetic disease-modifying antirheumatic drugs (methotrexate, leflunomide, sulfasalazine) and antimalarials (hydroxychloroquine and chloroquine)
tsDMARD: Synthetic target-specific disease-modifying antirheumatic drugs – tofacitinib
bDMARD: biological disease-modifying drugs – tumor necrosis factor inhibitors/TNFi (adalimumab, certolizumab, etanercept, golimumab, infliximab), T-lymphocyte costimulation modulator (abatacept), anti-CD20 (rituximab), and IL-6 receptor blocker (tocilizumab)

preferably before the initiation of treatment and kept updated during follow-up.

General principle 3: Treatment of patients with RA should be based on decisions that are shared by the patient and the physician after clarification about the disease and the available therapeutic options. (level of agreement: 9.93)

Patients with RA should be informed about the nature and prognosis of the disease. Moreover, patients should be informed about the available therapeutic options, their benefits, potential adverse effects, and costs.

General principle 4: The goal of RA treatment is sustained clinical remission or, when this is not feasible, low disease activity. (level of agreement: 9.83)

The rheumatologist and the patient should acknowledge that the goal of treatment is sustained clinical remission or, in cases where this is not feasible, low disease activity. In the long term, these outcomes are related to the best clinical, structural, and functional evolution [13–15].

Regular monitoring of clinical, laboratory, and imaging parameters is necessary to achieve this goal. In the initial stage of RA (the first 6 months of symptoms) and whenever the disease presents with significant inflammatory activity, follow-up should be performed monthly to allow dosage adjustment or changes in medication for disease management.

Recommendations

Recommendation 1: The first line of treatment should be a csDMARD started as soon as the diagnosis of RA is established. (level of agreement: 9.93)

The efficacy (ACR50 response) of methotrexate (MTX) monotherapy is similar to that of bDMARD monotherapy, except for tocilizumab, which was more effective than MTX [16–23].

Although monotherapy with tofacitinib has been shown more effective than with MTX, the limited availability of long-term safety data on the former requires caution and precludes its use as the first line of treatment, until more data become available [24].

In addition, the lower cost of csDMARD should be taken into account, although few cost-effectiveness

