2012 Brazilian Society of Rheumatology Consensus for the treatment of rheumatoid arthritis

Licia Maria Henrique da Mota[1], Boris Afonso Cruz[2], Claiton Viegas Brenol[3], Ivanio Alves Pereira[4], Lucila Stange Rezende-Fronza[5], Manoel Barros Bertolo[6], Max Victor Carioca de Freitas[7], Nilzio Antonio da Silva[8], Paulo Louzada-Júnior[9], Rina Dalva Neubarth Giorgi[10], Rodrigo Aires Corrêa Lima[11], Geraldo da Rocha Castelar Pinheiro[12]

ABSTRACT

Objective: To elaborate recommendations for the treatment of rheumatoid arthritis in Brazil. **Method:** Literature review with articles' selection based on evidence and the expert opinion of the Rheumatoid Arthritis Committee of the Brazilian Society of Rheumatology. **Results and conclusions:** 1) The therapeutic decision should be shared with the patient; 2) immediately after the diagnosis, a disease-modifying antirheumatic drug (DMARD) should be prescribed, and the treatment adjusted to achieve remission; 3) treatment should be conducted by a rheumatologist; 4) the initial treatment includes synthetic DMARDs; 5) methotrexate is the drug of choice; 6) patients who fail to respond after two schedules of synthetic DMARDs should be assessed for the use of biologic DMARDs; 7) exceptionally, biologic DMARDs can be considered earlier; 8) anti-TNF agents are preferentially recommended as the initial biologic therapy; 9) after therapeutic failure of a first biologic DMARD, other biologics can be used; 10) cyclophosphamide and azathioprine can be used in severe extra-articular manifestations; 11) oral corticoid is recommended at low doses and for short periods of time; 12) non-steroidal anti-inflammatory drugs should always be prescribed in association with a DMARD; 13) clinical assessments should be performed on a monthly basis at the beginning of treatment; 14) physical therapy, rehabilitation, and occupational therapy are indicated; 15) surgical treatment is recommended to correct sequelae; 16) alternative therapy does not replace traditional therapy; 17) family planning is recommended; 18) the active search and management of comorbidities are recommended; 19) the patient's vaccination status should be recorded and updated; 20) endemic-epidemic transmissible diseases should be investigated and treated

Keywords: rheumatoid arthritis, therapy, Brazil, antirheumatic agents, consensus.

Received on 11/19/2011. Approved on 12/13/2011. Authors' conflict of interest are declared at the end of this article.
Brazilian Society of Rheumatology.

1. PhD in Medical Sciences, Medical School, Universidade de Brasília – FM-UnB; Supervisor of the Medical Sciences Post-graduation Program, UnB
2. Rheumatologist of the Biocor Instituto, Belo Horizonte
3. Adjunct Professor of the Department of Internal Medicine, Medical School, Universidade Federal do Rio Grande do Sul – UFRGS; Coordinator of the Rheumatoid Arthritis Referral Center, Hospital de Clínicas de Porto Alegre/SES-RS
4. PhD in Rheumatology, Medical School, Universidade de São Paulo – FMUSP; Chief of the Rheumatology Sector, Hospital Universitário, Universidade Federal de Santa Catarina – UFSC
5. Rheumatologist of the Hospital de Clínicas, Universidade Federal do Paraná – HC-UFPR; Ex-fellow of the Rheumatology Service, Hospital Geral AKH, Austria; Research Physician at the Center of Innovative Studies and Therapies (CETI)
6. Associate Professor and Coordinator of the Discipline of Rheumatology, Medical Sciences School, Universidade Estadual de Campinas – Unicamp; Superintendent of the Hospital de Clínicas, Unicamp
7. Adjunct Professor, Medical School, Universidade Federal do Ceará – UFCE
8. Full Professor of Rheumatology, Medical School, Universidade Federal de Goiás – UFG
9. Associate Professor, Medical School of Ribeirão Preto, Universidade de São Paulo – FMUSP
10. Rheumatologist, Chief of the Diagnosis and Therapy Section of the Rheumatology Service, Hospital do Servidor Público Estadual de São Paulo – HSPE-FMO
11. Rheumatologist, Chief of the Rheumatology Service of the HUB and preceptor of the Medical Residency, HBDF
12. Adjunct Professor and Coordinator of the Discipline of Rheumatology, Medical Sciences School, Universidade do Estado do Rio de Janeiro – UERJ
Correspondence to: Licia Maria Henrique da Mota. Av. Brigadeiro Luís Antônio, 2466 – Jardim Paulista. CEP: 01402-000. São Paulo, SP, Brasil. E-mail: liciamhmota@yahoo.com.br

INTRODUCTION

Rheumatoid arthritis (RA) is a systemic inflammatory autoimmune disease that affects the synovial membrane of peripheral joints. Its prevalence is estimated at around 0.5%–1% of the population, predominantly in women, and higher incidence in the age group from 30–50 years.[1,2]

The main characteristic of RA is the symmetrical impairment of small and large joints, with a more frequent involvement of the hands and feet. The chronic and destructive character of the disease can lead to important functional limitation, with loss of work capacity and quality of life, unless the diagnosis is established at an early phase of the disease and clinical improvement results from treatment.[3] In addition to irreversible deformity and functional limitation, patients with RA and advanced disease can have a shorter survival, confirming the severity of that disease.[4,5]

The costs related to RA are high, resulting from both direct (expenditure with several medications, some of which are expensive, such as biologic drugs, in addition to medical and hospital costs) and indirect (loss of personal productivity, absenteeism, and retirement due to disability for those with total work capacity loss) factors. [6]

Over the past 10 years, the knowledge about the pathophysiological mechanisms of RA has advanced dramatically, with the development of new therapeutic classes of drugs and the implementation of different strategies of treatment and follow-up, such as intensive control of the disease and intervention at the beginning of the symptoms.[7] The initial period of the disease, especially its first 12 months (the so-called early RA),[5] is considered a therapeutic window, that is, when prompt and effective pharmacological intervention can change the disease course in the long run. Those factors have resulted in RA better clinical control, with the possibility of its sustained remission.[7,8]

The present consensus aimed at elaborating recommendations for the management of RA, with an emphasis on treatment, considering peculiar aspects of the Brazilian socioeconomic reality. The purpose of this document was to synthesize the current position of the Brazilian Society of Rheumatology (BSR) about the subject, aiming at better educating Brazilian physicians, especially rheumatologists, on the rational therapeutic management of RA in Brazil.

