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Guidelines

Guidelines for the drug treatment of rheumatoid arthritis

Diretrizes para o tratamento da artrite reumatoide

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Description of evidence collection method
A literature review of the scientific articles referenced in these guidelines was conducted with the MEDLINE database. The evidence search was based on real clinical scenarios, and the following keywords (MeSH terms) were used: Arthritis, Rheumatoid, Therapy (early OR late OR later OR time factors OR delay), Prognosis, Remission, Steroids, Anti-Inflammatory Agents, Non-Steroidal, NSAIDs, Diclofenac, Ibuprofen, Indomethacin, Piroxicam, COX-2, Celecoxib, Etoricoxib, Disease-modifying antirheumatic drug OR DMARD, Methotrexate, Gold sodium, Leflunomide, Sulfasalazine, Hydroxychloroquine, Tumor Necrosis Factor-alpha, Adalimumab, Certolizumab, Etanercept, Infliximab, Golimumab, Rituximab, Tocilizumab and Abatacept.

Grade of recommendation and strength of evidence
- **A:** Most consistent experimental and observational studies.
- **B:** Less consistent experimental and observational studies.
- **C:** Case reports (uncontrolled studies).
- **D:** Opinion that is not substantiated by critical evaluation, based on consensus, physiological studies or animal models.

Objective
These guidelines aim to provide recommendations for the treatment of rheumatoid arthritis in Brazil. Although North American and European guidelines for the treatment of rheumatoid arthritis have been recently published, it is important to review the subject with regard to specific aspects of Brazilian reality. Thus, the ultimate purpose of the establishment of consensus guidelines for the treatment of rheumatoid arthritis in Brazil is to provide an orientation and foundation for Brazilian rheumatologists with evidence from scientific studies and the experience of a committee of experts on the subject. Thus, therapeutic approaches to rheumatoid arthritis within the Brazilian socioeconomic context will be standardized, while physician autonomy will be maintained with regard to the indication/selection of available treatment options.

As knowledge in this scientific field progresses rapidly, we suggest biannual updates to these guidelines.

Introduction

Rheumatoid arthritis (RA) is a systemic and inflammatory autoimmune disease that is characterized by the preferential impairment of the synovial membranes of peripheral joints. The RA prevalence varies between 0.5% and 1% of the population, and RA affects predominantly women and adults in the 30- to 50-year age group[1,2](**B**).

The generally symmetrical involvement of small and large joints is the main feature of RA, and involvement of the hands and feet is common. The chronic and destructive nature of the disease can lead to significant functional limitations, including the loss of ability to work and an impaired quality of life, unless a diagnosis is made at an early stage of the disease and treatment leads to clinical improvements[3](**B**). In addition to the ir-

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reversible deformity and functional limitations, patients with advanced-stage RA might have lower survival rates, a finding that highlights the severity of this disease[4](B) [5](D).

RA-related costs are high as the result of both direct (spending on various medications, such as expensive biologic drugs, and medical and hospital expenses) and indirect (loss of personal productivity, absenteeism, payment of disability pensions and a total loss of working capacity) factors[6](B).

In the last two decades, there have been significant advances in an understanding of RA physiopathology, accompanied by the development of new therapeutic categories and the implementation of different treatment strategies, patient monitoring and intensive intervention and disease control at early symptomatic stages[7](D). The initial period of the disease, particularly the first 12 months, is known as early RA[5](D) and is considered to be a window of therapeutic opportunity, a time during which rapid and effective pharmaceutical intervention can change the long-term disease course. These interventions result in better disease control and the possibility of sustained RA remission[7,8](D).

Treatment of RA

RA treatment includes patient and family education, drug therapy, physiotherapy, psychosocial support, occupational therapy and surgical approaches. Drug therapies that will be addressed in this document include non-steroidal anti-inflammatory drugs (NSAIDs), corticosteroids, biologic and synthetic disease-modifying anti-rheumatic drugs (DMARDs) and immunosuppressive drugs.

DMARDs should be indicated for all patients once a diagnosis of RA[9](B) has been established. The use of DMARDs can be considered for patients with undifferentiated arthritis and positive test levels for RA predictive biomarkers such as anti-cyclic citrullinated peptides (anti-CCPs) and/or rheumatoid factors (RFs)[10](B).

Table 1[11-44](A) [45-64](B) [65-80](D) summarizes the DMARDs that are most frequently used in Brazil along with their presentations, doses and monitoring considerations.

1. Is disease treatment with the intent to achieve remission a feasible goal?

Once a diagnosis of RA has been established, an initial disease assessment is important and should include the adequate monitoring of disease activity by assessing not only articular but also extra-articular manifestations and the presence of comorbidities.

Some of the parameters that have been found to correlate with RA activity include patient visual pain scales, patient and physician-reported disease activity, the number of tender and swollen joints, instruments for functional capacity assessments (e.g., the Health Assessment Questionnaire – HAQ), inflammatory markers (e.g., erythrocyte sedimentation rate – ESR and/or C-reactive protein – CRP), fatigue, duration of morning stiffness, radiography of the hands, wrists and feet and quality of life indices (e.g., the Short Form – SF-36)[81-83](A) [84](B) [85,86](C).

Composite indices of disease activity (CIDAs) have been created and validated with these parameters. The main indices are the one based on 28 joint count (Disease Activity Score 28 – DAS-28), the simplified disease activity index (SDAI) and the clinical disease activity index (CDAI). These indices use a more simplified count of 28 joints (bilateral proximal interphalangeal, metacarpophalangeal (MCP), wrist, elbow, shoulder and knee joints) and determine a numerical value for RA activity. Tables 2, 3 and 4 detail the calculations and uses for these indices[87-95](A) [96](B).

There are good correlations between the CIDAs (CDAI, SDAI and DAS-28), and any of these indices can be used alone. Patients who are in remission or have low disease activity according to any index also have reduced radiographic progression and improved functional outcomes. Therefore, the aim should always be to keep the patient in clinical remission or, if this outcome is not possible, in a state of low disease activity[87](A).

The use of methotrexate (MTX), especially in combination with other DMARDs (gold, chloroquine or sulfasalazine), led to clinical remission in 14.0%[97](B), 33.3%[98](A), 38.0%[3](B) and 95%[99](A) of adult patients with active RA of a duration ranging between four months and five years (mostly between one and two years), according to the American College of Rheumatology (ACR) criteria. The best results were observed in the first 6 months after treatment. According to DAS-28 criteria, the remission rate at 24 months is 76%[100](B).

A combination of MTX and infliximab led to remission in 70% (ACR criteria)[101](A) and 21.3% (SDAI criteria)[102](A) of patients with RA of a duration less than 36 months who were evaluated between 54 weeks and 24 months. Similarly, MTX and etanercept combinations have achieved remission rates in a period of 12 to 36 months in 37% (DAS-44 ≤ 1.6)[103](A), 50% (DAS-28 ≤ 2.6)[43,45,104](A) and 50% (DAS-28 ≤ 3.2) of patients[105](A).

Remission, as measured by the DAS-28 ≤ 2.6 parameter, was achieved in 43% to 45% of patients with active RA (12 months) within four to nine years with a combination of adalimumab and MTX[28,106](A). The remission rate, as measured by SDAI criteria, was 15% at 24 months[107](B). The rates of early (in the first 12 months) remission in these patients, according to different criteria, were 47.7%, 50.8% and 32.3% for EULAR (European League against Rheumatism; DAS-28), ACR70 and DAS-28, respectively[108](B).

Responses to recent RA treatments (less than 24 months of illness) with combinations of DMARDs (MTX, gold, chloroquine or sulfasalazine) have also been measured according to several criteria or parameters during remission periods ranging from 2–11 years; the different criteria included ACR (14%–48%)[109-113](B), DAS ≤ 2.4 (39%–43%)[114,115](B) and DAS-28 ≤ 2.6 (23%–51%)[116,117](B).

Recommendation

RA patient remission, as measured by any of the objective parameters of disease activity (DAS, DAS-28, SDAI and CDAI), should be considered as central objective of patient treatment.

2. Does the early initiation of RA treatment offer benefits over a later initiation with respect to clinical and radiographic prognosis?

In patients who began treatment with non-biologic DMARDs, the remission rate at 12 months, defined as a CDAI score <

Table 1 – Disease-modifying antirheumatic drugs used for treating rheumatoid arthritis in Brazil.

Drug	Presentation	Dose	Clinical response and monitoring
Synthetic disease-modifying antirheumatic drugs			
Methotrexate	Tablets: 2.5 mg Solution for injection: 50 mg/2 mL	10–30 mg/week (orally, IM or SC)	Reduces signs and symptoms of disease activity, improves the functional status, and reduces the radiographic disease progression. Currently considered the standard drug for treating RA. Monitoring: blood count, creatinine and liver enzymes every 4–12 weeks.
Sulfasalazine	Tablets: 500 mg	1–3 g/day (orally)	Reduces signs and symptoms of disease activity, improves the functional status, and reduces the radiographic disease progression. Monitoring: blood count and liver enzymes every 8–12 weeks. Can be associated with MTX and other DMARDs.
Leflunomide	Tablets: 20 mg	20 mg/day or alternate days (orally)	Reduces signs and symptoms of disease activity, improves the functional status, and reduces the radiographic disease progression. Monitoring: blood count, creatinine and liver enzymes every 4–12 weeks. Can be associated with MTX and other DMARDs.
Hydroxychloroquine sulfate	Tablets: 400 mg	Up to 6 mg/kg/day (orally)	Antimalarials are currently considered less potent drugs, and should be used at initial cases of RA or undifferentiated arthritis, with low erosive potential. Can be associated with MTX and other DMARDs. Monitoring: initial ophthalmologic exam and annually after five years (or annually since the beginning, in the presence of risk factors for maculopathy or retinopathy).
Chloroquine disphophate	Tablets or capsules: 150 mg or 250 mg	Up to 4 mg/kg/day (orally)	
Gold salts (aurothioglucose or sodium aurothiomalate)	Solution for injection: 50 mg/0.5 mL	50 mg/week, deeply IM, usually initiating with 25 mg/week. After control, fortnightly and monthly doses. The cumulative dose should not exceed 3 g	Effective in controlling symptoms and reducing the radiographic disease progression, rarely used in Brazil, due to their adverse effects and low availability. Monitoring: monthly; blood count, liver enzymes, and urinalysis.
Biologic disease-modyfing antirheumatic drugs			
Tumor necrosis factor blockers			Effective in controlling symptoms and reducing the radiographic disease progression. Should be preferably prescribed after failure of two schedules with synthetic DMARDs (one of which should include the combination with synthetic DMARDs, with MTX preferably as the anchor drug), associated with MTX or other synthetic DMARD. Monitoring: investigation of latent TB before starting treatment (clinical history, chest radiography, PPD and/or IGRA), blood count, liver enzymes every 4–12 weeks. Careful monitoring of the occurrence of infection, particularly during the first year of use.
Adalimumab	Prefilled syringes: 40 mg	40 mg SC every 15 days	
Certolizumab	Prefilled syringes: 200 mg	400 mg SC every two weeks, in weeks 0, 2 and 4, and, then, 200 mg every two weeks, or 400 mg every four weeks	
Etanercept	25-mg and 50-mg vials or 50-mg prefilled syringes	50 mg/week	
Infliximab	Vials: 100 mg	3–5 mg/kg/dose IV infusion in weeks 0, 2 and 6, followed by the same dose every 6–8 weeks	
Golimumab	Prefilled pen: 50 mg	50 mg SC monthly	