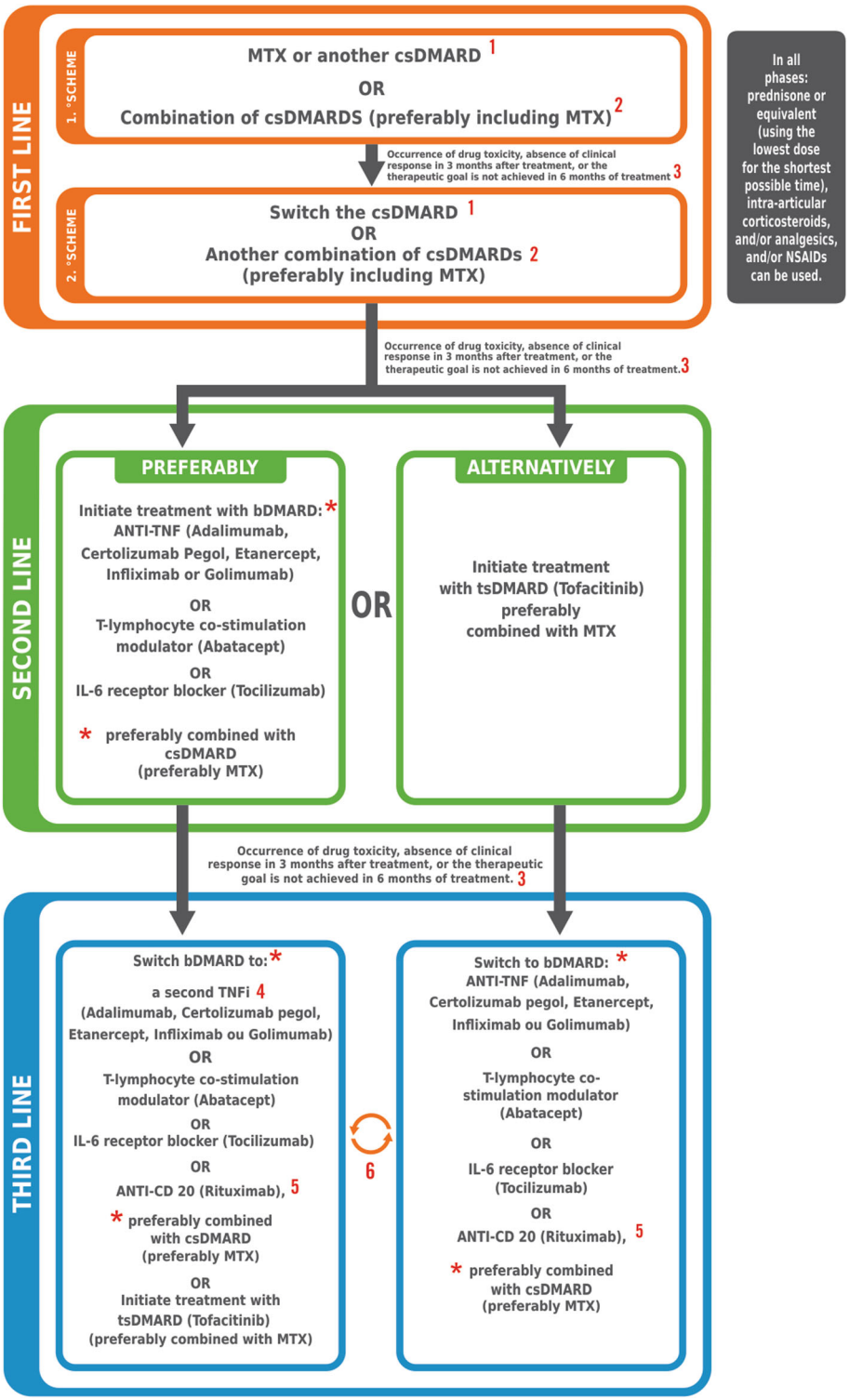

Fig. 1 (See legend on next page.)

(See figure on previous page.)
Fig. 1 Flowchart - 2017 Recommendations of the Brazillan Society of Rheumatology for pharmacological treatment of rheumatoid arthritis. 1: Sulfasalazine or leflunomide may be used in cases of contraindication to MTX. Antimalarials (hydroxychloroquine or chloroquine) as monotherapy may be considered in cases of low probability of development of radiographic erosions. 2: The most used combinations in Brazil are MTX + antimalarials, MTX + leflunomide (with or without antimalarials), MTX + sulfasalazine (with or without antimalarials). 3: The goal of treatment is remission according to ACR/EULAR criteria or, in cases where this is not possible, low disease activity, as assessed by one of the composite disease activity indices defined in the 2011 SBR Consensus (5). 4: The use of a third TNFi after failure of two TNFi drugs is not recommended. 5: In Brazil, rituximab is recommended in combination with methotrexate for patients with a poor response or intolerance to one or more TNFi drugs. 6: In case of failure or toxicity to a drug used in the third line of treatment, the next step is switching to another drug (bDMARD or tsDMARD) with the same level of complexity and that has not been used previously

studies have evaluated the use of csDMARD as the first line of treatment. The quality of evidence for this recommendation is low to moderate.

Recommendation 2: Methotrexate is the first-choice csDMARD. (level of agreement: 10)

There were no significant differences in the efficacy of csDMARD for most of the relevant outcomes (ACR50 and ACR70 response, number of painful and swollen joints, disease activity, pain, and functional capacity – moderate evidence) [25–36].

Compared with MTX, leflunomide causes more adverse events (discontinuation of treatment, rashes, and systemic arterial hypertension– high evidence) [30–33].

However, MTX has the highest risk of hepatic and pulmonary adverse events (low to very low evidence) [37, 38].

Subcutaneous MTX was shown to be superior to oral MTX in ACR70 and pain control, with fewer gastrointestinal adverse reactions (moderate evidence) [39].

MTX remains the first-choice drug for the RA treatment because of its efficacy and safety, possibility of individualizing the dose and route of administration, and relatively low cost [30, 40].

Recommendation 3: Combination of two or more csDMARD, including MTX, may be used as the first line of treatment. (level of agreement: 9.62)

As a first line of treatment, among the possible combinations of csDMARD, triple therapy with MTX + sulfasalazine + hydroxychloroquine, and MTX + leflunomide, both schemes compared with MTX monotherapy, showed an improved ACR response (high to moderate evidence) [25, 41, 42]. However, the cost of combination therapy is higher [43], and there is no evidence of a clinically significant difference between MTX alone and the combination of DMARDs (MTX + leflunomide, and triple therapy) in other disease activity indices [25, 42, 44–47] (moderate to low evidence), radiographic progression [41, 42, 48] (moderate to low evidence), and therapeutic safety [25, 41, 47, 49] (moderate to low evidence).