METHOD OF CONSENSUS BUILDING

The method of consensus building for the development of recommendations included literature review and consultation of the opinion of the BSR Rheumatoid Arthritis Committee expert members. The bibliographic survey comprised publications in the MEDLINE, SciELO, PubMed, and EMBASE bases up to November 2011. The recommendations have been written and reassessed by all participants during five meetings held on October and December 2010, and February, July and October 2011, in addition to several rounds of questionings and corrections conducted via Internet.

TREATMENT OF RHEUMATOID ARTHRITIS

The RA treatment comprises education of patients and their families, medicamentous therapy, physical therapy, psychosocial support, occupational therapy and surgical approaches. The medicamentous therapy includes the use of nonsteroidal anti-inflammatory drugs (NSAIDs), corticoids, synthetic and biologic disease-modifying antirheumatic drugs (DMARDs), and immunosuppressive drugs.

Educational measures

Before starting any form of treatment, patients should be educated about their disease, and, particularly, about its possible evolution, therapy and prognosis. They should be instructed about inadequate information provided through several communication media, especially the Internet. Education should start on the first consultation and include the family members, so that all of them can share information on the disease, which results in better management of the medicamentous and non-medicamentous treatments.[9,10]

Educational activities are essential to guarantee patients' collaboration. Patients have the right to know about their health conditions and the available therapeutic options, and actively participate in the choices. Patients who understand their conditions and know about the medications action, the methods to prevent deformities, and the rehabilitation process, have a better clinical evolution.[11]

Patients should be instructed about the role played by exercises and joint protection, and specific techniques of physical therapy and rehabilitation, so that they can get more involved with such activities to prevent joint deformities. In addition, they should be educated about the possible adaptation of household appliances and modifications in the work environment.[12]

Because patients with RA are often followed up by a multidisciplinary team, all professionals should have the same objectives and work together harmoniously.[13]

Medicamentous treatment

Nonsteroidal anti-inflammatory drugs – NSAIDs

The NSAIDs are useful to reduce the inflammatory process and pain, mainly at the early phase of disease, because DMARDs do not act immediately. In addition, NSAIDs can be used when complete control of disease activity is not achieved and in disease relapse.[14,15]

The choice of NSAIDs should be individualized, because there is no known superiority of any drug in that class. More control, substitution, suspension, shorter use, and lower doses should be considered in the presence of clinical conditions that can be aggravated by NSAIDs, such as previous hypersensitivity to NSAIDs, systemic arterial hypertension (SAH), heart failure, renal failure, gastrointestinal disease, arterial failure, hepatopathy, and coagulation disorders.[16]

For patients with previous history of gastrointestinal disease, selective cyclooxygenase 2 inhibitors have lower risk as compared with other NSAIDs.[17] For those at greater risk for cardiovascular disease, the use of anti-inflammatory drugs in general should be cautious.[18]

Corticoids

The most known and expected effect of corticoids in RA is the improvement in the inflammatory process and pain. However, there is current evidence for their indication as participants in the disease course modification in association with DMARDs.[19,20]

Most studies on the use of corticoids for the treatment of RA have suggested the use of prednisone or prednisolone at low doses (≤ 15 mg/day). There are no comparative studies indicating the preferential use of higher doses at the beginning of treatment.[19,20]

Because corticoids can cause several side effects, their use should be shortened as much as possible. If the corticoid administration is expected to last three or more months, calcium and vitamin D supplementation should be performed. Depending on the bone densitometry result, and in patients with risk factors for fractures, the use of antiresorptive drugs, such as bisphosphonates, can be considered.[21] In patients who maintain active disease in few joints, intraarticular corticoid can be used at any time during treatment[22] – nevertheless, one joint should not be infiltrated more than three to four times a year. In patients using concomitantly corticoid and NSAIDs, gastric protection with proton pump inhibitors is recommended.[22]

Disease-modifying antirheumatic drugs – DMARDs

The DMARDs should be indicated to patients from the time RA is diagnosed.[23] The use of DMARDs in patients with undifferentiated arthritis and biomarkers for RA, such as positivity for anti-cyclic citrullinated peptide antibody (anti-CCP) and/or rheumatoid factor (RF), should be considered.[24]

Table 1 shows the most often used DMARDs in Brazil, their presentation, dosage, and considerations about treatment monitoring. [20,25–94]

Synthetic DMARDs

a) Methotrexate – MTX

MTX is an immunomodulatory agent, which inhibits the synthesis of DNA, RNA, thymidine, and proteins. The anti-inflammatory effects of MTX on RA seem to be related, at least partially, to the modulation of the adenosine metabolism, and to other possible effects on the tumor necrosis factor (TNF) pathways. The immunosuppressive and toxic effects of MTX are due to the inhibition of dihydrofolate reductase, the enzyme involved in the folic acid metabolism, which prevents the reduction of dihydrofolate to active tetrahydrofolate. Maximum concentration is obtained in 1–5 hours, by oral administration, and in 30–60 minutes by intramuscular (IM) or subcutaneous (SC) routes. Renal excretion of 40% to 90% of MTX in its unaltered form occurs.[25]

MTX is currently considered the first choice for treating RA.[26] Its capacity to reduce signs and symptoms of RA activity and improve the patient's functional status has been demonstrated.[27] In addition, MTX reduces radiographic disease progression.

The initial MTX dose recommended is 10–15 mg/week, by oral or parenteral administration (IM or SC). If neither disease improvement nor disease control is observed with the initial dose, it should be progressively increased every 2–4 weeks until reaching the dose of 20–30 mg/week, preferentially in the first 12 weeks. The parenteral administration can be indicated to patients with gastrointestinal intolerance or with an inadequate response to the oral administration.[28]

The most frequently observed side effects are as follows: anemia, neutropenia, nausea and vomiting, mucositis, and an elevation in liver enzymes. Interstitial pneumonia is a less frequent manifestation. To minimize side effects, folic acid should be associated with MTX, at the dose of 5–10 mg/week, and administered 24–48 hours after MTX.[28] To patients with renal failure, liver disorders, alcoholism, and bone marrow suppression, in addition to women of childbearing age who are not using contraception, MTX is contraindicated. Pregnancy and breast-feeding are formally contraindicated to patients on