(continued on next page)

Table 1 – Disease-modifying antirheumatic drugs used for treating rheumatoid arthritis in Brazil. *(continued)*

Drug	Presentation	Dose	Clinical response and monitoring
		Biologic DMARDs	
Costimulation modulator *Abatacept*	250-mg vials	IV infusion of 500 mg in patients weighing less than 60 kg, of 750 mg in patients weighing 60-100 kg, and of 1,000 mg in patients over 100 kg, every four weeks	Reduces signs and symptoms of disease activity and the radiographic disease progression . Can be prescribed after failure of synthetic DMARDs or failure of and/or intolerance to biologic DMARDs. It is preferentially used in association with MTX or other synthetic DMARDs. Monitoring: blood count and liver enzymes every 4–8 weeks. Occurrence of infection should be monitored.
B lymphocyte depletion agent *Rituximab*	500-mg vials	500 mg to 1 g IV on days 0 and 14 (1–2 g/cycle)	Effective in reducing signs and symptoms of RA and the radiographic disease progression. Can be prescribed after failure of and/or intolerance to anti-TNF or other biologic DMARDs. It should not be prescribed after failure of synthetic DMARDs, except for exceptional situations. The presence of RF and/or anti-CCP predicts better therapeutic response to rituximab. It should be preferably prescribed in association with MTX or other synthetic DMARD. The cycles can be repeated at minimum intervals of six months, according to disease evolution. Monitoring: blood count and liver enzymes every 4–12 weeks. Occurrence of infection should be assessed.
IL-6 receptor blocker *Tocilizumab*	80-mg or 200-mg vials	8 mg/kg/dose on IV infusion every four weeks	Effective in reducing signs and symptoms of RA and the radiographic disease progression. Can be prescribed after failure of synthetic DMARDs or failure of and/or intolerance to anti-TNF or other biologic DMARDs. Preferential use in association with MTX or other synthetic DMARDs, although it can be used as monotherapy. Monitoring: blood count, liver enzymes, and lipid profile at every infusion.
Immunosuppressive drugs			Considered less effective in controlling signs and symptoms of RA and reducing radiographic disease progression. They are inferior options compared with DMARDs. They are mainly indicated to treat extra-articular manifestations and vasculitis.
Azathioprine	Tablets: 50 mg	1–3 mg/kg/day, orally	Monitoring: blood count and liver enzymes every 4–8 weeks.
Cyclophosphamide	Tablets: 50 mg 200-mg or 1,000-mg vials	2–2.5 mg/kg/day, orally, or monthly pulse therapy with 750 mg to 1 g/m^2 of body surface, IV, every four weeks	Reserved for patients with severe extra-articular manifestations. Monitoring: blood count, liver enzymes, and urinalysis (due to the risk of hemorrhagic cystitis) every four weeks.
Cyclosporine	Tablets: 50 and 100 mg	3–5.0 mg/kg/day, orally	Blood pressure and renal function every 2–4 weeks.

RA, rheumatoid arthritis; DMARD, disease-modifying antirheumatic drug; IGRA, interferon gamma release assays; IM, intramuscular; IV, intravenous; MTX, methotrexate; PPD, tuberculin skin test; RTX, rituximab; SC, subcutaneous.

2.8, was 21.3% in those with a disease duration of five years or less, compared to 19.6% in patients with a disease duration between 6–10 years and 13.5% in those with a disease duration of at least 11 years. Therefore, there is a 1.7% (number needed to treat – NNT: 60) and 7.8% (NNT: 13) greater chance of response (remission) when synthetic non-biologic DMARD treatment is initiated within the first five years of the disease, compared with 6–10 years or after 11 years of the disease, respectively[51](**B**).

In patients who received anti-TNF biologic DMARD treatment, the benefit of early treatment in the first five years of the disease was 4.6% (NNT: 22) or 9.5% (NNT: 10) compared with treatment after 6–10 years or more than 11 years, respectively[51](**B**). The percentage of patients who achieved sustained remission remained higher in patients who were treated in the first five years of disease throughout the course of treatment.

In patients who were diagnosed with RA within the first five years since the onset of symptoms, the use of synthetic DMARDs (MTX, leflunomide, sulfasalazine, chloroquine/hydroxychloroquine, intravenous (IV) gold sodium, cyclosporine) within the first year of symptoms led to reduced radiographic disease progression (measured by joint damage according to the Ratingen score) than for patients whose treatment started after symptoms had occurred for one to five years. Patients with for years of symptoms had a

Table 2 – Calculation and total value of composite indices of disease activity (CIDAs).

Elements	SDAI	CDAI	DAS-28 (4 variables)
Swollen joint count	(0-28) Simple sum	(0-28) Simple sum	Square root of the simple sum
Painful joint count	(0-28) Simple sum	(0-28) Simple sum	Square root of the simple sum
Acute phase reactants	CRP (0.1–10 mg/dL)	-	ESR 2-100 mm
Overall assessment of health (patient)		-	or CRP 0.1-10 mg/dL logarithmic transformation
Global assessment of disease (patient)	(0-10 cm)	(0-10 cm)	0-100 mm
Global assessment of disease (evaluator)	(0-10 cm)	(0-10 cm)	-
Total index	Simple sum	Simple sum	-
(Change in rate)	(0.1-86)	(0–76)	Number requires entry into the calculator (0.49-9.07)

SDAI, simplified disease activity index; CDAI, clinical disease activity index; DAS-28, disease activity index (28 joints); CRP, C-reactive protein; ESR, erythrocyte sedimentation rate. Ranges of 2-100 mm/h for ESR and 0.1-10 mg/dL for CRP are assumed.

Table 3 – Cutoffs for composite indices according to RA activity.

Index	State of disease activity	Cutoffs
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
DAS-28	Remission	≤≤ 2.6
	Low	> 2.6 and ≤ 3.2
	Moderate	> 3.2 and ≤ 5.1
	High	> 5.1

SDAI, simplified disease activity index; CDAI, clinical disease activity index; DAS-28, disease activity index (28 joints).
Modified from Aletaha D, Smolen JS. The Simplified Disease Activity Index (SDAI) and the Clinical Disease Activity Index (CDAI): A review of their usefulness and validity in rheumatoid arthritis. Clin Exp Rheumatol 2005; 23(39):S100–8.

Table 4 – Responses according to variations in the Composite Indices of Disease Activity points.

Index	Response Type
Response EULAR-DAS-28[87,88](A)	Good: down > 1.2 points and patients achieve DAS-28 with low activity (≤ 3.2). Moderate: down 1.2 points on DAS-28; down between 0.6 and 1.2 points with a decline in disease activity from high to moderate activity or moderate to low activity.
SDAI response[90] (A)	Good: down 17 points. Moderate: down 7 points.
CDAI response[90] (A)	BGood: down 14 points. Moderate: down 6 points.

SDAI, simplified disease activity index; CDAI, clinical disease activity index, DAS-28; disease activity index (28 joints).
Modification of: Aletaha D, Funovits J, Wards MM, Smolen JS, Kvie TK. Perception of improvement in patients with rheumatoid arthritis varies with disease activity levels at baseline. Arthritis Rheum. 2009;61:313–20.

0.31% greater chance of joint damage progression per year than patients who were treated after less than one year of symptoms[118](**B**).

Early administration of DMARD treatment (less than nine months from symptom onset) produced a 33% relative reduction in radiographic disease progression during the following three years[119](**B**).

It was also found that for patients whose treatment began with 3 g/day of sulfasalazine or more than 15 mg/week of MTX in the first three months after symptom onset, the following results were observed in comparison to patients whose treatment began after 12 months: a 40% increase in the number of patients with responses within 32 months (as measured by DAS-28 < 3.2; NNT: 2); a 4-fold reduction in joint damage progression (measured by the Larsen radiographic score) and a 35% increase (NNT: 3) in the number of patients who achieved 50% and 70% ICR[120](**B**).

However, in patients with symptom durations of less than 24 months, no differences in the ACR (20 or 50) or DAS-44 < 1.6 response rates were found between patients who began non-biologic DMARD therapy after less than five months of symptoms and those who started treatment after more than five months [121](**B**).

If four months after symptom onset is set as the cutoff for delayed or retarded treatment with 1.0 g of sulfasalazine (monotherapy) or 500 mg of sulfasalazine twice per day, 7.5 mg of methotrexate per week, 300 mg of hydroxychloroquine and 5 mg of prednisone per day (combination therapy), the disease remission rate in response to earlier treatment (< 4 months) is 24% greater (NNT: 4) in patients who underwent monotherapy, despite the similar time course for those who underwent combination therapy[110](**B**).

In patients with early RA who were treated for two years with DMARDs (MTX, combined or not with adalimumab), the additional time to achieve remission (SDAI) in the first year of treatment was accompanied by an increase in joint damage progression, as evaluated by imaging, in the second year[107](**B**).

Recommendation

Treatment introduction for patients with early RA should be early (in the first few months after symptom onset) to

increase the clinical response rate (NNT: 2–4) and reduce radiological joint damage progression in the early years of treatment.

3. Does corticosteroid use in early-stage disease improve patient outcomes?

Improvements in inflammation and pain are the best-known and expected effects of corticosteroids in RA. However, some studies have indicated that corticosteroids, when combined with DMARDs, can modify the course of the disease[14](**A**) [66](**D**).

Most studies on the use of corticosteroids in RA treatment suggest the use of prednisone or prednisolone at low doses (≤ 15 mg/day). There are no comparative studies that have preferentially indicated higher doses at the beginning of treatment[14](**A**) [66](**D**).

Because corticosteroids have many side effects, their usage should be kept to a minimum. If corticosteroid use for three or more months is foreseen, calcium and vitamin D supplements should be taken. The use of antiresorptive drugs such as bisphosphonates could be considered in patients with risk factors as determined by fractures or bone densitometry results[50](**B**).

Gastric protection via proton pump inhibitors is recommended for patients who concomitantly use corticosteroids and NSAIDs[67](**D**).

The use of intra-articular corticosteroids can be considered at any treatment stage during which the disease remains active in a small number of joints[67](**D**). In patients with early RA (less than 12 months of symptoms) and involvement of the MCP joints, the use of MTX in combination with intra-articular methylprednisolone infiltration can reduce bone loss in the inflamed joints[122](**B**).

Prednisone (12.5 mg/day for two weeks and 6.25 mg/day for 12 months), when combined with MTX (15 mg/month), led to an increase of 43.4% (NNT: 2) in the 6-month remission rate (according to DAS) in patients with early RA (less than 12 months of disease)[115](**B**).

In patients with early-stage arthritis (less than 16 weeks of symptoms), the use of an intramuscular glucocorticoid (single injection of 120 mg methylprednisolone) offered no benefit with respect to symptom remission or RA development at 52 weeks[123](**B**).

The use of 1–4 mg of prednisone per day for 24 weeks reduced the risk of loss of treatment adherence due to a lack of efficacy by 31% (NNT: 3) in RA patients[124](**A**).

In RA patients, combined treatment with MTX (15 mg weekly) and prednisone (60 mg per day with gradual reduction) for 24 months reduced radiological progression and improved functional responses (HAQ) but increased the number of patients with a loss of treatment adherence by 7% (number needed to harm – NNH: 14)[125](**A**).