Recommendation 4: After failure of first-line therapy with MTX, therapeutic strategies include combining MTX with another csDMARD (leflunomide), with two csDMARDs (hydroxychloroquine and sulfasalazine), or switching MTX for another csDMARD (leflunomide or sulfasalazine) alone. (level of agreement: 9.12)

After failure of MTX as the first line of treatment, leflunomide (20 mg/day, without a loading dose) or sulfasalazine (with an increase in dosage to 3 g/day) are monotherapy alternatives [31, 50, 51]. Both the combination of MTX with leflunomide or with hydroxychloroquine + sulfasalazine provided better ACR50 response rates compared with MTX alone (moderate evidence), with no significant difference in radiographic progression and discontinuation of treatment due to adverse events (low evidence) [50]. The combination of sulfasalazine with MTX (without hydroxychloroquine) compared to MTX alone did not show an incremental benefit (low evidence) [41].

After failure of leflunomide, replacement with sulfasalazine or the combination of sulfasalazine and leflunomide had no additional benefit in ACR50 response, pain, quality of life, and treatment dropout (moderate evidence) [52].

After failure of sulfasalazine, the inclusion of MTX did not provide additional benefits in ACR20, ACR50, and ACR70 (moderate evidence), although an improvement of the disease activity score (DAS) with the combination of csDMARDs was observed after 18 months of treatment [53].

Recommendation 5: After failure of two schemes with csDMARD, a bDMARD may be preferably used or, alternatively, a tsDMARD, preferably combined, in both cases, with a csDMARD. (level of agreement: 9.5)

The combination of bDMARD and MTX produces higher ACR20, ACR50, and ACR70 response rates after 6 months of treatment compared with MTX monotherapy [54]. Higher ACR70 response rates at 6 to 12 months of treatment were also observed with the combination of bDMARD and csDMARD (not necessarily MTX) versus csDMARD alone [18]. The addition of bDMARD in cases of a poor response to csDMARD was effective

[24]. In cases of poor response to a csDMARD, the addition of a bDMARD was effective.

The tsDMARD tofacitinib in monotherapy or in combination with MTX was effective and safe in patients with a poor response to csDMARD, with improvement in disease activity and physical function and a reduction of radiographic progression [55, 56].

However, long-term safety and real-life data are not yet available for tsDMARD, and thus, a preference for bDMARD over tofacitinib after csDMARD failure has been proposed.

Recommendation 6: The different bDMARDs in combination with MTX have similar efficacy, and therefore, the therapeutic choice should take into account the peculiarities of each drug in terms of safety and cost. (level of agreement: 9.31)

The available bDMARDs have similar levels of effectiveness for the number of painful or swollen joints, disease activity, quality of life, functional capacity, and pain control [16, 57–62]. However, total annual costs of treatment vary among the different bDMARDs and these differences need to be taken into consideration at the time of drug selection (low to moderate evidence) [63]. All bDMARDs have consistently demonstrated superior efficacy when used in combination with MTX compared with MTX monotherapy [24, 40].

Patients using bDMARDs compared with those using csDMARDs have an increased risk of severe infections [64–68]. In general, different bDMARDs have similar levels of safety. Some SLRs of randomized trials have reported a possible increase in the incidence of severe infections with the use of certolizumab in the (indirect) comparison with other bDMARDs (moderate evidence), but this result has not been observed in registry studies [65–67, 69]. Lower intestinal perforation was more common in patients treated with tocilizumab (moderate evidence) [70]. Tuberculosis (TB) was more common in TNFi users than non-TNFi users. Among TNFi users, TB was more common in patients treated with adalimumab and infliximab compared with those treated with etanercept (moderate evidence) [68]. There were no differences among the bDMARD in the incidence of herpes zoster or neoplasia except for a possible increase in the rate of melanoma with the use of TNFi (very low evidence) [64, 71].

Recommendation 7: The combination of bDMARD and MTX is preferred over the use of bDMARD alone. (level of agreement: 9.87)

bDMARDs are more effective when combined with csDMARDs, particularly MTX [19, 72–75].

Adalimumab + MTX improved ACR20, ACR50, ACR70, and ACR90 responses and functional capacity and pain (high evidence) and did not significantly increase the rate of treatment dropout due to adverse effects compared with adalimumab monotherapy (moderate evidence) [72].

Etanercept + MTX provided a better ACR50 response and lower radiographic progression compared with etanercept monotherapy (high evidence) and did not significantly affect the ACR70 response and dropout due to adverse events (moderate evidence) [73].