MTX, which should be cautiously administered to patients with mild lung disorders, and avoided in individuals with moderate or severe lung impairment.[28]

b) Sulfasalazine – SSZ

SSZ belongs to the group of salicylates and sulfonamides, being metabolized by intestinal bacteria to sulfapyridine and 5-aminosalicylic acid. Sulfapyridine has several immunomodulatory effects, such as the inhibition of prostaglandin production, of several neutrophilic and lymphocytic functions, and of chemotaxis. It also inhibits folate-dependent enzymes. Its serum concentration peaks in approximately 1.5–6 hours, and its half-life is of 5–10 hours. SSZ is metabolized in the gastrointestinal tract (by the intestinal flora), and excreted through the kidneys (75%–91%).[29]

SSZ is considered more effective than placebo in reducing disease activity, controlling pain, and for global clinical assessment. Its clinical efficacy and the interference with the radiographic disease progression are confirmed.[29] It is usually prescribed at the dose of 1–3 g/day, orally.[29,30]

The side effects of SSZ are as follows: gastrointestinal intolerance (anorexia, nausea, vomiting), skin rash, elevation in liver enzymes, oral ulcers, and myelosuppression (leukopenia with neutropenia). More rarely, hypersensitivity pneumonia, neurological manifestations, and male fertility changes are observed. Most effects are benign and are reversed with drug suspension.[30]

SSZ is contraindicated in patients with history of hypersensitivity to sulfa drugs, salicylates or any component of the SSZ formula, and in individuals with porphyria.[29,30]

c) Leflunomide – LEF

LEF is an immunomodulatory agent with antiproliferative activity that inhibits the enzyme dihydroorotate dehydrogenase, which is involved in pyrimidine synthesis. LEF is absorbed through the gastrointestinal tract, and its biotransformation probably occurs in the liver and gastrointestinal wall, where LEF is mainly transformed into M1, the active metabolite responsible for all the drug's effects. The concentration of M1 peaks in 6–12 hours, and that metabolite is eliminated through the kidneys and intestines.[31]

LEF improves disease activity and quality of life, and reduces the radiographic disease progression.[32,33] It is prescribed at the dose of 20 mg/day, orally,[31–33] but 20 mg on alternate days can be used.

The side effects of LEF include nausea, vomiting, abdominal pain, diarrhea, changes in liver enzymes, skin rash, and SAH.[31] It is contraindicated to women of childbearing age who are not using contraception, and to patients with renal failure and liver disorders. Pregnancy and breast-feeding are formally contraindicated to patients on LEF. Its suspension is recommended two years before a possible pregnancy. In case of incidents, especially during pregnancy, LEF can be eliminated by using cholestyramine, at the dosage of 8 g, three times a day, for 11 days.[31]

d) Antimalarials (chloroquine diphosphate – CQD and hydroxychloroquine sulfate – HCQ)

Antimalarials have been used in the treatment of RA for over 50 years. They are safe and effective, mainly in the early and mild forms of the disease. The mechanism of action is not completely understood, but it seems to involve multiple factors, such as anti-inflammatory activity (stabilization of lysosomal membranes, and inhibition of lysosomal enzymes, and of polymorphonuclear chemotaxis and phagocytosis), and interference with prostaglandin production.[34,35]

The two available forms of antimalarials are CQD and HCQ, the latter being preferred due to its better safety profile, especially the ophthalmologic one. The maximum daily dose of CQD is 4 mg/kg/day, and of HCQ is 6 mg/kg/day, orally. The drug takes a while to start acting, requiring 3–4 months to reach its peak efficacy in approximately 50% of the patients.

The side effects vary and comprise the following: gastrointestinal intolerance (nausea, vomiting, abdominal pain), skin hyperpigmentation, headache, dizziness, myopathy, and retinopathy. The last side effect is not frequent, but regular ophthalmologic monitoring is indicated (initial assessment, annual assessment after five years, or annual assessment since the beginning, in the presence of risk factors, such as renal or liver dysfunction, maculopathy, advanced age, or cumulative dose greater than 1,000 g for HCQ or 460 g for CQD).[36]

As compared with placebo, HCQ is effective, reducing the clinical and laboratory parameters (erythrocyte sedimentation rate, ESR) analyzed, although, in isolation, it has not changed the radiographic disease progression.[34,35,37] Similar results have been reported with CQD, which is less expensive. Both are contraindicated in patients with alterations of the retina and visual field.[36,37]

Although antimalarials have been traditionally used in Brazil, often in association with other DMARDs, they are currently considered less potent drugs, and should be used for early RA or undifferentiated arthritis, with low erosive potential.

e) Gold salts

Gold salts, specifically the injectable forms (aurothioglucose and aurothiomalate), can both reduce constitutional and articular symptoms and slow the radiographic progression of RA.[38] They can be used in monotherapy or combined with other agents.[39]

Their usual dose is 50 mg/week, usually beginning with 25 mg/week. The intervals between applications can be increased

to fortnightly and monthly doses after disease control. The cumulative dose should not exceed 3 g.[38,39] Their toxicity profile includes myelotoxicity (mainly thrombocytopenia), oral ulcers, skin reactions (exfoliative dermatitis), nephropathy (nephrotic proteinuria can occur), and interstitial pulmonary disease.[38,39]

Although they have been mentioned in recent international recommendations,[20] gold salts are currently rarely used in Brazil, due to their side effects and restricted availability in the country.

Biologic DMARDs

One of the most relevant advances in the therapy of RA was the development of biologic DMARDs.[40] Although they are effective in controlling RA, their long-term safety has not been established.[41]

The following biologic DMARDs have been approved by the Brazilian Agency of Sanitary Surveillance (ANVISA) to be used in Brazil:[42]

- Anti-TNF agents: adalimumab, certolizumab, etanercept, infliximab, and golimumab;
- B lymphocyte depletion agent: rituximab;
- T lymphocyte costimulation inhibitor: abatacept;
- Interleukin-6 (IL-6) receptor blocker: tocilizumab.