The combination of MTX (15 mg/week) and prednisone (60 mg/day) led to an increase in the 24-month remission rate (DAS ≤ 2.4) of 18% (NNT: 6), increases in clinical responses (ICR) and functional capacity (HAQ), and reductions in radiographic progression in RA patients, compared to treatment without prednisone[56](**B**) [126](**A**). However, despite the lack of increased adverse events, patients reported greater intolerance to this combination[127](**B**).

The combination of DMARDs and prednisolone (7.5 mg/day) over 24 months reduced radiological joint damage progression (Sharp score) and increased disease remission (DAS-28) by 22.7% (NNT: 4), with few adverse events in patients with early RA (less than 12 months of symptoms)[128](**A**).

The use of budesonide (9 mg/day) or prednisone (7.5 mg/day) in RA patients (less than 12 months of disease) for 12 weeks caused improvements in disease activity (number of involved joints) and function (HAQ)[129](**B**).

There was no increased clinical benefit from the use of prednisone at 10 mg/day for 24 months in patients with early-stage RA. However, there is evidence for reduced radiographic joint damage progression, and no increases in the rates of bone fractures have been reported[130,131](**A**).

The combination of prednisolone (initial dose of 30 mg/day and maintenance of 4.5 mg/day) and DMARDs only caused a reduction in radiographic injury progression (Larsen score) at 12 months in patients with early RA[132](**B**).

Recommendation

The use of corticosteroids, particularly daily prednisone, in combination with drugs that modify the disease course, especially MTX, for 12 to 24 months offers radiological and clinical benefits to patients with early RA. Because corticosteroids have many side effects, their usage should be kept to a minimum, and their dose should be the smallest possible.

4. Does the prescription of anti-inflammatory drugs alter the disease prognosis with regard to clinical and radiographic progression?

NSAIDs are useful because they decrease inflammation and pain, especially early in the disease, as DMARDs are not immediately effective. NSAIDs can also be used when disease activity is not completely controlled and when disease flare-ups occur[47](**B**)[65](**D**).

Patients who were diagnosed with RA within the past 12 months and who initially received NSAID treatment (12 months) alone or, if necessary, with DMARDs, had worse clinical responses within five years than those who initially received DMARDs (gold sodium, chloroquine, MTX or sulfasalazine), as measured by ESR (in mm/hour), mean pain score (visual analogue scale – VAS-100 mm), articular score (Thompson articular index of edema and joint pain, 0–534), general well-being (VAS-100 mm), duration of morning stiffness (maximum, 720 minutes), grip strength (kPa; measured with a vigorimeter), and functional disability (HAQ) (0–3)[133](**B**). Of the patients who used NSAIDs for the first 14 months (on average), 86% discontinued the treatment due to ineffectiveness and were subsequently treated with DMARDs for an average of 42 months. Patients who remained on NSAIDs for five years had worse clinical and radiological progressions in comparison to those who discontinued treatment[133](**B**).

Furthermore, adult patients who had RA for at least six months and had previous clinical responses to NSAIDs had varying lower discontinuance rates due to ineffectiveness

of 12%–20% and 10%–50% after 12-week treatments with 90 mg/day of etoricoxib or 500 mg of naproxen twice daily, respectively. However, there were measurable benefits for patients who remained on the treatment, according to the patient global assessment scores (PGA), Investigator of Global Assessment of Disease Activity scores and the number of joints with edema[134,135](**A**).

Patients who had been diagnosed with RA in the previous 12 months were treated with either 1.2 g/day of sulfasalazine or 100 mg/day of diclofenac; 11% and 20%, respectively, did not complete the 12-month treatment course due to ineffectiveness. The number of radiographic erosions was significantly higher in patients treated with diclofenac. Furthermore, with regard to the disease activity scores (ESR and DAS), swollen joints, patient global assessments and HAQ, the patients treated with sulfasalazine had 65% to 82% better responses than those treated with NSAIDs[136](**B**).

Despite a discontinuation rate of 15%, the use of diclofenac for active RA treatment produced significant responses at 12 weeks according to the ACR20 criteria, patient global assessments, VAS for pain, functional HAQ scores and joint swelling. CRP and ESR outcomes did not show significant benefits[137](**A**).

RA patients (duration of more than three months) who used different doses of celecoxib (100 mg, 200 mg or 400 mg) or a dose of naproxen (500 mg twice daily) showed functional (HAQ) and quality of life (SF-36) improvements at 12 weeks according to the ACR20 and also the number of involved joints, VAS for pain, HAQ and PGA, with no differences in response between these medications. However, naproxen produced adverse gastrointestinal events in a number of patients[138,139](**A**).

Patients with RA for at least six months who used 200 mg of celecoxib or 75 mg of diclofenac twice daily for 24 weeks were found to have reduced edema, joint stiffness and PGA score indices with no differences between the treatments. However, adverse gastrointestinal events were significantly more frequent in patients treated with diclofenac[140](**A**).

There are indications that the combination of NSAIDs and DMARDs is a favorable prognostic factor for RA remission[141](**B**). The chosen NSAID should be personalized, as there is no known superiority of any drug in this class. Greater control, replacement, suspension, shorter usage time and lower dose should be considered if there are any medical conditions that might be aggravated by NSAIDs such as previous NSAID hypersensitivity, hypertension, heart failure, renal failure, gastrointestinal disease, arterial failure, liver disease or clotting disorders[48](**B**).

For patients with a history of gastrointestinal disease, the selective cyclooxygenase 2 (COXIB) inhibitors present a lower risk than other NSAIDs[49](**B**). For those with a higher risk of cardiovascular disease, anti-inflammatory drugs should generally be used with caution[13](**A**).

Recommendation

The use of NSAIDs alone as an early treatment in patients with active RA produces a worse clinical response in the first 24 months than combined treatment with DMARDs and also suffers from a high rate of treatment discontinuation due to inefficacy. The rate of adverse gastrointestinal events associated with treatment discontinuation, the short treatment response evaluation time, as well as the worse radiological clinical prognosis means that RA treatment with NSAIDs alone is not recommended. Apparently, the use of NSAIDs in combination with DMARDs during early-stage disease is a favorable prognostic factor for RA remission.

5. Should methotrexate be the first treatment option?

MTX is an immunomodulatory agent that acts by inhibiting the synthesis of DNA, RNA, thymidylate and proteins. In RA, the anti-inflammatory effects of MTX appear to be at least partly related to the modulation of adenosine metabolism and to possible effects on tumor necrosis factor (TNF) activity. The immunosuppressive and toxic effects of MTX are due to the inhibition of dihydrofolate reductase, an enzyme involved in folic acid metabolism that prevents the reduction of dihydrofolate to active tetrahydrofolate. The time to maximum concentration is 1–5 hours orally (OR) and 30–60 minutes intramuscularly (IM) or subcutaneously (SC). After administration, 40% - 90% is eliminated renally in an unaltered form[68](**D**). MTX is currently considered the standard drug for RA treatment[69](**D**). Its abilities to reduce the signs and symptoms of RA activity and improve patient functionality have been demonstrated[15](**A**). Additionally, MTX reduces the progression of radiographic lesions.

An initial dose of 10–15 mg/week MTX, administered orally or parenterally (IM or SC), is recommended. If disease improvement or control is not observed in response to the initial dose, the dose should be gradually increased every 2–4 weeks to a final dose of 20–30 mg/week, preferably within the first 12 weeks. Parenteral presentation may be indicated in patients with gastrointestinal intolerances or inadequate responses to the oral form[70](**D**).

The adverse events most frequently reported in response to MTX are anemia, neutropenia, nausea and vomiting, mucositis, and elevated liver enzyme levels. Less frequent manifestations include interstitial pneumonia. It is contraindicated in patients with renal failure, liver disease, alcoholism, bone marrow suppression and in women of childbearing potential who are not using contraception. Pregnancy and breastfeeding are formally contraindicated in MTX-treated patients. MTX should be used with caution in patients with mild lung disease and avoided in patients with moderate or severe pulmonary disorders[70](**D**).

It has been suggested that MTX administration should be combined with folic acid at doses of 5–10 mg/week, given 24–48 hours after MTX, to minimize adverse events[70](**D**).

Recommendation

The efficacy of MTX for the treatment of active and early RA is well established. MTX is currently considered the standard drug for RA treatment. Its abilities to reduce the signs and symptoms of RA activity and improve patient functionality have been demonstrated. MTX also reduces the progression of radiographic lesions.

6. Are other DMARDs such as leflunomide, sulfasalazine and gold sodium equivalent to MTX in terms of safety and efficacy for disease treatment?

Leflunomide

Leflunomide is an immunomodulatory agent that inhibits the enzyme dihydroorotate dehydrogenase, which is involved in pyrimidine synthesis, and thus presents with antiproliferative activity. It is absorbed via the gastrointestinal tract, and biotransformation most likely occurs in the liver and gastrointestinal wall, where leflunomide is mainly transformed into M1, the active metabolite responsible for all leflunomide-associated actions. The time to maximum concentration (peak) of M1 is 6-12 hours, and elimination is renal and intestinal[71](**D**).

Leflunomide improves disease activity and patient quality of life and reduces radiographic progression[18](**A**) [53](**B**).

Leflunomide is prescribed at a dose of 20 mg/day (OR)[18](**A**) [53](**B**) [71](**D**), although a dose of 20 mg on alternate days may be used.

Adverse events in response to leflunomide include nausea, vomiting, abdominal pain and diarrhea, abnormal liver enzyme levels, rash and hypertension[71](**D**). It is contraindicated in women of childbearing potential who are not using contraception, as well as in patients with renal and hepatic disease. Pregnancy and breastfeeding are formally contraindicated in leflunomide-treated patients, and its suspension is recommended for two years before a possible pregnancy. In cases of complications, especially in pregnancy, leflunomide can be eliminated by the administration of cholestyramine, given in 8-g doses three times daily for 11 days[71](**D**).

A comparison between MTX (25 mg/day) and leflunomide (20 mg/day) combined with prednisone, given for 24 weeks, showed no difference in clinical response in patients with RA for more than 2.4 years as measured by DAS-28[142](**B**).

In a systematic review of randomized controlled trials (RCTs) that studied the use of leflunomide in patients with active RA, it was concluded that there was no difference in clinical outcomes compared to MTX[143](**A**) .

In patients with active RA, the use of leflunomide (20 mg/day) for four months showed no differences in clinical (ICR and VAS) or functional (HAQ) responses compared with MTX (15 mg/week) but showed better results according to MR imaging criteria[144](**A**). However, this comparison was performed with submaximal doses of MTX.

There was no difference between leflunomide (20 mg/day) and MTX (15 mg/week) with respect to clinical response (ICR) in RA patients after a 24-month treatment, but functional responses (HAQ) were higher in response to leflunomide[145](**A**).

In a 24-month RA treatment with leflunomide (20 mg/day) or MTX (15 mg/week), the results were similar for the two forms of treatment with regard to ICR, joint swelling, overall evaluations and radiological responses[146](**A**). The functional response (HAQ) was also similar for the two forms of treatment[146](**A**).

Leflunomide treatment (20 mg/day) in patients with active RA produced similar effects to MTX (15 mg/week) with regard to radiological disease progression[147](**B**).

The clinical (ICR) and radiological responses in patients with RA for more than 6 months were similar when the patients were treated for 52 weeks with leflunomide (20 mg/day) or MTX (7.5 mg/week)[148](**A**). However, the functional results in some components of the HAQ and SF-36 were better in the leflunomide-treated patients[149](**A**). Again, we must emphasize that the dose of methotrexate used in this study was lower than the doses typically used for RA treatment.