Golimumab + MTX improved the ACR50 response rate and did not significantly affect the ACR70 response, dropout due to adverse events, severe adverse events, and functional capacity compared with golimumab monotherapy (moderate evidence) [76].

Abatacept + MTX increased the remission rates (DAS28 < 2.6) compared with abatacept monotherapy [19].

Higher ACR50 and ACR70 response rates were observed with rituximab + MTX compared with rituximab alone (the groups were compared with MTX monotherapy) [75].

In a randomized trial, tocilizumab monotherapy was not significantly different from tocilizumab + MTX for ACR50 and ACR70 responses, dropout due to adverse events, severe adverse events, and functional capacity after 24 weeks of treatment. However, other randomized trial found higher remission rates (DAS28 < 2.6) and lower radiographic progression with tocilizumab + MTX compared with tocilizumab monotherapy [77–79].

The use of csDMARD in combination with bDMARD appears to reduce the formation of antibodies against the biological agent, secondary failure. Studies that used bDMARDs combined with csDMARDs, such as leflunomide, confirmed the efficacy of this combination strategy, particularly in patients who presented adverse events or contraindications to MTX [80, 81].

Recommendation 8: In case of failure of an initial treatment scheme with bDMARD, a scheme with another bDMARD can be used. In cases of failure with TNFi, a second bDMARD of the same class or with another mechanism of action is effective and safe. (level of agreement: 9.37)

The use of another bDMARD is safe and effective after therapeutic failure of an initial treatment with bDMARD [24, 82]. When the first bDMARD was an TNFi agent, the use of another TNFi agent was safe and effective in cases of treatment failure [83, 84].

Abatacept (high evidence), rituximab (high evidence), golimumab (moderate evidence), and tocilizumab (moderate evidence) were better than placebo for decreasing the number of painful and swollen joints after failure of TNFi treatment [82, 85–87].

Indirect comparisons did not allow the determination of superiority among abatacept, golimumab, rituximab, or tocilizumab in ACR50 and ACR70 responses when used after failure of the first bDMARD [88]. The risk of adverse events, including severe ones, and severe

infections caused by these four biologicals after failure of the first bDMARD, was similar to placebo.

Although the use of a second TNFi agent after failure of the first is safe and effective, some studies suggest superior results for the ACR20 response, EULAR response criterion, and disease activity reduction when switching to a bDMARD with a different mechanism of action [82, 87, 89, 90]. These data must be confirmed in further studies. In other countries, rituximab has been shown to be the most cost-effective alternative among bDMARDs for the treatment of patients with previous failure to TNFi (very low evidence) [82, 85–87, 89, 91].

However, these results cannot be directly applied to the Brazilian context.

Recommendation 9: Tofacitinib can be used to treat RA after failure of bDMARD. (level of agreement: 9.81)

Tofacitinib + MTX is effective after failure of TNFi, promoting a rapid and favorable ACR20 response and improving functional capacity and disease remission [92–97].

There are no available radiographic progression data for the use of tofacitinib after failure of bDMARD.

Recommendation 10: Corticosteroids, preferably at low doses for the shortest possible time, should be considered during periods of disease activity, and the risk-benefit ratio should also be considered. (level of agreement: 9.81)

Corticosteroids are effective in treating RA when combined with csDMARD. Most of the analyzed studies used oral prednisone. The use of corticosteroids in RA reduced pain [98] (moderate evidence) and radiographic progression (high to low evidence) [99–102]. Prednisone + MTX compared with MTX alone reduced the need to switch treatment to bDMARD and did not increase the rate of adverse events [103]. However, low doses (≤10 mg/day of prednisone or equivalent) for the shortest possible time are recommended for managing periods of increased disease activity and minimizing adverse events. Special caution is necessary in patients with comorbidities that are potentially aggravated by corticosteroids.

Recommendation 11: Reducing or spacing out bDMARD doses is possible in patients in sustained remission. (level of agreement: 9.31)

Patients using bDMARD combined with csDMARD and in sustained remission (for at least 6 months) according to any composite disease activity index may receive lower bDMARD doses or the dose interval may be increased (moderate to low evidence) [104–112].

Patients with recent-onset RA (less than 6 months of symptoms) and low disease activity, suggestive of residual inflammation, rather than undergoing bDMARD dose reduction or dose interval increase, should be treated with another bDMARD or tsDMARD [113].

However, in patients with established RA and low disease activity or remission, bDMARD dose reduction or a dose interval increase should be evaluated on an individual basis [107–112, 114–116].

Lowering the bDMARD dose reduces costs (high evidence) [114, 117].