Biologic DMARDs are indicated to patients with persistent disease activity, despite the treatment with at least two schedules of synthetic DMARDs, of which at least one of them is a combination of DMARD. Biologics should be associated with a DMARD, preferably MTX. Exceptionally, as discussed below, a biologic DMARD can be prescribed earlier in the course of the treatment for RA, especially in cases of disease with signs of poor prognosis (high number of involved joints, radiographic erosions at the initial phase of disease, and high titers of RF and/or anti-CCP).[13,20,43–46]

Social/educational/demographic characteristics of the different Brazilian macroregions, such as the difficulty in the SC administration of medications experienced by some patients and their families, and the lack of infusion centers for the administration of intravenous (IV) medication in certain areas, can determine the choice of one or other biologic DMARD. The public or private centers of drug dispensation/infusion should instruct patients and their families about the adequate storage of each drug, or send them directly to infusion sites, to prevent loss of treatment efficacy. It is recommended that rheumatologists indicate and monitor the use of those drugs.[47]

Biologic DMARDs should not be associated because of the potential risk of severe infections.[48,49] Currently, anti-TNF agents are the most used biologic DMARDs, but there are evidences that the other biologic DMARDs also control RA signs and symptoms and inhibit the radiographic disease progression.

a) Anti-TNF agents

TNF is a potent inflammatory cytokine expressed in large amounts in the serum and synovial fluid of individuals with RA. It causes the release of other inflammatory cytokines, particularly interleukins IL-1, IL-6 and IL-8, and stimulates the production of proteases. The inhibition of TNF has proved to be an effective and rapid form to control disease activity.[50]

In terms of efficacy, there are no data confirming the superiority of any of the five anti-TNF agents approved in Brazil for the treatment of RA.[51,52]

Anti-TNF agents should be used in association with MTX or other DMARDs, because their combined use proved to be safe and provided rapid benefit in controlling disease activity, as compared with the use of anti-TNF as monotherapy. For patients with contraindications to the use of synthetic DMARDs, anti-TNF agents can be occasionally prescribed as monotherapy.[46,53–63]

- Adalimumab – ADA

ADA is a human antibody against TNF, prescribed for SC administration at the dose of 40 mg, once every two weeks.[55,56,64–68]

- Certolizumab – CERT

CERT pegol is a Fab fragment of the humanized anti-TNF antibody, with high affinity with TNF, conjugated with two molecules of polyethylene glycol. It is prescribed for SC administration at the dose of 400 mg every two weeks, in weeks 0, 2 and 4, and, after that, at the dose of 200 mg every two weeks, or 400 mg every four weeks.[61,62,69]

- Etanercept – ETN

ETN is a fusion protein composed of the soluble TNF receptor plus the Fc region of IgG, prescribed at a single weekly dose of 50 mg via SC administration.[57,58,68,70]

- Infliximab – IFX

IFX is a chimeric human-mouse monoclonal anti-TNF antibody, prescribed at the initial dose of 3 mg/kg IV, followed by the same dose (3 mg/kg) in the second and sixth weeks, and then every eight weeks. In patients with insufficient response, the dose can be elevated to 5 mg/kg per infusion, or the interval between doses can be reduced. Higher doses offer little therapeutic benefit and greater risk of infectious complications, and, thus, should be avoided in the treatment of RA.[54,59,63,68,71]

- Golimumab – GOL

GOL is a monoclonal human anti-TNF antibody administered at the dose of 50 mg, SC, once a month.[60,72]

- Adverse effects and contraindications of the anti-TNF agents

The adverse effects of the anti-TNF agents include infusion reactions for the IV drugs (fever, shivering, chest pain, blood pressure oscillation, dyspnea, pruritus and/or urticaria) and manifestations on the injection sites for the SC drugs (erythema, pruritus, local pain, and/or urticaria). Those drugs increase the likelihood of the following: infections, especially in their first year of use, including severe infections and those caused by intracellular pathogens (tubercle bacillus, listeria, histoplasma, atypical mycobacteria, and legionella); cardiac dysfunction; demyelinating diseases; autoimmune phenomena (autoantibody production); cutaneous vasculitis; interstitial lung disease; and occasional increased risk for lymphoma.[68,73–75] Human anti-chimeric antibodies can result from the use of any drug in that class, but their effect on the efficacy of the therapy is uncertain.[76,77]

The anti-TNF agents are contraindicated to women during pregnancy or breast-feeding, and to patients with the following: New York Heart Association functional classes III and IV congestive heart failure, active infection or high risk for the development of infections (chronic ulcer of the lower limbs, septic arthritis in the last 12 months), recurring lung infections, multiple sclerosis, and current or previous diagnosis of neoplasia (less than five years). Patients should be carefully followed up, with assessment of possible signs of infection, which should be addressed immediately.[73–75]

b) Costimulation modulator

- Abatacept – ABAT

ABAT is a fusion protein CTLA-4-IgG that inhibits T lymphocyte costimulation. It is indicated to patients with active RA who failed a DMARD or anti-TNF agents. It can be used in association with DMARDs or in monotherapy. ABAT should be administered in IV infusion, for 30 minutes, at the dose of 500 mg in patients weighing less than 60 kg, 750 mg in patients weighing 60–100 kg, and 1,000 mg in patients weighing over 100 kg. The next dose should be administered two to four weeks after the initial dose, and, then, every four weeks.[78–80]

The use of ABAT has been associated with higher occurrence of infectious complications as compared with placebo, similarly to that observed with other biologic DMARDs. Infusion reactions with ABAT are rare, being mainly hypersensitivity reactions that manifest as exanthem or bronchospasm. It is contraindicated for patients with chronic obstructive pulmonary disease, because of the exacerbation of dyspnea and greater occurrence of infections.[78,81]

c) B lymphocyte depletion agent

- Rituximab – RTX

RTX is a monoclonal chimeric antibody directed against CD20+ lymphocyte, indicated for patients with RA of moderate to severe activity, who failed to respond to an anti-TNF agent. RTX is administered at the dose of 1,000 mg in two IV infusions at a 14-day interval. Sixty minutes before each infusion, 100 mg of methylprednisolone, IV, and 1 g of paracetamol and an antihistamine should be administered to reduce the severity and frequency of infusion reactions.[82–85]

RTX is preferentially used in association with MTX, and can be prescribed in association with other DMARDs. It is worth noting that a three to four month delay can occur until symptom improvement is observed.[82–84] Individuals with positive serology for RF and/or anti-CCP show better therapeutic response to RTX.[86] Individuals with good therapeutic response to RTX can undergo a new course of RTX in case of disease reactivation, at a time interval no shorter than six months.[82–85]

The most frequent adverse events are infusion reactions, which affect 35% of the patients at the first infusion and approximately 10% at the second infusion. In addition, infectious complications, interstitial pneumonia, neutropenia, and thrombocytopenia can occur.[82–85]

d) Interleukin-6 receptor blocker

- Tocilizumab – TOCI

TOCI is a humanized monoclonal antibody that binds the IL-6 receptor, inhibiting the biologic effect of IL-6. It can be used as monotherapy, or in association with MTX or other DMARDs. The incidence of infections and severe infections is equivalent to that of other biologic agents. It is prescribed at the dose of 8 mg/kg, IV, every four weeks.[87–89]

The dose-dependent side effects of the use of TOCI are as follows: neutropenia; thrombocytopenia; elevation in transaminases, total cholesterol, and low-density lipoprotein; and increased occurrence of infections.[87–89] It should be avoided in patients at higher risk for intestinal perforation, such as those with diverticular disease of the colon.[90]

Infection in patients on biologic DMARDs

Screening for infectious diseases is recommended before beginning biologic DMARDs, including thorough clinical assessment, serologies for hepatitis B and hepatitis C, and, when pertinent, HIV and/or other endemic diseases. Screening for endemic diseases is better detailed below.