Patients with active RA showed a greater tolerance to MTX treatment (15 mg/week) than to leflunomide treatment (20 mg/day), but the clinical and radiological efficacies over 12 months were similar[150,151](**A**) [152](**B**).

Sulfasalazine

Sulfasalazine belongs to the group of salicylates and sulfonamides. It is produced by intestinal bacteria from sulfapyridine and 5-aminosalicylic acid. Sulfapyridine has multiple immunomodulatory effects, including the inhibition of prostaglandin production, various neutrophilic and lymphocytic functions and chemotaxis. It also inhibits folate-dependent enzymes. The peak serum concentration of sulfasalazine is approximately 1.5–6 hours, and it has an elimination half-life of 5–10 hours. The drug is metabolized in the gastrointestinal tract (via the intestinal flora), and its excretion is renal (75%–91%)[16](**A**).

Sulfasalazine is considered to be more effective than a placebo with regard to disease activity reduction, pain control and global clinical assessments. Its clinical efficacy and interference with radiographic progression have been confirmed[16](**A**).

Sulfasalazine is usually prescribed at a dose of 1-3 g/day (OR)[16,17](**A**).

Side effects include gastrointestinal intolerance (anorexia, nausea, vomiting), rash, elevated liver enzyme levels, oral ulcers and myelosuppression (leukopenia with neutropenia). Hypersensitivity pneumonitis, neurological manifestations and changes in male fertility are rarely observed. Most effects are benign and reversible with drug withdrawal[17](**A**).

Salicylates or any components of the sulfasalazine formula are contraindicated in patients with known sulfonamide hypersensitivity and individuals with porphyria[16,17](**A**).

There was no difference in the clinical responses (DAS ≤ 2.4) of RA patients who received MTX monotherapy (15 mg/week) or sulfasalazine (40 mg/kg/day), although the combination of the two forms of treatment produced better outcomes at 18 months[14](**A**).

In patients with RA for less than 12 months, sulfasalazine treatment (2 g/day) produced similar results (DAS, EULAR and ACR) as MTX treatment (15 mg/week) over 52 weeks; however the combined therapies appeared to increase the treatment benefits, according to DAS measurements[66](**D**).

Gold sodium

Gold sodium, specifically in injectable forms (aurothioglucose and aurothiomalate), is able to reduce both the constitutional and articular symptoms and slow the radiographic evolution of RA[22](**A**). It can be used alone or in combination with other agents[23](**A**).

The usual dose of gold sodium is 50 mg/week; the treatment is usually initiated at 25 mg/week, and it is possible to increase the application interval to biweekly and monthly doses after the symptoms are controlled. The cumulative dose should not exceed 3 g[22,23](**A**).

Its toxicity profile includes myelotoxicity (particularly thrombocytopenia), oral ulcers, skin reactions (exfoliative dermatitis), nephropathy (possibly including involving proteinuria) and interstitial lung disease[22,23](**A**).

Although it has been recommended in recent international reports[66](**D**), gold sodium is currently used very rarely in Brazil due to its adverse effects and the difficulty of drug acquisition in this area.

A comparison between MTX (15 mg/week) and gold sodium (50 mg/week) for the treatment of RA patients (duration > 4 months) demonstrated improved clinical outcomes (swelling and stiffness) in the first year for patients treated with gold sodium but similar outcomes in the third year of follow up. There was greater toxicity in the first and third year (increased risk of 38%; NNH: 3)[98,153](**A**) and similar results with regard to radiological progression in one[154](**A**) and three years[22](**A**).

Gold sodium (50 mg/week) has a similar treatment efficacy (clinical and functional) as MTX (20 mg/week) for RA patients but also has an increase in toxicity of 24% (NNH: 4)[154](**A**).

Recommendation

Leflunomide, sulfasalazine and gold sodium appear to have similar efficacies to that of MTX for the treatment of active RA; however, there is a greater risk of intolerance and toxicity and discontinuation with these drugs relative to MTX.

7. Are antimalarial drugs effective in RA treatment?

Antimalarials have been used in RA treatment for more than 50 years. These drugs are safe and effective, especially for early and mild forms of RA. The action mechanism is still unclear, although it appears to involve multiple factors, including anti-inflammatory activity (stabilization of lysosomal membranes, inhibition of lysosomal enzymes and chemotaxis and polymorphonuclear phagocytosis) and interference in prostaglandin production, among others[19,20](**A**).

The two available forms are chloroquine diphosphate and hydroxychloroquine sulfate; the latter is preferred due to its better safety profile, especially with regard to ophthalmologic factors. The maximum daily doses of chloroquine phosphate and hydroxychloroquine sulfate are 4 mg/kg/day and 6 mg/kg/day orally, respectively, depending on the ideal weight of the patient. The onset of action is slow and requires three to four months to achieve peak efficiency in approximately 50% of patients.

The side effects are diverse and include gastrointestinal intolerance (nausea, vomiting, abdominal pain), skin hyperpigmentation, headache, dizziness, myopathy and retinopathy. The latter is infrequent, but regular ophthalmologic monitoring is indicated (baseline and annually after five years, or annually from the outset in patients with risk factors such as those with renal or hepatic impairment or maculopathy, those who are elderly or those with a cumulative dose greater than 1,000 g of hydroxychloroquine sulfate or 460 g of chloroquine diphosphate)[72](**D**).

Hydroxychloroquine was more effective than a placebo in reducing the analyzed clinical and laboratory parameters (ESR), although in isolation it did not alter radiographic progression[19-21](**A**). Similar results were observed with chloroquine, which is less expensive. These drugs are contraindicated in patients with retinal and visual field abnormalities[21](**A**)[72](**D**).

Although these drugs are traditionally used in Brazil, often in combination with other DMARDs, antimalarials are currently considered less potent drugs and should only be used in early cases of RA or undifferentiated arthritis with a low erosion potential.

Several therapeutic regimen studies have included hydroxychloroquine; however, these studies did not permit a specific and individualized analysis of the effects of hydroxychloroquine in early-stage RA treatment.

In RA patients who did not respond to NSAID use, hydroxychloroquine treatment (200-400 mg/day) for 12 weeks led to reduced swelling, stiffness and joint pain (20%, 23% and 26%, respectively) and increased clinical responses (ICR)(ACR20) of 20% (NNT: 5). There was no increase in adverse events[155](**A**).

Hydroxychloroquine treatment (7 mg/kg/day) in RA patients (disease duration less than 24 months) for 36 weeks reduced joint involvement and pain and improved functional responses[20](**A**). A follow-up after 36 months showed better outcomes for these patients than for those who were treated later (after nine months)[156](**B**).

There were no differences in treatment responses and numbers of adverse events between three different doses of hydroxychloroquine (400 mg/day, 800 mg/day or 1.2 g/day) during a 24-week period in patients with early-stage RA[157](**B**).

Patients (more than six months of RA) who were previously treated with a combination of MTX (15 mg/week) and hydroxychloroquine (400 mg/day) for 24 weeks have benefited from a 12-week maintenance regimen of hydroxychloroquine[158](**B**).

In early-stage RA patients, hydroxychloroquine treatment (400 mg/day for 24 weeks) reduced joint involvement by 10% (NNT: 10) and pain by 19% (NNT: 5), while overall patient and physician evaluations improved by 16% (NNT: 6) and 12% (NNT: 8), respectively. There was an increase in adverse events in 13% of patients (NNT: 8)[19](**A**).

The combination of MTX (15 mg/week) and hydroxychloroquine (200 mg/day) for six months for the treatment of early-stage RA patients increased clinical responses and reduced pain and joint impairment when compared with hydroxychloroquine treatment alone[159](**B**).

The addition of hydroxychloroquine (400 mg/day) to the treatment regimens of patients with partial responses to gold sodium (six months) added no benefits with respect to pain and joint involvement[160](**B**).

Recommendation

The treatment of early-stage RA with hydroxychloroquine at doses of 200–400 mg/day provides benefits related to pain, joint involvement and clinical responses, although the evi-

dence for these benefits is weak, whether due to improper measures used to demonstrate the benefits, the reduced size of the benefits or weak supporting evidence. Although these drugs are traditionally used in Brazil, often in combination with other DMARDs, antimalarials are currently considered less potent drugs and should be used in early cases of RA or undifferentiated arthritis with low erosion potential.

Biologic DMARDs

One of the most important advances in RA therapy has been the development of biologic DMARDs. While these medications effectively control RA, studies are needed to determine their long-term safety. The following biologic DMARDs are approved by the National Agency for Sanitary Surveillance (Agência Nacional de Vigilância Sanitária (ANVISA)) for use in Brazil:

- TNF blockers: adalimumab, certolizumab, etanercept, infliximab and golimumab;
- B lymphocyte depletion: rituximab;
- Costimulatory blocker: abatacept;
- Interleukin-6 (IL-6) receptor blocker: tocilizumab.

These drugs are indicated for patients with persistent disease activity despite treatment with at least two synthetic DMARD regimens (at least one in combination with DMARDs). Biologic agents must be combined with a DMARD, preferably MTX. However, one biologic DMARD may be prescribed earlier in the course of RA treatment, especially in cases of disease with signs of poor prognosis (a high number of involved joints, radiographic erosions in early-stage disease, high rheumatoid factor and/or anti-CCP levels); this exception is described below.

Social, educational and demographic characteristics of different macro-regions of Brazil, including difficulties in the administration of SC medications for certain patients and their families, as well as the absence of infusion centers for the administration of IV medications in certain places, may determine the choice of biologic DMARDs. Public or private drug dispensing and infusion centers should inform patients and families about the appropriate conditions for each medication or send them directly to the infusion sites to avoid losses in treatment efficacy. It is recommended that these drugs be used as indicated and monitored by a rheumatologist[78](**D**).

Biologic DMARDs should not be combined due to the potential risk of serious infection.

8. Is the introduction of biologic therapy with anti-TNF drugs such as adalimumab, certolizumab, etanercept, infliximab and golimumab effective and safe for RA patients?

Currently, the most commonly used biologic DMARDs are TNF blockers. TNF is a potent inflammatory cytokine that is expressed in large amounts in the serum and synovial fluid of RA patients. TNF promotes the release of other cytokines, particularly IL-1, IL-6 and IL-8, and stimulates protease production. TNF inhibition has been shown to be an effective and rapid method of controlling disease activity[79](**D**).

In terms of effectiveness, no evidence suggests the superiority of any of the 5 anti-TNF agents approved in Brazil for RA treatment[55,56] (**B**).

Anti-TNFs should be used in combination with MTX or other DMARDs because the combined use of these drugs is safe and effective and provides rapid control of disease activity, compared to anti-TNF monotherapy. In patients who have contraindications to the use of synthetic DMARDs, anti-TNF may eventually be prescribed as a monotherapy[77](**D**) [26-31,43,44](**A**) [45,57,58](**B**).

Adalimumab

Adalimumab is a human monoclonal anti-TNF antibody prescribed for SC use at a biweekly dose of 40 mg[28,33-37,45](**A**). A 52-week follow-up of RA patients who were treated with MTX and adalimumab (40 mg or 20 mg biweekly) showed increased clinical responses (ACR50) of 32% (NNT: 3) and 28.2% (NNT: 4), respectively, with combination therapy compared to MTX monotherapy. There was also a reduction in radiographic progression and functional improvement (HAQ) with the combination therapy, with no increase in adverse events[161](**A**) [162](**B**).