Therapeutic strategies for treating RA in Brazil

Treatment with DMARDs should be initiated as soon as the diagnosis of RA is established. Treatment should be adjusted as necessary by frequent clinical reassessments at 30–90-day intervals. Therapeutic strategies based on specific goals produce better outcomes for disease activity and functional capacity, with less radiographic structural damage compared with conventional treatments [4, 6, 113]. The goal is sustained remission [118, 119] or at least low disease activity, as assessed by a composite measure of disease activity, also taking into consideration the absolute decrease in the composite measure score (Tables 4, 5, and 6) [7, 113].

First-line treatment: csDMARD

First scheme

MTX is the first-choice csDMARD [6, 40, 120]. MTX may be initially prescribed as monotherapy or in combination with other csDMARD (example: MTX + leflunomide) [17]. Subcutaneous MTX is an alternative to cases of drug intolerance or poor response to oral MTX before changing or adding other csDMARD. Subcutaneous MTX is better tolerated and has greater bioavailability, potentially improving clinical efficacy compared with oral administration at the same dose [39].

In cases in which MTX is contraindicated, sulfasalazine [28] or leflunomide [25] may be used as the first option. Hydroxychloroquine (or when unavailable, chloroquine) may be used in monotherapy in cases of undifferentiated arthritis or disease with low potential for the development of radiographic erosions [6].

Second scheme

In cases in which there is no clinical response in 3 months or the therapeutic goal (sustained remission or low disease activity according to a composite measure of disease activity) is not achieved within 6 months with an optimum dose of MTX or in the presence of adverse effects, it is recommended to switch MTX for another csDMARD in monotherapy, such as leflunomide [25] or sulfasalazine [28], or a combination of MTX and other csDMARDs [41, 46]. The suggested combinations are MTX + hydroxychloroquine + sulfasalazine [41] or MTX + leflunomide [121]. Therapeutic progression should be rapid, with monthly assessments in the first 6 months of treatment and adjustment of doses and schedules as needed.

Table 4 Composite measures of disease activity used in rheumatoid arthritis: components, calculation formula, and range of results

Components	SDAI	CDAI	DAS28 (with 4 variables)
Number of swollen joints	(0–28) Simple sum	(0–28) Simple sum	Square root of the simple sum
Number of painful joints	(0–28) Simple sum	(0–28) Simple sum	Square root of the simple sum
Acute phase reagents	CRP (0.1–10 mg/dL)	–	ESR 2–100 mm or CRP 0.1–10 mg/dL logarithmic transformation
Global health assessment (Patient)		–	0–100 mm
Assessment of disease activity (Patient)	(0–10 cm)	(0–10 cm)	–
Assessment of disease activity (Examiner)	(0–10 cm)	(0–10 cm)	–
Total index	Simple sum	Simple sum	Calculation formula (requires a calculator)
Index variation	(0.1–86.0)	(0–76)	(0.49–9.07)

CDAI, clinical disease activity index; DAS28, disease activity index (28 joints); CRP, C-reactive protein; SDAI, simplified disease activity index; ESR, erythrocyte sedimentation rate. Assuming a variation of 2 to 100 mm/h for ESR and of 0.1 to 10 mg/dL for CRP [6, 142].

Corticosteroids, analgesics, and non-steroidal anti-inflammatory drugs

Low doses of corticosteroids (maximum of 10 mg/day of prednisone or equivalent) may be used at the beginning of treatment or when disease worsens. However, treatment for the shortest possible time is recommended to reduce the occurrence of adverse events. Intra-articular corticosteroids may be used when necessary for symptom control, particularly for monoarticular or oligoarticular arthritis [6]. Common analgesics (paracetamol and dipyrone) and weak opioids (tramadol and codeine) may be used on demand for the control of pain symptoms [6].

Non-steroidal anti-inflammatory drugs (NSAIDs) reduce pain (low to moderate evidence) and disease activity (low evidence) and improve functional capacity (low evidence) in RA [122–127]. NSAIDs may be useful primarily at disease onset (because DMARDs do not have immediate action) and in cases of RA exacerbation [128, 129].

The choice of NSAID should be individualized because there is no demonstrated superior efficacy of one NSAID over another. Use for the shortest possible time is recommended. Additional caution is necessary in cases of risk factors for adverse events caused by NSAIDs, including advanced age, systemic arterial hypertension, heart failure, renal or hepatic dysfunction, gastrointestinal disease, arterial insufficiency, and coagulation disorders [130].