Immunosuppressive drugs

The use of immunosuppressive drugs for the treatment of RA is based on the evidence of multiple immune mechanisms mediating the synovitis and other extra-articular manifestations of the disease.

Several mechanisms of action have been described, such as the reduction in cell response (and, less effectively, in humoral response) and anti-inflammatory properties (interference with the migration and action of neutrophils, lymphocytes and monocytes).

The use of immunosuppressive drugs is restricted to the most severe forms of RA, because most of such drugs are considerably toxic (severe myelosuppression, increased occurrence of infections, sterility, urinary bladder toxicity, increased occurrence of neoplasias).

Azathioprine – AZA

Despite its acceptable safety profile, its action as a DMARD remains controversial. AZA is considered a therapeutic option;[91] its lower effect on the control of signs and symptoms and the lack of proof on reduction of the radiographic disease progression, however, make it an alternative only for exceptional cases.[20]

The usual dose of AZA is 1–3 mg/kg/day, orally. It is used for treating moderate to severe RA, refractory to other treatments, or for controlling severe extra-articular manifestations, such as vasculitis.[20,91]

Cyclophosphamide – CF

An alkylating agent with an unfavorable toxicity profile and limited benefit in controlling synovitis, CF can be used either orally (1–2 mg/kg/day) or preferably IV (pulses of 0.5–1 g/m^2 of body surface). Its use is justified only in severe extra-articular forms, mainly vasculitis.[92]

Cyclosporine – CS

CS is an effective alternative to control the signs and symptoms of RA. It can slow the progression of joint damage even in patients with severe RA refractory to other treatments, although its effect seems to be inferior to that of MTX, SSZ and LEF. It can be used as monotherapy, but is usually prescribed in association with MTX.[20,93,94]

Immunomodulation relatively specific to T-lymphocyte has been proposed as the mechanism of action of cyclosporine. It is prescribed orally at the dose of 3–5 mg/kg/day. Cyclosporine is contraindicated in patients with altered renal function, uncontrolled hypertension, and malignancies. Its toxicity, however, limits its use to patients with disease non-responsive to other DMARDs, making it a drug that should only be used in exceptional circumstances for the treatment of RA. It is used preferentially in patients with extra-articular manifestations, such as vasculitis, being a safe alternative for patients with liver disorders and lung involvement. If hypertension or a 30%-increase in baseline creatinine occurs, the cyclosporine dose should be reduced by 25%–50%. If hypertension or increased creatinine persists, the treatment should be discontinued.[20,93,94]

THERAPEUTIC STRATEGIES FOR THE TREATMENT OF RA IN BRAZIL

Disease-modifying antirheumatic drugs should be initiated immediately after the diagnosis of RA. Whenever necessary, the treatment should be adjusted at frequent clinical assessments at 30–90-day intervals.

Therapeutic strategies aimed at specific goals produce better clinical outcomes and functional capacity, in addition to lower radiographic structural damage, as compared with conventional treatments.[95] The goal is to reach remission, or at least low disease activity, assessed by use of compound indices of disease activity (CIDA), considering as therapeutic response the reduction in CIDA, according to the 2011 Brazilian Society of Rheumatology consensus for diagnosis and early assessment of RA.[5]

Figure 1 depicts the flowchart of the medicamentous treatment for RA in Brazil, proposed by the Rheumatoid Arthritis Committee of the Brazilian Society of Rheumatology.

First line – synthetic DMARDs

Methotrexate should be the first-choice DMARD.[20,96,97] When contraindicated, SSZ[98] or LEF[99] can be used as the first option.[100] The use of antimalarials (CQD and HCQ),[101] can be indicated only for patients with mild disease or undifferentiated arthritis with low erosive potential. In exceptional cases, such as patients with hypersensitivity to other DMARDs, or with viral hepatitis, gold salts can be used. MTX should be preferentially prescribed in monotherapy, at the beginning of treatment.[102]

When the aimed clinical response (remission or low disease activity) is not obtained with the maximum tolerated dose of MTX, or in the presence of adverse effects, change to another DMARD as monotherapy or use of DMARD combinations is recommended. The most used combinations of MTX are with the following: CQD/HCQ, SSZ, an association of those three drugs,[27] and LEF.[103] The progression of therapy should be rapid, with monthly assessments in the first six months of treatment, and adjustment of the dosing schedules as required. A maximum period of six months should be observed to define lack of response to the first-line treatment instituted.[20]

Table 1
Disease-modifying antirheumatic drugs used for treating rheumatoid arthritis in Brazil[20,25–94]

Drug	Presentation	Dose	Clinical response and monitoring
Synthetic disease-modyfing 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.
Lefl unomide	Tablets: 500 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 fi ve 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)	
Sais de ouro (aurotioglicose ou aurotiomalato de sódio)	Solucão injetável: 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 fi rst year of use.
Adalimumab	Prefi lled syringes: 40 mg	40 mg SC every 15 days	
Certolizumab	Prefi lled 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 prefi lled syringes	50 mg/week	

(Continue...)

Drug	Presentation	Dose	Clinical response and monitoring
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	Prefi lled pen: 50 mg	50 mg SC monthly	
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	Eficaz na redução de sinais e sintomas da AR e na redução da progressão radiográfica. Pode ser prescrito após falha de DMCD sintéticas ou após falha e/ou intolerância a DMCD biológicas. Uso preferencial associado ao MTX ou a outras DMCD sintéticas. Monitoração: hemograma e enzimas hepáticas a cada 4–8 semanas. Monitorar ocorrência de infecção.
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 RTX. 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 profi le 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/m2 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 mg 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.