Treatment of RA patients with a combination of biweekly 40 mg adalimumab and MTX (20 mg weekly) increased clinical responses (ACR50) by 21% (NNT: 5) and 16% (NNT: 6) compared to adalimumab and MTX monotherapies, respectively. There was also a reduction in radiographic progression, as well as an increase in clinical remission (DAS-28 ≤ 2.6) of 20% (NNT: 5) and of 22% (NNT: 5) compared to adalimumab and MTX monotherapy, respectively[57](**B**).

The clinical response (ACR50) obtained with biweekly 40 mg adalimumab for 24 weeks in RA treatment concomitantly with the use of synthetic DMARDs increased clinical responses (ACR50) by 17.6% (NNT: 6) and did not increase the risk of adverse events or serious adverse events[34](**A**).

The combination of adalimumab in doses of 20 mg, 40 mg or 80 mg and MTX (15 mg/week) for 24 weeks produced increases in clinical response (ACR50) of 23.8% (NNT: 4), 47.1% (NNT: 2) and 30.4% (NNT: 3), respectively, compared to MTX monotherapy, with no difference in adverse events[163](**A**).

Certolizumab

Certolizumab pegol is a Fab fragment of a humanized, high-affinity anti-TNF antibody linked to two polyethylene glycol molecules. It is prescribed for SC use at a biweekly dose of 400 mg during weeks 0, 2 and 4 and at a dose of 200 mg every two weeks or 400 mg every four weeks thereafter[30,31,37](**A**).

Certolizumab treatment at 200 mg or 400 mg biweekly for 52 weeks, combined with MTX (15 mg/week), increased clinical responses (ACR50) by 29.5% (NNT: 3), reduced the progression of radiological lesions and increased functional responses (HAQ) when compared to MTX monotherapy. There was a 35% increase in serious adverse events (NNH: 3) with both certolizumab regimens. There were no differences in response or adverse events between the certolizumab doses[164](**A**). There was also evidence of a positive impact on patient quality of life [30](**A**). According to RAPID3 criteria, there was an increase in remission of 32% (NNT: 3) in patients treated with

certolizumab[165](**B**), and clinical responses were also higher than the hybrid ICR score[166](**B**).

Etanercept

Etanercept is a fusion protein composed of the TNF soluble receptor that binds more strongly to the Fc region than to the IgG. This therapy is prescribed at a weekly dose of 50 mg SC[36](**A**) [43,45,59](**B**).

At a 52-week follow-up of RA patients, it was concluded that a combined treatment of etanercept (50 mg/week) and MTX (15 mg/week) increased remission by 22.5% (NNT: 5) and reduced radiographic lesion progression when compared to MTX monotherapy[105](**A**). This effect was maintained after 24 months of follow-up[45](**B**).

The use of etanercept (50 mg/week) for 24 weeks in patients with active RA, with or without sulfasalazine (2–3 g/day), demonstrated superior clinical responses (ACR50) of 32% to 38% (NNT: 3); however there was a 19.6% increase in the number of infections (NNH: 5), as well as infusion reactions[167](**A**). At a 24-month follow-up, there was less treatment discontinuation due to lack of efficacy in patients undergoing etanercept treatment (NNT: 2), and the benefits were permanently sustained. There was, however, an increase in infectious adverse events and adverse events from local application[168](**B**).

An ACR-N analysis of the clinical responses of RA patients after 24 weeks of treatment with etanercept (50 mg/week) combined with MTX (15 mg/week) showed a 6.1% increase (NNT: 17)[169](**A**). After 52 weeks, remission remained evident in 18.2% (NNT: 6) and 12.4% (NNT: 8) of patients who received etanercept alone or combined with MTX, respectively[170](**B**). Additionally, after 52 weeks, there was a reduction in radiological lesion progression in these patients[171](**B**).

Of the RA patients who were treated with etanercept (50 mg/week), 51% showed a clinical response (ACR50) after three years, and this response was maintained after five years. There was a reduction in disease activity (DAS < 2.4) in 44% of the patients. However, 44% of the patients experienced episodes of infection, which can induce cancer and treatment-related death[172,173](**C**).

After a 12-month treatment, the use of 50 mg etanercept per week conferred greater benefits to RA patients than a dose of 20 mg/week. When compared with MTX (15 mg/week), the clinical responses (ACR50) was similar, although there were greater radiological lesion progression and more adverse events in MTX-treated patients[174](**A**). These results were maintained at a 24-month follow-up, and the functional responses (HAQ) were better in 18% (NNT: 6) of the etanercept-treated patients[59](**B**).

In patients with inadequate responses to a combination of MTX (15 mg/week) and etanercept (50 mg/week), an increased dose of etanercept (100 mg/week) did not improve the patient clinical responses[175](**A**).

Infliximab

Infliximab is a monoclonal mouse-human chimeric anti-TNF antibody that is prescribed at an initial dose of 3 mg/kg, given IV, followed by the same dose (3 mg/kg) in the second and sixth weeks and every eight weeks thereafter[76](**D**). In patients with insufficient responses, the dose can be increased to 5 mg/kg by infusion, or the dose interval can be reduced. Larger doses add little therapeutic benefit and increase the risk of infectious complications; thus, this approach should be avoided in RA treatment[27,58](**B**) [36,38,44](**A**).

In RA patients who are nonresponsive to MTX (15 mg/week), when combined with infliximab (3 mg/kg initially at weeks 0, 2 and 6 and every 8 weeks thereafter), there were increases in clinical response according to the EULAR and ACR50 criteria of 14% (NNT: 7) and 10% (NNT: 10), respectively, compared to a combination of sulfasalazine and hydroxychloroquine[58](**B**).

Treatment of RA patients with a combination of infliximab (3 mg/kg or 10 mg/kg at weeks 0, 2 and 6, and every 8 weeks thereafter) and MTX (15 mg/week) for 22 weeks increased clinical responses by 22.4% (NNT: 5) and 25.7% (NNT: 4) and remission (DAS-28 < 2.6) by 17.0% (NNT: 6) and 18.0 % (NNT: 6), respectively. There was no difference in response between the two infliximab dose regimens. There was no difference in adverse events related to infliximab treatment, regardless of the dose[176](**A**).

Treatment of RA patients with a combination of 3 mg/kg or 6 mg/kg infliximab (initially at weeks 0, 2 and 6, and every 8 weeks thereafter) and MTX (15 mg/week) for 54 weeks increased ACR-N clinical responses by 12.5% (NNT: 8) and 20.3% (NNT: 5), respectively, ACR50 clinical responses by 13.5% (NNT: 7) and 18.3% (NNT: 6), reduced the progression of radiological damage (Sharp score) and increased functional responses by 6.2% (NNT: 16) and 16.0% (NNT: 6), respectively. No difference in efficacy was observed between the two treatment regimens. There were increases in the rates of serious adverse events of 3.5% (NNH: 30) and 2.9% (NNH: 33) with the doses of 3 mg/kg and 6 mg/kg, respectively[177](**A**).

Golimumab

Golimumab is a human monoclonal anti-TNF antibody that is administered at a dose of 50 mg/month SC[44,60](**B**).

Treatment of RA patients with a combination of MTX (15 mg/week) and golimumab (50 mg every 4 weeks) for 24 weeks increased remission rates (ACR50) by 10.9% (NNT: 10) and 13.9% (NNT: 7) (DAS-28 ≤ 2.6) compared to MTX monotherapy. There were no increases in adverse events for this combination over monotherapy[44](**B**). The radiological response (Sharp score) was also higher in response to golimumab (50 mg) plus MTX[178](**B**).

In RA patients, a 14-week treatment with a combination of MTX (15 mg/week) and golimumab (50 mg or 100 mg every four weeks) yielded increases of 25.0% (NNT: 4) and 19.4% (NNT: 5), respectively, in clinical responses and of 14.2% (NNT: 7) and 16.5% (NNT: 6), respectively, in remission (DAS-28). However, there was an increase in adverse events and serious adverse events with the 100 mg dose of golimumab compared to the 50 mg dose[179](**A**). After a 52-week follow-up, there were no differences with respect to monotherapy, although the clinical response and remission rates were maintained[43](**B**).

After a 24-week treatment with a combination of golimumab (2 mg/kg or 4 mg/kg) and MTX, the proportion of patients who achieved clinical responses (ACR50) increased by 9.3% (NNT: 10) and 17.7% (NNT: 6), respectively, compared to MTX monotherapy. Remission (DAS-29 ≤ 2.6) over the same period was greater only with a golimumab dose of 4 mg/kg. There were no differences in adverse events and serious ad-

verse events between the combination of MTX and golimumab and MTX monotherapy[180](**A**).

RA treatment with a combination of MTX and golimumab (50 mg or 100 mg every two or four weeks for 16 weeks) resulted in similarly increased clinical response rates (ACR50) and remission rates (DAS-28 ≤ 2.6) with all regimens; the only treatment regimen that showed no benefit compared to MTX monotherapy was a 50-mg dose every four weeks. There were no differences in adverse events between the various forms of treatment[181](**A**).

Adverse events and contraindications of TNF blockers

Adverse events include infusion reactions to IV drugs (fever, chills, chest pain, blood pressure fluctuation, dyspnea, rash and/or hives) and manifestations at SC drug injection sites (erythema, itching, local pain and/or hives). These drugs increase the risk of infections, especially in the first year of use (including serious infections and those caused by intracellular pathogens such as tuberculosis bacillus, listeria, histoplasma, atypical mycobacteria, legionella) cardiac dysfunction, demyelinating diseases, autoimmune phenomena (autoantibody production), cutaneous vasculitis, interstitial lung disease and a possible increased risk of lymphoma[37,39](**A**) [61,62](**B**).

Human anti-chimeric antibodies (HACA) can occur in response to all drugs in this class, but their effects on treatment efficacy are uncertain[63,64](**B**).

Anti-TNF drugs are contraindicated in women who are pregnant or breastfeeding; in patients with class III and IV congestive heart failure, according to the New York Heart Association classification; in patients with infection; or in those who have a high risk of infection development (chronic ulcers of the lower limbs, septic arthritis in the past 12 months), recurrent pulmonary infections, multiple sclerosis, or current or previous cancer diagnoses (less than five years). Patients should be carefully monitored for the possible emergence of signs of infection, which should be treated promptly and immediately[39](**A**) [61,62](**B**).

Recommendation

RA patients can be treated with anti-TNF biologic DMARDs, including adalimumab (40 mg SC every two weeks), certolizumab (400 mg SC every two weeks at weeks 0, 2 and 4 and 200 mg every two weeks thereafter or 400 mg every four weeks, or monthly), etarnecept (50 mg SC weekly), golimumab (50 SC every four weeks or monthly), or infliximab (3 mg/kg IV at weeks 0, 2 and 6 and every 8 weeks thereafter). All anti-TNF biologic DMARDs should be preferentially prescribed in combination with MTX (15 mg weekly) or another synthetic DMARD to achieve clinical, radiological and functional benefits and remission. There may be an increased risk of serious adverse events and local reactions to treatment administration.

9. Is rituximab a safe and effective alternative treatment for RA patients?

Rituximab is a chimeric monoclonal antibody directed against CD20+ lymphocytes. It is indicated for patients with moderate to severe active RA who failed to respond to anti-TNF agents. Rituximab is administered at a dose of 1,000 mg in two IV infusions at 14-day intervals. Each infusion is preceded by a dose of 100 mg of IV methylprednisolone 60 minutes before the rituximab, as well as 1 g of paracetamol and antihistamine to decrease the severity and frequency of infusion reactions[81-83](**A**) [86](**C**).