Table 5 Definition of the status of activity of rheumatoid arthritis and respective cutoff points using composite disease activity indices

Index	Disease activity status	Cutoff points
SDAI	Remission	≤5
	Low	> 5 and ≤ 20
	Moderate	> 20 and ≤ 40
	High	> 40
CDAI	Remission	≤2.8
	Low	≤10
	Moderate	> 10 and ≤ 22
	High	> 22
DAS28	Remission	≤2.6
	Low	> 2.6 and ≤ 3.2
	Moderate	> 3.2 and ≤ 5.1
	High	> 5.1

CDAI, clinical disease activity index; DAS28, disease activity index (28 joints); SDAI, simplified disease activity index [142].

Second-line treatment: bDMARD or tsDMARD

The use of bDMARD or tsDMARD is recommended in cases in which there is no clinical response after 3 months using the second scheme of the first-line treatment, the therapeutic goal is not achieved in 6 months (remission or low disease activity according to a composite measure of disease activity), or in cases of drug toxicity or intolerance.

The bDMARD drugs used in the second-line treatment are TNFi (adalimumab, certolizumab, etanercept, golimumab, or infliximab), T-lymphocyte costimulation modulator (abatacept), and IL-6 receptor blocker (tocilizumab), combined with csDMARD (preferably MTX) [24, 41, 58, 94, 95].

Tocilizumab demonstrated similar efficacy in monotherapy compared to tocilizumab + MTX for most of the relevant clinical outcomes [58, 77, 131].

Adalimumab, etanercept, certolizumab, golimumab, and abatacept can be used in monotherapy [16], but their efficacy may be lower compared with the combinations with csDMARDs [17].

Table 6 Classification of the therapeutic response in rheumatoid arthritis according to the variation in scores of the composite disease activity indices

Index	Response classification
EULAR-DAS28 response	Good: drop ≥ 1.2 points, reaching DAS28 ≤ 3.2 Moderate: drop > 1.2 points, maintenance of DAS28 > 3.2; or drop > 0.6 and ≤ 1.2 points, reaching DAS28 ≤ 5.1 Unresponsive: drop > 0.6 and ≤ 1.2 points, maintenance of DAS28 > 5.1; or drop ≤0.6 points
SDAI and CDAI response	Good: drop ≥ 85% in the score value Moderate: decrease ≥70 and < 85% in the score value Weak: drop ≥ 50% and < 70% in the score value Unresponsive: drop < 50% in the score value

CDAI, clinical disease activity index; DAS28, disease activity index (28 joints); SDAI, simplified disease activity index [142–144].

Different bDMARDs have similar levels of clinical efficacy and safety [24, 42, 120]. Therefore, bDMARDs should be chosen on an individual basis, taking into account the costs and the presence of comorbidities that may be positively or negatively affected by the treatment choice. There is not necessarily a preference for one mechanism of action relative to another for treating RA.

The tsDMARD tofacitinib may be prescribed as the second line of treatment, preferably in combination with MTX [41] or in monotherapy in cases of contraindication to MTX. However, because of the higher availability of long-term safety and real-life data for bDMARDs, at present these regimens are preferred as the second-line treatment, and tsDMARDs are considered an alternative to bDMARDs [9]. Although evidence supports the use of the bDMARD rituximab after failure of csDMARD, anti-CD20 is formally approved for treating RA only after TNFi failure and has been used as the third-line treatment in this therapeutic strategy. Nonetheless, rituximab may be considered as the first choice among bDMARDs for patients with rheumatoid factor (RF) or antibodies against citrullinated cyclic peptide (anti-CCP), with contraindications to other bDMARDs, or an associated diagnosis of lymphoma [132]. Patients with poor prognosis factors [5], including high disease activity, high number of painful or swollen joints, high RF and/or anti-CCP titers, and early occurrence of radiographic erosions, may benefit from a more aggressive treatment, including indication of a bDMARD after failure of the first csDMARD scheme, although more evidence is required to support this indication.

There is no evidence of cost-effectiveness supporting the use of bDMARD as the first-line treatment for RA in Brazil. The concomitant use of two bDMARDs or one bDMARD combined with a tsDMARD is not recommended [42].

Third-line treatment: After failure of the first bDMARD or tsDMARD

The third-line treatment is used in cases the therapeutic goal (sustained remission or low disease activity according to a composite measure of disease activity) is not achieved in 6 months using the second-line treatment (indicating primary failure to bDMARD or tsDMARD), or loss of the previous response (secondary failure to bDMARD or tsDMARD), or cases of drug toxicity or intolerance.