Low doses of corticoids (maximum of 15 mg/day of prednisone or equivalent), as well as anti-inflammatory drugs, can be used at the beginning of treatment; however, caution and the use for the shortest time possible to reduce the occurrence of adverse effects are recommended.[20]

Second line – biologic DMARDs

Immunobiologic therapy for RA is indicated for patients with persistently moderate to high disease activity (according to CIDA), despite the use of at least two of the schedules proposed in the first-line treatment. Of the biologics, anti-TNF drugs are the first choice in Brazil after the schedules with synthetic DMARDs fail. That is justified by the more comprehensive post-commercialization experience, and the greater volume of safety information originating from national[104] and international[20] clinical trials, registries, and recommendations. However, other drugs, such as ABAT and TOCI, can be prescribed at the physician's discretion after failure of the synthetic DMARD, based on the publication of randomized clinical trials.[78,89] RTX should be avoided as a first-choice biologic,[20] except for the following specific cases: patients with contraindication to other biologics, preferentially those positive to RF and/or anti-CCP, and those diagnosed with associated lymphoma.

On exceptional situations, a biologic DMARD can be indicated after failure of the first synthetic DMARD schedule for patients with several factors of poor prognosis, such as very intense disease activity, elevated number of tender/inflamed joints, high titers of RF and/or anti-CCP, and early occurrence of radiographic erosions.[20] The worse prognosis factors are better detailed in the 2011 Brazilian Society of Rheumatology Consensus for diagnosis and early assessment of RA.[5]

Biologic DMARDs are not recommended as first-line treatment for RA in Brazil, because there is no evidence of cost-effectiveness in that country.

Third line – failure of biologic DMARDs or intolerance to them

In the clinical settings of no response to the initial biologic treatment, evolution to loss of the response obtained, or presence of important adverse events, one biologic agent can be exchanged for another. The biologics that showed benefits on randomized clinical trials with patients who failed anti-TNF agents were ABAT, RTX, and TOCI.[105] Patients who failed the first anti-TNF agent have also shown to benefit from the use of a second drug of the same class, such as ADA, CERT, ETN, IFX, or GOL, in prospective observational studies and also in double-blind controlled randomized trials (GOL), but the magnitude of their therapeutic effects and cost-effectiveness of that strategy remain controversial.[106]

The choice of the treatment sequence to be applied is at the physician's discretion, depending on the particularities of each case. A minimum period of three months and maximum of six months of clinical assessment is recommended prior to exchanging the therapeutic schedule (exchange between biologic DMARDs).

Medication withdrawal and occasional therapy suspension

Data defining the duration of the therapy for RA still lack. Currently, the medication indicated and to which the patient responds properly should be maintained indefinitely, at the physician's discretion. In case of complete (remission) and sustained (for more than 6–12 months) response, gradual and careful drug withdrawal can be attempted at the following sequence: at first, NSAIDs; then, corticoids and biologic DMARDs; synthetic DMARDs should be maintained.[107] Exceptionally, if remission persists, the synthetic DMARD withdrawal can be carefully attempted.[20] Drug-free sustained remission is rare, especially in patients with biomarkers such as anti-CCP and/or RF.

Treatment monitoring

Regarding early disease, for patients with active disease and symptoms up to one year, intensive follow-up is recommended with monthly visits and rapid medicamentous progression, when necessary.[108,109] Therapeutic schedules and their possible adverse effects have already been approached in the previous sections.

At every visit, the efficacy and safety of the therapeutic intervention should be assessed, considering the patient's comorbidities and aiming preferentially at remission or the lowest possible disease activity, as well as the improvement in functional capacity and quality of life. For patients with established disease, and especially those with controlled disease, the visits can be performed every three months.[108,109]

Table 2 shows the monitoring frequency of the major parameters for properly assessing patients with RA undergoing treatment.