Given the severity of the condition, it should be noted that reports have linked the occurrence of progressive multifocal leukoencephalopathy to rituximab use[182](**C**).

Rituximab is preferentially used in combination with MTX and can be prescribed in combination with other DMARDs. It is important to stress that there might be a delay of 3–4 months before the onset of symptomatic improvement[81-83](**A**). Rituximab induces better therapeutic responses in individuals who are seropositive for RF and/or anti-CCP[84](**B**).

Should the disease reactivate, individuals with good treatment responses can be subjected to new courses of rituximab at intervals of no less than six months[81-83](**A**) [86](**C**).

The most frequent adverse events are infusion reactions, which occur in 35% of patients during the first infusion and approximately 10% during the second infusion. Infectious complications may occur, as well as interstitial pneumonia, neutropenia and thrombocytopenia[81-83](**A**) [86](**C**).

In RA patients, treatment with rituximab (two IV 500 g doses at 15 day intervals) combined with MTX (10–25 mg/week) and etanercept (50 mg/week) or adalimumab (40 mg every 15 days) for 24 weeks did not cause an increase in adverse events, including serious adverse events, relative to the placebo combined with MTX. There were increased risks of 22% (NNH: 5) for infusion reactions and of 15% (NNH: 7) for grade three infections. There were no differences in the clinical response (ACR50) or remission rates (DAS-28 < 2.6)[183](**A**).

Treatment of RA patients (disease duration of 8 weeks to 4 years) over 52 weeks with 1 g or 2 g of rituximab combined with MTX increased clinical responses (ACR50) by 17% and 23%, respectively, and remission rates (DAS-28 ≤ 2.6) by 20% and 23%, respectively. There were also increases in functional response (HAQ), and there were no increases in adverse events[184](**A**).

Treatment of RA patients whose conditions were nonresponsive to MTX treatment with 1 g or 2 g rituximab increased the clinical response rate (ACR50) by 17% (NNT: 6) after 24 weeks. There was no increase in adverse events[82](**A**).

A comparison of 1-g, 1-g escalated to 2-g after 24 weeks and 2-g rituximab doses for the treatment of RA patients (with inadequate responses to MTX) after 48 weeks demonstrated similar clinical responses between the treatments (ACR50), a higher EULAR clinical response to the 2-g dose, compared to the 1-g dose and a higher remission rate (DAS-28 < 2.6) with the 1-g dose, compared to the escalated dose. There were no differences in adverse events[185](**A**).

The treatment of anti-TNF-α and MTX-nonresponsive RA patients with 1 g rituximab led to reduced radiological disease progression, decreased pain (FACIT-F) and improved functional responses (HAQ) and quality of life (SF-36) after 24 weeks[83,186](**A**). The clinical responses (ACR50 and EULAR) increased by 22% (NNT: 5) and 43% (NNT: 2), respectively[81](**A**).

Treatment of RF-positive RA patients with a combination of rituximab and MTX for 24 weeks resulted in increased clin-

ical response rates that (ACR50) ranged from 10%–20%, compared to monotherapy. A greater number of patients did not require additional treatment for 48 months, due to the positive effects on functional capacity (NNT: 4)[187](**A**).

In patients who were nonresponsive to synthetic DMARD treatment, the use of 1 g or 2 g rituximab for 24 weeks increased the proportion of patients with clinical responses (ACR50 or EULAR) by 20% and reduced disease activity (DAS-28)[188](**A**).

The combination of rituximab (1 g) and MTX (10 mg/week) for the treatment of RA patients produced better results after 24 weeks than monotherapy with either of these drugs, increased the clinical response rates (ACR50) by 10%–30%, and increased clinical responses (EULAR) and rates of disease remission (DAS-28). There were no differences in the numbers of adverse events[189](**A**).

Recommendation

In RA patients with inadequate responses to MTX or other synthetic DMARDs and anti-TNF, the use of rituximab (1-g and 2-g doses), primarily in combination with MTX, improved clinical, radiological and functional progress while increasing the risk of adverse events.

10. Is tocilizumab proven for use in RA treatment?

Tocilizumab is a humanized monoclonal antibody that binds to the IL-6 receptor, thus inhibiting the biological effects of IL-6. It can be used alone or in combination with MTX or other DMARDs. The incidence of infections and serious infections with tocilizumab is equivalent to that of other biologic agents. It is prescribed at a dose of 8 mg/kg IV every four weeks[87,88](**A**) [96](**B**).

Tocilizumab can cause dose-dependent adverse events such as neutropenia, thrombocytopenia and elevated transaminase levels. There may even be elevated levels of total and low-density lipoprotein (LDL) cholesterol, as well as an increased risk of infections[87,88](**A**) [96](**B**). Tocilizumab should be avoided in patients who have a greater risk of bowel perforation and those with diverticular disease of the colon[89](**A**).

RA patients with inadequate responses to MTX have shown positive results in response to tocilizumab (4 mg/kg or 8 mg/kg every four weeks for 52 weeks) with respect to clinical response (ACR70), remission (DAS < 2.6), and functional (HAQ) and radiological (Sharp score) responses. Radiological disease progression was reduced by 74% and 70%, respectively, compared to MTX monotherapy. There were significant functional improvements of 15.4% (NNT: 6) and 9.9% (NNT: 10), respectively, and a functional response of > 0.3 units was maintained. The clinical response rates were 6.0% (NNT: 16) and 3.5% (NNT: 30), respectively. Disease remission rates were 39.3% (NNT: 2) and 22.3% (NNT: 5), respectively. There was a 2% incidence of neoplasias in patients who received tocilizumab, a 2.5% incidence of severe anaphylactic reactions (4 mg/kg), and a 5% increase in the risk of severe adverse events (NNH: 20)[190](**A**).

In RA patients between six months and five years, the administration of 8 mg/kg tocilizumab every four weeks for 52 weeks led to a reduction in radiographic disease progression of 15% (NNT: 7) compared to synthetic DMARDs, and this effect was greater in patients at a high risk for progression[191](**A**). The clinical efficacy (ACR50) was 51% (NNT: 2). The remission rate was 56% higher (NNT: 2), and the functional response rate improved by 28% (NNT: 4). There was an increase of 5% in the occurrence of serious adverse events in response to tocilizumab (NNH: 20) and 2% and 7% increases in cancer incidence and infusion reaction rates, respectively. There were no differences in mild to moderate adverse events between the two forms of treatment[191](**A**).

A comparison between 8 mg/kg tocilizumab, given every four weeks, and 15 mg/week MTX for a 24-week treatment of RA patients provided results in favor of tocilizumab. Tocilizumab was found to increase the clinical response rate (ACR50) by 10.6% (NNT: 9) and the remission rate (DAS-28 < 2.6) by 21.5% (NNT: 5). The most common adverse reactions were infections, although no difference was observed between the two forms of treatment. There was an increase of 3.8% in the infusion reaction rate with tocilizumab (NNH: 30)[96](**A**).

In RA patients (more than six months), treatment with 8 mg/kg tocilizumab every four weeks in combination with DMARDs (MTX, chloroquine, gold sodium, sulfasalazine, azathioprine or leflunomide) produced an increased clinical response rate (ACR50) of 29% (NNT: 3), an increase in remission (DAS-28 < 2.6) and a functional response rate of (HAQ) of 26% after 24 weeks (NNT: 4) compared to monotherapy with these drugs. There was an increase of 11.7% in the risk of adverse events (NNH: 9)[192](**A**).

RA patients with inadequate responses to MTX showed positive results after treatment with tocilizumab (4 mg/kg or 8 mg/kg every four weeks for 24 weeks) with respect to clinical response (ACR50), remission (DAS < 2.6), and functional (HAQ) response. There were significant functional improvements with both doses. The clinical response rates were 20.0% (NNT: 5) and 33% (NNT: 3), respectively. Disease remission rates were 12.2% (NNT: 8) and 26.2% (NNT: 4), respectively. There were no differences in the various adverse events, of which infection was the most frequent[193](**A**).

Recommendation

Tocilizumab treatment of RA patients, especially those with inadequate responses to MTX, when combined with MTX or synthetic DMARDs or as a monotherapy, produces effective clinical, functional, radiological and remission responses. Tocilizumab is also effective in patients who are nonresponsive to anti-TNFs. There may be an increased risk of adverse events.

11. Is abatacept a treatment option for patients with RA, considering its safety and efficacy profile?

Abatacept is a CTLA-4-IgG fusion protein that acts as an inhibitor of T lymphocyte costimulation. It is indicated for patients with active RA who have experienced DMARD or anti-TNF agent treatment failure. Abatacept can be used in combination with DMARDs or as a monotherapy. Abatacept should be administered as an IV infusion over a 30-minute period and

should be administered at a dose of 500 mg to patients with a body weight less than 60 kg, 750 mg to patients between 60–100 kg and 1,000 mg to patients greater than 100 kg. The next dose should be administered 2 to 4 weeks after the initial dose and every four weeks thereafter[40-42](**A**). Abatacept is associated with a greater risk of infectious complications than a placebo, similarly to other biologic DMARDs. Infusion reactions to abatacept are uncommon and are mainly hypersensitivity reactions that manifest as a rash or bronchospasms. Abatacept is contraindicated in patients with symptoms of chronic obstructive pulmonary disease (COPD) due to its exacerbation of dyspnea and the increased risk of infections[40](**A**) [85](**C**).

Abatacept treatment (10 mg/kg every four weeks) produces benefits (ACR50) in 30% of patients with RA of an average 8.5-year duration. According to ACR50, for every three patients treated, one experiences no increase in adverse events[194](**A**).

RA patients (of at least a 12-month duration) who were nonresponsive to MTX yielded increases in clinical response rates of 12.1% (NNT: 9), 9.9% (NNT: 10) and 9.1% (NNT: 11) according to the EULAR, DAS-28 and ACR50 criteria, respectively, after treatment with 500–1000 mg abatacept every 30 days for 12 months. The functional improvement rate (HAQ) was 20.6% (NNT: 5). There was no increase in adverse events[195](**A**).

In RA patients who were nonresponsive to anti-TNF-α, treatment with 500-1000 mg abatacept for six months led to a clinical response rate of 16.5% (NNT: 6; ACR50 criteria) and a functional response rate of 24.0% (NNT: 4). There was no increase in adverse events[196](**A**). At 24 months, there were improvements of 32.3% and 20.3% in the clinical response (ACR50) and remission rates (DAS-28), respectively. The functional response rate was 47.9% [197](**B**).

After a year of treatment with 500–1,000 mg abatacept, RA patients who were nonresponsive to MTX had a clinical improvement rate (ACR50) of 30.1% (NNT: 3). Physical function improved by 24.7% (NNT: 4), with no difference in the rate of adverse events[198](**A**). After 24 months of treatment, the patients had a clinical improvement rate (ACR50) of 55.6% and a remission rate (DAS-28) of 30.9%[199](**B**).

Recommendation

In RA patients who are nonresponsive to MTX or anti-TNF therapy, the use of abatacept at doses between 500–1,000 mg led to increased clinical responses (ACR50), remission (DAS-28) and functional responses (HAQ) over 6–12 months, and these rates were maintained over a 24-month period. However, there may be an increased risk of adverse events.