The drugs available for the third-line treatment are the bDMARDs TNFi (adalimumab, certolizumab, etanercept, golimumab, or infliximab), T-lymphocyte co-stimulation modulator (abatacept), IL-6 receptor blocker (tocilizumab), anti-CD20 (rituximab), and the tsDMARD tofacitinib, combined with csDMARD (preferably MTX) [96]. Rituximab, when considered, should be indicated to patients with positive RF or anti-CCP [96, 132].

When a bDMARD is used as the second-line treatment, switching to another bDMARD or to a tsDMARD is recommended as the third-line treatment. A second TNFi drug (particularly in cases of secondary failure), switching to a bDMARD with a different mechanism of action (abatacept, tocilizumab, or rituximab) [82] or switching to a tsDMARD (tofacitinib) is recommended in cases in which the first bDMARD is a TNFi [82, 97]. Patients with failure to a first TNFi show improvements with a second TNFi [24, 59, 84, 91]. However, there are uncertainties about the cost-effectiveness of this strategy because it can result in lower response rates compared with switching the mechanism of action [87, 90, 91]. If the first bDMARD is not a TNFi, the options include prescribing another bDMARD with a mechanism of action distinct from that of the first bDMARD (including TNFi) or the use of tsDMARD.

When a tsDMARD is used as the second-line treatment, the option for the third-line treatment is switching to bDMARDs. However, this strategy requires careful clinical observation because there is no available evidence to date on the efficacy and safety of the sequential use of bDMARDs after failure of tsDMARD (tofacitinib). Until specific information is available, caution is advised on the sequential use of drugs that interfere with IL-6 (tocilizumab) and the JAK-STAT signaling pathway (tofacitinib) in patients with toxicity to any of these medications because the effects of IL-6 are mediated by the JAK-STAT pathway [40].

The treatment sequence depends on the specificities of each case and the discretion of the physician. In the

case of failure or toxicity to a drug used in the third line of treatment, the next step is to switch to another (bDMARD or tsDMARD) with the same level of complexity and that has not been used previously. A minimum of 3 months and maximum of 6 months of clinical evaluation are recommended before switching a therapeutic regimen due to poor clinical response.

Gradual reduction of medication dose and treatment discontinuation

There are no data to support setting any limit for the RA treatment duration. However, patients using bDMARD in sustained remission may receive a bDMARD dose reduction or dose interval increase. Although disease reactivation may occur in some cases, disease control is usually reestablished with the return to the previous dose schedule (moderate to low evidence) [19, 23, 104, 105, 114, 133]. In cases of complete and sustained remission (at least 6 months), gradual and careful treatment withdrawal may be attempted in the following sequence: first NSAIDs, followed by corticosteroids, and bDMARD or tsDMARD, but maintaining the use of csDMARD. After the withdrawal of bDMARD, if sustained clinical remission is maintained, reduction of the csDMARD dose can be carefully attempted. Exceptionally, withdrawal of csDMARD might be feasible in cases in which clinical remission continues to be sustained [40, 116].

Sustained drug-free remission is rare, and the probability of disease exacerbation (flares) is higher in patients with long-standing disease, the presence of synovitis on ultrasound (gray scale or power Doppler), and a positive anti-CCP [116].

Biosimilar drugs

Biosimilar bDMARDs (bsDMARDs) are very similar to their original bDMARDs (boDMARDs) regarding quality, molecular structure, biological activity, clinical efficacy, safety, and immunogenicity in comparability tests, and these drugs fulfill strict regulatory criteria [134].

bsDMARDs have been shown to be safe and effective when used as an alternative to boDMARDs (moderate evidence). There were no differences in ACR20 and ACR70 response rates, disease activity (moderate evidence), or severe adverse events of the bsDMARDs adalimumab, etanercept, infliximab, and rituximab compared with their respective boDMARDs [134–140]. The development of anti-drug antibodies was similar between bsDMARDs and boDMARDs (moderate evidence), and lower for the bsDMARD of etanercept compared with the boDMARD (high evidence) [134].

However, the demonstration of biosimilarity should not be understood as evidence of interchangeability. Interchangeability, when referring to bsDMARDs, is defined by the simultaneous presence of two requirements [1]: the expected clinical outcome using the bsDMARD is similar to that produced by the corresponding boDMARD in any patient [2]; repeated switching between the boDMARD and the bsDMARD presents no additional safety or efficacy risk compared with the continued use of the reference product [141].