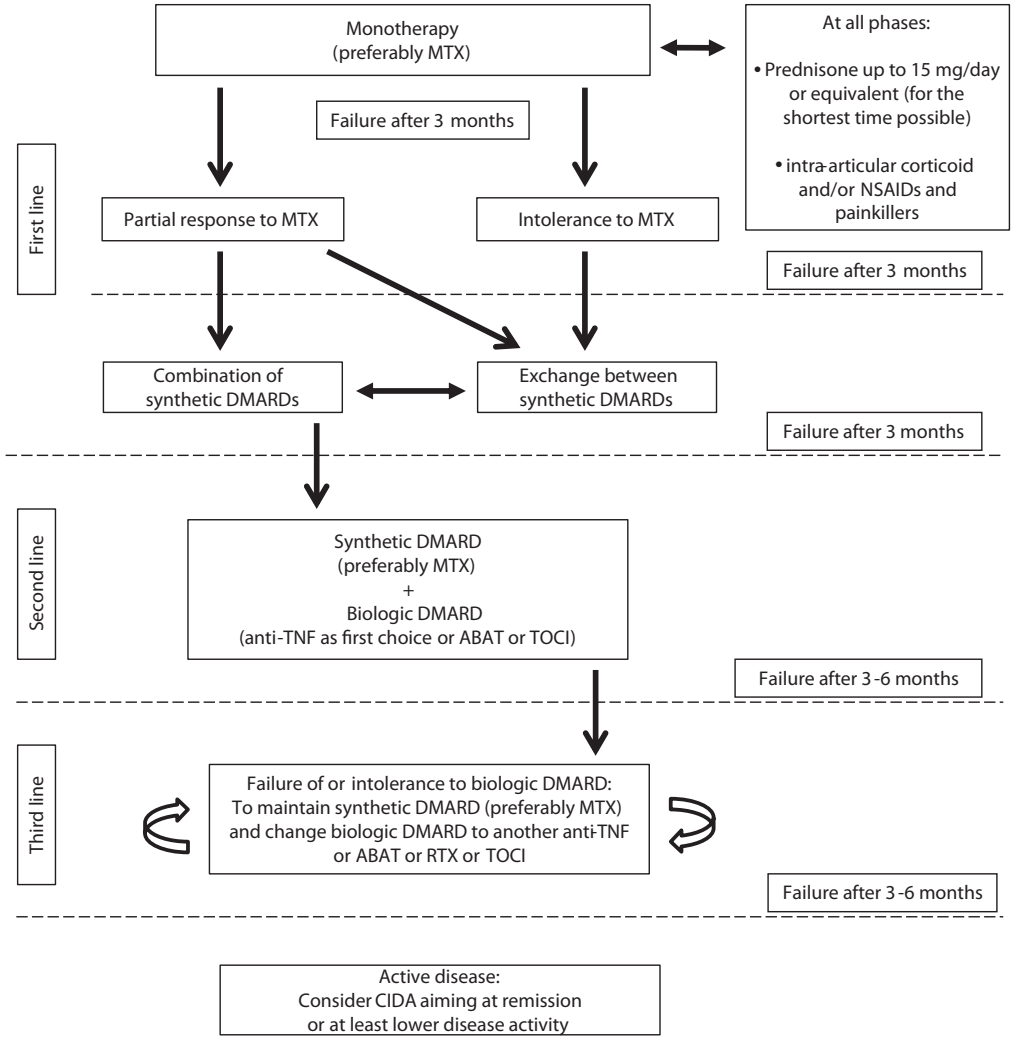

Figure 1
Flowchart for the medicamentous treatment of RA.
ABAT: abatacept; CIDA: compound indices of disease activity; DMARD: disease-modifying antirheumatic drug; MTX: methotrexate; NSAIDs: nonsteroidal anti-inflammatory drugs; RTX: rituximab; TOCI: tocilizumab.

Physical therapy and rehabilitation

During the phases of disease activity, rest helps to reduce the inflammatory process; however, the possibility of complications, such as joint stiffness and flexion deformities, should be considered.[110]

Kinesiotherapy can comprise passive exercises, in the initial phases, and active, isometric and/or isotonic, exercises. Those exercise programs are aimed at assuring maintenance, restoration, or gain of joint range of motion, muscle strength and stretching, aerobic capacity, and performance of specific abilities.[110]

Most programs of dynamic exercises follow the recommendations of the American College of Sports Medicine (ACSM).[111] We recommend at least 20 minutes of exercise, at least twice a week, which leads to a 60% increase in the heart rate predicted for age, so that it can provide positive clinical effects with neither worsening RA activity nor causing pain. When dynamic exercise is compared with the conventional joint rehabilitation program, a significant increase in the quality of life of patients with RA is observed.[112–114]

Aerobic activities, such as bicycle riding, jogging, running, water aerobics, and swimming provide better cardiovascular

Table 2
Monitoring the treatment of rheumatoid arthritis

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.

conditioning and can aid to prevent RA-related limitation.[110] Physical means can be used as adjuncts to control pain, muscle contraction, and joint stiffness.[115–119]

Occupational therapy

Occupational therapy uses several techniques for joint protection and energy conservation. The treatment is aimed at reducing pain by planning stimulation activities, regular rest, joint motion pattern alternation, and use of orthoses and other devices.[120]

Adaptations in the household and work environment help to preserve the independence of individuals with RA-related limitations.[121]

Orthosis is any medical device applied to the patient's body to support, align, position, immobilize, prevent or correct deformities, help with muscle strength or improve joint function. Orthoses reduce pain and local inflammation by relieving tension and load on a certain joint.[121,122] The use of rest orthoses/braces, such as wrist brace, prevents flexion contractures. Functional wrist braces should be used intermittently during activities for movement restriction, aiming at joint protection.[123] Spinal orthoses are indicated to limit motion, especially flexion, with consequent reduction in pain, muscle tension and paresthesia in cases of atlantoaxial subluxation.[120]

Surgical treatment

Properly indicated surgical treatment contributes to improve function, mobility, pain control, and quality of life of patients with RA. The surgical procedures comprise the following: synovectomy, release of compressive neuropathies (carpal tunnel), tendon repair and transfer, total arthroplasty, and stabilization of cervical unstable vertebrae.[124,125]

Radiation synovectomy

Yttrium-90 (Y-90) or samarium-153 (Sm-153 PHYP) radiation synovectomy can be indicated, as an alternative to surgical synovectomy, for patients with residual synovitis in a few joints despite the optimization of other treatments instituted.[126]

Alternative therapies

Patients with chronic diseases, such as RA, frequently seek alternative therapies, and sometimes to the detriment of the traditional treatment. Those therapies include diets, meditation, biofeedback, acupuncture, massages, chiropractic, and homeopathy. Most of the time, scientific studies about the safety and efficacy of those treatments lack.[127]

Patients should be instructed to always consult with their physicians before beginning one of those therapies. It is up to the physician to assess whether the intended alternative treatment can harm the patient, and it is the physician's responsibility to instruct the patient that those methods should not replace the traditional therapy for RA.

Managing comorbidities

Comorbidities in patients with RA are frequent and comprise SAH, type 2 diabetes mellitus, dyslipidemia, and osteoporosis.[128–130] In addition, neoplasias, infections and lung diseases, such as bronchiectasis and interstitial pneumonitis, are also more prevalent in those patients.[131–134] The presence of those comorbidities contributes to poor quality of life and increases the mortality of patients with RA; thus, comorbidities should be diagnosed and treated in the initial phase of the disease.[135] The management of comorbidities will be reviewed in a specific recommendation by the BSR.

Treatment of the extra-articular manifestations of rheumatoid arthritis

The treatment of the majority of severe extra-articular manifestations of RA (rheumatoid vasculitis, scleritis, some histological subtypes of interstitial lung disease, recalcitrant serositis) includes systemic corticoids (oral or venous) and immunosuppressive drugs, such as CF, CS, and AZA.[136] Anecdotal evidence of clinical improvement of cases of rheumatoid vasculitis and lung involvement have been reported, but are conflicting and lack confirming studies.

Autologous cell transplantation

So far, conclusive data confirming the role of hematopoietic stem-cell transplantation as inductor of prolonged RA remission in the adult still lack.[137] Because the toxicity and mortality associated with the procedure are still significant, autologous cell transplantation in Brazil is reserved to severe forms, with multiple extra-articular manifestations, refractory to the treatments instituted and with risk of death.

PHARMACOECONOMICS' CONSIDERATIONS OF RHEUMATOID ARTHRITIS TREATMENT IN BRAZIL

The introduction of potent biologic DMARDs has widen the alternatives for the effective treatment of RA.[138] However, those drugs have substantially high costs as compared with those of traditional synthetic DMARDs, competing with the limited health resources in other essential interventions.