12. Are there indications that some biologic treatment regimens are superior to others in the treatment of RA patients?

Treatment of RA patients with a combination of MTX (15 mg/week) and golimumab (50 mg every four weeks) for 24 weeks yielded increases (ACR50) of 10.9% (NNT: 10) and 13.9% (NNT: 7) in the remission rate (DAS-28 ≤ 2.6) compared to MTX monotherapy[44](**A**).

A 52-week follow-up of RA patients who were treated with MTX and adalimumab (40 mg every other week) showed an increase (ACR50) of 32% (NNT: 3) in the clinical response rate compared with MTX monotherapy[162](**A**). A decrease in radiographic progression and an increase in clinical remission (DAS-28 ≤ 2.6) of 23% (NNT: 5) were observed in comparison to MTX monotherapy[74](**D**).

At a 52-week follow-up of RA patients, it was concluded that treatment with etanercept (50 mg/week) in combination with MTX (15 mg/week) increased the remission rate (DAS-28) by 22.5% (NNT: 5) compared to MTX monotherapy. Additionally, the clinical response rate (ACR50) was 22% higher (NNT: 5)[105](**A**).

Treatment of RA patients with 3 mg/kg infliximab (initially at weeks 0, 2 and 6 and every eight weeks thereafter) in combination with MTX (15 mg/week) for 22 weeks increased the clinical response rate (ACR50) by 22.4% (NNT: 5) and the disease remission rate (DAS-28 < 2.6) by 17.0% (NNT: 6)[176](**A**).

Treatment with 200 mg or 400 mg of certolizumab (every two weeks for 52 weeks) in combination with MTX (15 mg/week) increased the clinical response rate (ACR50) by 29.5% (NNT: 3), compared to MTX monotherapy. The remission rate (DAS-28) was 16% (NNT: 6). There was an increase of 35% in the rate of serious adverse events (NNH: 3)[164](**A**) [165](**B**).

Treatment of RA patients (disease duration between eight weeks and four years) for 52 weeks with rituximab (1.0 g IV infusion at intervals of 15 days) in combination with MTX increased the clinical response rate (ACR50) by 17% (NNT: 6) and the remission rate (DAS-28 ≤ 2.6) by 20% (NNT: 5)[184](**A**). RA patients with inadequate responses to MTX who were treated with tocilizumab (8 mg/kg every four weeks for 24 weeks) in combination with MTX showed positive results with respect to clinical response (ACR50) and remission (DAS ≤ 2.6). There were significant functional improvements at both doses. The clinical response rate was 33% (NNT: 3). The remission rate was 26.2% (NNT: 4). There were no differences in the various adverse events, of which infection was the most frequent[193](**A**).

Patients with RA (duration of at least 12 months) who were nonresponsive to MTX had 9.9% (DAS-28; NNT: 10) and 9.1% (ACR50; NNT: 11) increases in the clinical response rate after treatment with 500-1000 mg of abatacept every 30 days for 12 months[195](**A**).

Table 5 summarizes the ACR50 and DAS-28 measures, which are expressed as the estimated benefits with the NNT.

Recommendation

The various treatment regimens that use biologic DMARDs in combination with MTX in RA patients present similar results compared to MTX monotherapy, using ACR50 and DAS-28 as parameters with minor variations in the NNT (3–11 for ACR50 and 4–10 for DAS-28). There are no direct comparisons that enable an accurate estimate of the differences in benefits between the various biologics.

Strategies for RA treatment in Brazil

DMARD treatment should be initiated immediately after diagnosis. The treatment should be adjusted as needed after frequent clinical evaluations within a period of 30–90 days.

Treatment strategies based on specific goals produce better clinical outcomes and functional capacities as well as lower structural radiographic damage, compared to conventional treatments[94](A). The goal is remission or at least low disease activity; this outcome can be evaluated by composite indices of disease activity (CIDAs) while taking into consideration the role of treatment responses in reducing CIDA values, as established in the 2011 Consensus of the SBR for the Diagnosis and Initial Assessment of Rheumatoid Arthritis[5](D).

First line – synthetic drugs that alter the course of the disease

MTX should be the first choice for DMARD treatment[95](A) [66,200](D). In cases with contraindications, sulfasalazine[201](A) or leflunomide[143](A) can be used as a first option[202](B). Antimalarial drugs (chloroquine diphosphate and hydroxychloroquine)[203](B) might be indicated only for patients with mild disease or undifferentiated arthritis with low erosion potential. In exceptional cases, such as patients with hypersensitivity to other DMARDs or those with viral hepatitis, gold sodium can be used.

MTX should preferentially be prescribed as a monotherapy during early treatment[128](A).

In the absence of an objectified clinical response (remission or lower disease activity) to the maximum tolerated MTX dose or in the presence of adverse events, it is recommended that MTX be exchanged for another DMARD monotherapy or DMARD combinations. The most frequently used combinations are MTX with chloroquine, sulfasalazine, a combination of these three drugs[15](A) and MTX combined with leflunomide[204](A). Therapy progression should be rapid, with monthly patient evaluations during the first 6 months of treatment, and the doses and schedules should be adjusted as required. A maximum of six months should be allowed to define an absence of response to the first-line treatment[66](D).

Low doses of corticosteroids (up to 15 mg/day of prednisone or equivalent) and anti-inflammatories may be used at the beginning of the treatment regimen, although caution and usage for the shortest time possible are recommended to minimize the occurrence of adverse events[66](D).

Second line – biologic disease-modifying drugs

Immunobiological RA treatment is indicated for patients who persist with moderate to high disease activity (according to CIDAs) despite treatment with at least two of the regimens proposed for the first line of treatment. In Brazil, anti-TNF drugs are the first choice of biologic therapy after the failure of synthetic DMARD regimens. This approach is justified by the most comprehensive post-marketing experience, as well as the increased volume of safety information from clinical studies, registries and national[205](B) and international[66](D) recommendations. However, other drugs such as abatacept and tocilizumab may be prescribed at the discretion of the attending physician after a failure with synthetic DMARDs, given the publication of randomized controlled trials that support this indication[40,88](A). Rituximab should be avoided as a first-line biologic[66](D) except in specific cases (e.g., patients with contraindications to other biologics, preferably those who are positive for RF and/or anti-CCP or those who present with a diagnosis associated with lymphoma).

In exceptional situations, biologic DMARDs may be indicated after a failure of the first regimen of synthetic DMARDs in patients with associated poor prognostic factors, including very high disease activity, a high number of painful/inflamed joints, high RF and/or anti-CCP levels and the early occurrence of radiographic erosions[66](D). Poor prognosis factors are better detailed in the 2011 Consensus of the SBR Diagnosis and Initial Assessment of Rheumatoid Arthritis[5](D).

The use of biologic drugs as a first-line RA treatment is not indicated in Brazil because there is no evidence of cost-effectiveness in this country.

Table 5 – ACR50 and DAS-28 measures expressed as the estimated benefit using Number Needed to Treat (NNT).

Biologic	Dose	Time	NNT	
			ACR50	DAS-28
Golimumab	50 mg	24 weeks	10	7
Adalimumab	40 mg	52 weeks	3	5
Etanercept	50 mg	52 weeks	5	5
Infliximab	3 mg/kg	22 weeks	5	6
Certolizumab	200 mg	52 weeks	3	6
Rituximab	1,000 mg	52 weeks	6	5
Tocilizumab	8 mg/kg	24 weeks	3	4
Abatacept	500–1,000 mg	52 weeks	11	10

Third line – failure or intolerance to modifying drugs in the course of biological disease

In clinical scenarios where there is no response to the initial biologic treatment, a progression to loss of response, or major adverse events, one biologic agent may be exchanged for another. The biologics that have presented benefits in randomized clinical trials in patients for whom anti-TNF treatment failed are abatacept, rituximab and tocilizumab[206](B). Patients for whom the first anti-TNF agent failed have also derived benefits from the use of a second drug from the same class, including adalimumab, certolizumab, etanercept, golimumab or infliximab, in prospective observational studies and randomized controlled double-blind trials (golimumab), but uncertainties persist about the magnitude of the therapeutic effects and the cost-effectiveness of this strategy[207](B).

The choice of the employed treatment sequence remains at the discretion of the physician, depending on the particularities of each case. A minimum of three months and a maximum of six months of clinical evaluation are recommended before proceeding to a change in regimen (switching between biologic DMARDs).

Withdrawal of medications and eventual suspension of therapy

There are no data that allow us to define the RA treatment duration, and currently the medication to which the patient has an adequate response should be maintained for an indefinite period at the physician's discretion. In cases of complete (remission) and sustained (more than 6–12 months) responses, a gradual and careful withdrawal can be attempted according to the following sequence: first NSAIDs, then corticosteroids

and biologic DMARDs, while maintaining the use of synthetic DMARDs[208](B). In exceptional situations, if remission is maintained, the physician may very cautiously attempt to withdraw synthetic DMARDs[66](D). Sustained drug-free remission is uncommon, especially in patients with biomarkers such as anti-CCP and/or RF.

Fig. 1 summarizes RA drug treatment in Brazil as a flowchart, as proposed by the RA SBR Commission.

Treatment monitoring

In patients with active early-stage disease and symptoms of a 12-month duration or less, intensive monitoring with monthly visits is recommended with rapid medication progression when necessary[209](B) [210](D). The treatment regimens and their possible adverse events have been discussed in previous sections.

At each visit, physicians should evaluate the efficacy and safety of the therapeutic interventions while considering patient comorbidities and preferentially targeting remission or the lowest disease activity possible, as well as an improved functional status and quality of life. In patients with established disease, especially in those with controlled disease, visits can occur every three months[108,109,209](B) [210](D).

Table 6 summarizes in schematic form the monitoring frequencies for the main parameters considered appropriate for evaluations of a patient undergoing RA treatment.

Conflicts of interest

Mota LMH participated in clinical and/or experimental studies sponsored by the companies Roche and Mantecorp; received personal or institutional assistance from the companies Abbott, AstraZeneca, Merck, Pfizer and Roche; and was a speaker at events or activities sponsored by the companies Abbott, MSD, Novartis, Roche and Wyeth.

Cruz BA participated in clinical and/or experimental studies sponsored by Roche; received personal or institutional assistance from the companies Abbott, Bristol-Myers Squibb, Mantecorp, MSD, Novartis, Roche, Wyeth and Pfizer; and was a speaker at events or activities sponsored by the companies Abbott, MSD, Mantecorp, Novartis, Roche and Wyeth.