The SBR advocates the need for an objective demonstration of interchangeability between any boDMARD and its correspondent bsDMARD using studies specifically designed for this purpose. Until such studies are available and interchangeability conditions are regulated in Brazil, boDMARDs should not be automatically replaced with bsDMARDs without the consent of the prescriber and patient.

Pharmacological treatment flowchart for RA in Brazil

The therapeutic strategies proposed by the RA Committee of the SBR for RA treatment in Brazil are summarized in Fig. 1.

Treatment monitoring

For patients with active disease, especially in the initial phase of the disease (first 6 months of manifestations), intensive follow-up with monthly visits and, when necessary, rapid treatment escalation are recommended [6].

The efficacy and safety of the therapeutic intervention should be evaluated at each visit considering the comorbidities of the patient and aiming to achieve the lowest possible disease activity (if remission is not possible), as well as improve function and quality of life. Visits can be spaced out for patients with established disease, particularly those with controlled disease [6].

The clinical history of patients who are eligible for treatment with bDMARD should be analyzed for the presence of severe active infection, TB, or untreated latent TB, moderate to severe heart failure, multiple sclerosis or optic neuritis, previous hypersensitivity to TNFi, malignancy or lymphoma, and congenital or acquired immunodeficiency. Complementary examinations to identify hepatitis B virus, hepatitis C virus, and HIV, as well as chest X-ray and the tuberculin test, should be part of the pretreatment evaluation [6].

Conclusions

Advances in RA diagnosis and treatment have allowed improvements in disease outcome. The presence of a rheumatologist is critical in evaluating and treating patients with RA because these professionals are trained to make an early diagnosis and are familiar with the available drug therapies, indications, management, and adverse events.

The Brazilian scenario has specificities that require attention, including the local availability of medications

and the socioeconomic status of the population. Brazil is a large country with a growing population, requiring rational allocation of resources to allow broad and equitable access of the population to medications and other health technologies.

The recommendations presented herein seek to provide scientific evidence to Brazilian rheumatologists, considering the therapeutic efficacy, safety, and costs, together with the critical assessment and experience of a panel of experts to standardize the management of RA in the national socioeconomic context, but maintaining the autonomy of the physician in choosing different therapeutic options. These recommendations should be updated periodically because of the rapid development of this field of knowledge. The 2017 SBR recommendations and supporting documents could be accessed online

Additional file

Additional file 1: Methodological details, expanded results and rationale of the answers to the formulated questions of the SLR that supported the present recommendations. (DOCX 980 kb)

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Author details
[1]Programa de Pós-graduação em Ciências Médicas, Faculdade de Medicina-Universidade de Brasília; Serviço de Reumatologia, Hospital Universitário de Brasília, Universidade de Brasília, Brasília, Brazil. [2]Disciplina de Reumatologia, Faculdade de Medicina, Universidade Federal de Minas Gerais, Belo Horizonte, Brazil. [3]Centro Universitário de Brasília- UniCEUB, Brasília, Brazil. [4]Universidade Federal de Pernambuco, Recife, Brazil. [5]Hospital Vera Cruz, Belo Horizonte, Brazil. [6]Serviço de Reumatologia, Departamento de Medicina Interna, Serviço de Reumatologia, Hospital de Clínicas de Porto Alegre, Universidade Federal do Rio Grande do Sul, Porto Alegre, Brazil. [7]Serviço de Reumatologia, Hospital Universitário de Brasília, Universidade de Brasília, Brasília, Brazil. [8]Disciplina de Reumatologia, Departamento de Medicina Interna, Universidade do Estado do Rio de Janeiro, Rio de Janeiro, Brazil. [9]Universidade Nove de Julho, São Paulo, Brazil. [10]Universidade do Sul de Santa Catarina, Florianópolis, Brazil. [11]Disciplina de Reumatologia, Faculdade de Ciências Médicas, Universidade Estadual de Campinas, Campinas, Brazil. [12]Santa Casa de Belo Horizonte, Belo Horizonte, Brazil. [13]Universidade de Fortaleza, Fortaleza, Brazil. [14]Disciplina de Reumatologia, Faculdade de Medicina de Universidade de Ribeirão Preto, Universidade de São Paulo, Ribeirão Preto, Brazil. [15]Serviço de Reumatologia, Hospital do Servidor Público Estadual de São Paulo, Instituto de Assistência Médica ao Servidor Público Estadual, São Paulo, Brazil. [16]Rheos, Centro Médico Lúcio Costa, SGAS 610, bloco 1, salas T50- T51, L2 Sul, Asa Sul, Brasília, DF 70200700, Brazil.

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