Brenol CV participated in clinical and/or experimental studies sponsored by the companies Bristol-Myers Squibb, Pfizer, Roche and Wyeth; received personal or institutional assistance from the companies Abbott, Bristol-Myers Squibb, Mantecorp,

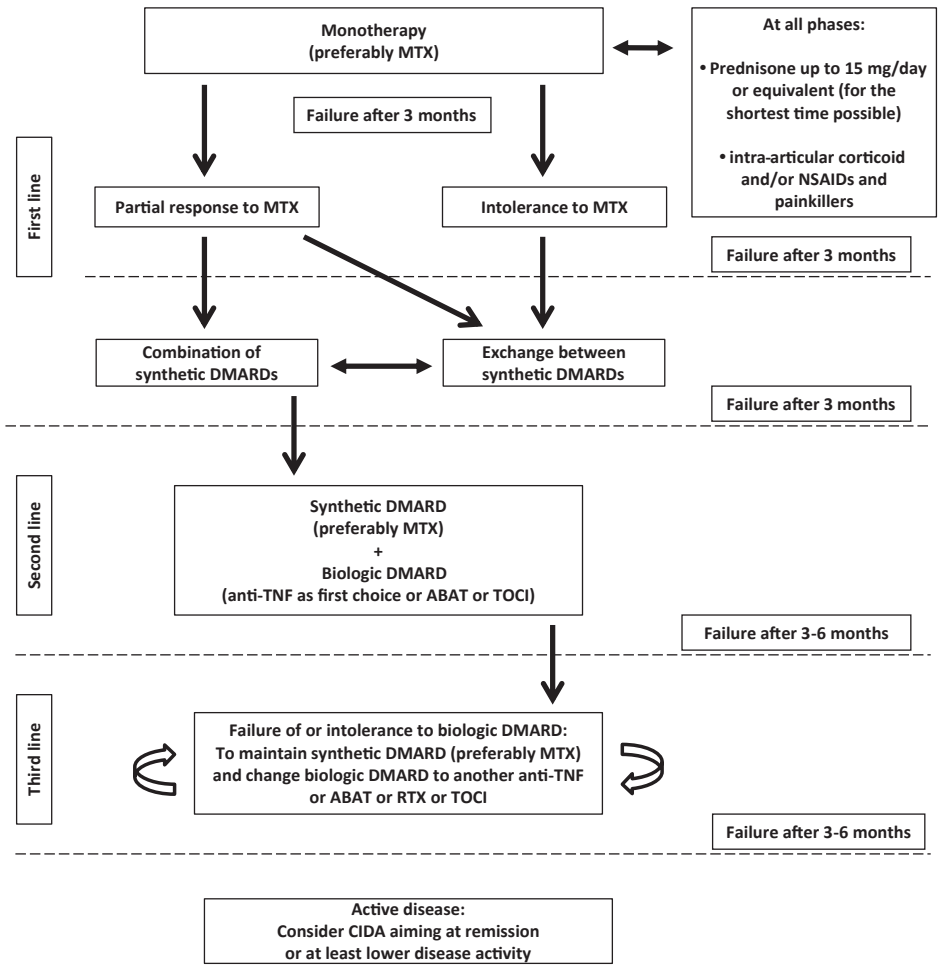

Fig. 1 – RA drug treatment flowchart for Brazil, as proposed by the RA SBR Commission.
ABAT, abatacept; CIDA, compound indices of disease activity; DMARD, diseasemodifying antirheumatic drug; MTX, methotrexate; NSAIDs, nonsteroidal anti-infl ammatory drugs; RTX, rituximab; TOCI, tocilizumab.

Table 6 – Monitoring the treatment of rheumatoid arthritis *(continued)*.

Parameter	Initial assessment	Monthly assessment (early RA)	Extra consultations	Assessment every three months (established RA)	Annual assessment
Education of patients and families	X	X	X	X	X
CIDA+	X	X	X	X	X
mHAQ or HAQ-DI (0–3 points)	X		X	X	X (minimum reduction desired: 0.22 points)
RF/anti-CCP	X				X (if negative at the first assessment, they can be repeated in the two initial years)
Conventional radiography (hands and wrists, feet and ankles, other joints affected)	X				X
Joint resonance or ultrasound (in doubt regarding the synovitis)	X				
Assessment of extra-articular manifestations *	X	X	X	X	X
Assessment of comorbidities**	X	X	X	X	X
Inflammatory activity tests (ESR and CRP)	X	X	X	X	X
Laboratory assessment***	X	X	X	X	X
Vaccination assessment	X				X
Specific medicamentous treatment for RA****	X	X	X	X	X
Medicamentous treatment of comorbidities	X	X	X	X	X
PPD (or IGRA) and chest radiography (if a biologic DMARD, specially anti-TNF, is prescribed)	X				
Occupational therapy	X	X	X	X	X
Rehabilitation	X	X	X	X	X
Evaluation of orthotic indication	X	X	X	X	X
Evaluation of surgical indication	X	X	X	X	X
Coordination of the multidisciplinary team	X	X	X	X	X
Gestational counseling	X	X	X	X	X
Evaluation of infections (clinical assessment and occasional complementary exams)	X Serologies (hepatitis B and hepatitis C at the beginning of the investigation, HIV in selected situations)	X	X	X	X
Evaluation and education regarding emergency situations*****	X	X	X	X	X

CIDA, compound indices of disease activity (SDAI – simple disease activity index; CDAI – clinical disease activity index; DAS28 – disease activity score - 28 joints); +, for CIDA goals, see the 2011 BSR Consensus for diagnosis and early assessment of RA; mHAQ, modified health assessment questionnaire; HAQ-DI, health assessment questionnaire - disability index; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; PPD, tuberculin skin test; IGRA, interferon gamma release assays.

* Extra-articular manifestations: rheumatoid nodules, interstitial lung disease, serositis, ocular inflammation, and vasculitides.

**Comorbidities: arterial hypertension, cardiovascular ischemia, diabetes mellitus, atherosclerosis, low bone mass, depression, fibromyalgia, etc.

***Laboratory exams: blood count, liver function, lipid profile, and renal function; depending on the comorbidities, consider additional exams.

****Medication for RA: consider the efficacy and safety issues of each medication detailed throughout the text.

*****Urgencies on RA: scleromalacia perforans, myelopathies, multiple mononeuritis and vasculitis, pregnant patients on teratogenic drugs.

MSD, Roche and Wyeth; and was a speaker at events or activities sponsored by the companies Abbott and Roche.

Rezende-Fronza LS participated in clinical and/or experimental studies sponsored by the companies Bristol-Myers Squibb, Pfizer, and Roche; and elaborated scientific papers in journals sponsored by Pfizer.

Bertolo MB was a speaker at events or activities sponsored by the companies Abbott, Pfizer and Sanofi Aventis.

Freitas MVC received personal or institutional assistance from the companies Abbott, MSD, Pfizer, Roche and Wyeth; was a speaker at events or activities sponsored by the companies Abbott, MSD, Pfizer, Roche Wyeth; is an advisory board member or director of pharmaceutical industry or advisory committees of scientific studies sponsored by the companies AstraZeneca, MSD and Wyeth; and elaborated scientific papers in journals sponsored by the companies Abbott, AstraZeneca, Bristol-Myers Squibb, Wyeth.

Silva NA participated in clinical and/or experimental studies sponsored by the companies Bristol-Myers Squibb and Roche; received personal or institutional assistance from the companies Abbott, MSD, Roche and Wyeth; and was a speaker at events or activities sponsored by the companies Janssen, Mantecorp, MSD and Roche.

Louzada-Junior P participated in clinical and/or experimental studies sponsored by the companies Merck and Roche; received personal or institutional assistance from Abbott; and was a speaker at events or activities sponsored by the companies Bristol-Meyers Squibb, Pfizer and Roche.

Giorgi RD received personal or institutional assistance from the companies Bristol-Myers Squibb and Roche; was a speaker at events or activities sponsored by the companies Bristol-Myers Squibb and Roche; and was a speaker at events or activities sponsored by the companies Bristol-Myers Squibb and Roche.

Lima RAC participated in clinical and/or experimental studies sponsored by the companies Mantecorp and Roche; received personal or institutional assistance from the companies Acteion, Lilly and Pfizer; and was a speaker at events or activities sponsored by the companies Acteion, Lilly and Pfizer.

Pinheiro GRC received personal or institutional assistance from the companies Janssen and Roche.

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Erratum

Erratum of Guidelines for the drug treatment of rheumatoid arthritis

Licia Maria Henrique da Mota[a,], Bóris Afonso Cruz[a], Claiton Viegas Brenol[a], Ivânio Alves Pereira[a], Lucila Stange Rezende-Fronza[a], Manoel Barros Bertolo[a], Max Vitor Carioca Freitas[a], Nilzio Antônio da Silva[a], Paulo Louzada-Junior[a], Rina Dalva Neubarth Giorgi[a], Rodrigo Aires Corrêa Lima[a], Wanderley Marques Bernardo[b], Geraldo da Rocha Castelar Pinheiro[a]*

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In the original article, "Guidelines for the drug treatment of rheumatoid arthritis" (Rev Bras Reumatol 2013;53(2):158-183), where it reads:

Guidelines for the drug treatment of rheumatoid arthritis

Sociedade Brasileira de Reumatologia (Brazilian Society of Rheumatology)

Projeto Diretrizes da Associação Médica Brasileira, São Paulo, SP, Brazil

Participants
Licia Maria Henrique da Mota, Bóris Afonso Cruz, Claiton Viegas Brenol, Ivânio Alves Pereira, Lucila Stange Rezende-Fronza, Manoel Barros Bertolo, Max Vitor Carioca Freitas, Nilzio Antônio da Silva, Paulo Louzada-Junior, Rina Dalva Neubarth Giorgio, Rodrigo Aires Corrêa Lima, Wanderley Marques Bernardo, Geraldo da Rocha Castelar Pinheiro*

It should read:

Guidelines for the drug treatment of rheumatoid arthritis

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At page 169, where it reads:

RA patients can be treated with anti-TNF biologic DMARDs, including adalimumab (40 mg SC every two weeks), certolizumab (400 mg SC every two weeks at weeks 0, 2 and 4 and 200 mg every two weeks thereafter or 400 mg every four weeks, or monthly), etarnecept (50 mg SC every two weeks), golimumab (50 SC every four weeks or monthly), or infliximab (3 mg/kg IV at weeks 0, 2 and 6 and every 8 weeks thereafter).

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it should reald:

RA patients can be treated with anti-TNF biologic DMARDs, including adalimumab (40 mg SC every two weeks), certolizumab (400 mg SC every two weeks at weeks 0, 2 and 4 and 200 mg every two weeks thereafter or 400 mg every four weeks, or monthly), etarnecept (50 mg SC weekly), golimumab (50 SC every four weeks or monthly), or infl iximab (3 mg/kg IV at weeks 0, 2 and 6 and every 8 weeks thereafter).

At page 172, table 5 [Portuguese edition only], where it reads:

Tabela 5 – Medidas de ACR50 e DAS-28 expressas pelo benefício estimado por meio do Número Necessário para Tratar (NNT).

Índice	Estado da atividade de doença	Pontos de corte	NNT	
			ACR50	DAS-28
Golimumabe	50 mg	24 semanas	10	7
Adalimumabe	40 mg	52 semanas	3	5
Etanercept	50 mg	52 semanas	5	5
Infliximabe	3 mg/kg	22 semanas	5	6
Certolizumabe	200 mg	52 semanas	3	6
Rituximabe	1000 mg	52 semanas	6	5
Tocilizumabe	8 mg/kg	24 semanas	3	4
Abatacepte	500–1000 mg	52 semanas	11	10

It should read:

Tabela 5 – Medidas de ACR50 e DAS-28 expressas pelo benefício estimado por meio do Número Necessário para Tratar (NNT).

Biológico	Dose	Tempo	NNT	
			ACR50	DAS-28
Golimumabe	50 mg	24 semanas	10	7
Adalimumabe	40 mg	52 semanas	3	5
Etanercept	50 mg	52 semanas	5	5
Infliximabe	3 mg/kg	22 semanas	5	6
Certolizumabe	200 mg	52 semanas	3	6
Rituximabe	1000 mg	52 semanas	6	5
Tocilizumabe	8 mg/kg	24 semanas	3	4
Abatacepte	500–1000 mg	52 semanas	11	10