In general, the use of MTX, SSZ, and LEF in patients with active RA with no previous treatment with DMARDs has proved to be cost-effective as compared with the use of NSAIDs and corticoids in international studies.[139,140] However, the use of biologic therapy in monotherapy or in combination with MTX in those patients is not cost-effective as compared with MTX in monotherapy.[139]

After failing the first synthetic DMARD, the introduction of LEF can be a cost-effective strategy, because it delays the use of biologics.[141] Similar data can be found in the Brazilian literature. A study using an economic model with Markov's principle has reported that the use of MTX in monotherapy was the most cost-effective therapy in a 48-month period.[142]

When the treatment with anti-TNF agents fails, RTX[143] and ABAT[144] can be cost-effective. However, regarding the use of second and third anti-TNF agents, in that context, there are no randomized clinical trials providing cost-effectiveness analysis.

Regarding the reality of the Brazilian rheumatological practice, Ferraz et al.[145] have published the results of a questionnaire applied to Brazilian rheumatologists about the RA diagnosis and treatment. Those authors have reported that approximately 50% of the patients with RA are being properly diagnosed, and that only half of them are undergoing regular treatment. The therapeutic practice in public and private health care services has not varied markedly. At both types of health care services, the most commonly used combined therapy (two or more DMARDs) was the MTX + CQD association, followed by MTX + CQD + SSZ at the public service, and MTX + LEF at the private service. When those agents failed, the most used biologic agent was IFX, probably because it was the only therapeutic option in the Brazilian Unified Public Health Care System (SUS) during the period studied. The major difficulties identified in the patients' treatment were their access to the public health care system and the cost of the medication in the private system. Other challenging aspects for the proper management of patients with RA at national level are the regional differences in access to health care services, the heterogeneous distribution of rheumatologists in the Brazilian territory, and the few specialized services available.[146]

Pharmacoeconomic studies based on the Brazilian reality need to be developed to generate information that can rationally guide decision making in the treatment of patients with RA.

SPECIAL SITUATIONS

Rheumatoid arthritis and pregnancy

RA by itself does not alter fertility, although some medications can reduce the ovulation rate. In addition, neither fetal nor maternal complications due to RA are increased, except in the severe forms that evolve with systemic vasculitis.[147]

During the gestational period, the clinical manifestations of RA usually improve in up to 75% of the patients, although 90% relapse in the first six puerperal months.[147]

Most drugs used in the RA treatment are contraindicated during pregnancy and breast-feeding, except for HCQ and SSZ, which seem to be relatively safe.[148–150] Patients on MTX, LEF, immunosuppressive agents, and biologic DMARDs should be instructed to use safe contraceptive methods to prevent pregnancy.[150,151]

Rheumatoid arthritis and vaccination

The overall risk of infection is known to be increased in RA, particularly for patients on immunobiologic agents. Thus, the need for vaccinating those patients should be considered.[152–154] Before starting synthetic or biologic DMARDs, the patient's vaccination status should be assessed and updated.

Vaccines that do not contain living organisms, such as the following, can be safely administered, and preferably 14 days before starting medication: anti-influenza (IM), pneumococcal (7V and 23V), tetanus, diphtheria, pertussis, haemophilus influenzae type B, viral hepatitis A and B, poliomyelitis (inactive – IPV), meningococcal, HPV, typhoid fever (IM), and rabies. In a more systematic manner, most protocols recommend the administration of at least the following vaccines before starting

therapy with biologic DMARDs: influenza (seasonal, annually, from April to September) and pneumococcal (initially, and booster dose after five years).[154]

Vaccines containing living organisms are contraindicated during immunosuppression and at least for three months after using such drugs. That group of vaccines includes the following: MMR (measles, mumps and rubella), BCG, influenza (nasal), varicella-zoster, typhoid fever, poliomyelitis (oral – OPV), smallpox, and yellow fever.[154] However, some specific situations, such as the indication of the yellow fever vaccine for the population living in endemic areas of the disease, should be considered.[155,156]

It is worth noting that vaccines, when indicated, should be administered preferably before the treatment with immunosuppressive agents or biologic DMARDs, because the response to the vaccine might be decreased.[153]

The management of vaccination in patients with RA will be reviewed in a specific recommendation of the BSR.

Brazilian endemic diseases

Endemic-epidemic transmissible diseases, such as tuberculosis infection (TB), leprosy, malaria, Chagas' disease, schistosomiasis, yellow fever, dengue, filariasis, helminth infections, hepatitis B and hepatitis C, are still a relevant problem of public health in Brazil.[157]

Although there are few studies on the relationship between infectious-contagious endemicities and RA, it is worth considering that those conditions can affect both the diagnosis (sometimes mimicking,[5] other times superimposing to the joint and systemic symptoms of RA, in addition to the possible occurrence of serological markers, such as anti-CCP and RF, in infectious diseases[158]) and the management of RA. The use of immunosuppressive therapies, especially biologic DMARDs, should be carefully assessed in specific situations.[159]

Because of the high prevalence of TB in Brazil and the reports about TB reactivation during immunosuppressive treatment,[104,160–164] biologic DMARDs should be carefully used in patients with susceptibility to TB or previous history of TB. All patients should undergo chest radiography and tuberculin skin test (PPD) before starting therapy.[165] The risk is higher with the use of anti-TNF therapy, especially monoclonal antibodies.[166] Brazil lacks controlled studies on the cost-effectiveness of performing PPD in two steps to assess the "booster" phenomenon in patients with RA who will undergo biologic therapy. The PPD can be negative in patients with RA due to their underlying immune disorder or the used therapy.[167] Although *in vitro* interferon gamma release assays (IGRA), such as Quantiferon® or Elispot®, are promissing,[168–170] because they are more specific, their role in investigating latent TB in Brazil is yet to be defined.[168–171]

The use of chest high resolution computed tomography to investigate latent TB should be assessed in each case. The treatment of latent TB forms with isoniazid at the dose of 5–10 mg/kg/day up to the maximum dose of 300 mg/day, for six months, should be performed in patients with the following characteristics: PPD reading ≥ 5 mm (or positive IGRA), radiological changes compatible with previous TB, or in patients that have had close contact with individuals with active TB.[165,172–174] The treatment of latent TB forms should be initiated at least one month before starting the biologic DMARD. Exceptionally, however, their beginning can be concomitant, when the inflammatory disease activity requires urgency in introducing the biologic therapy. Although, so far, studies have not shown an increase in the occurrence of TB cases with the use of non-anti-TNF biologic DMARDs, screening for latent infection is recommended.

In addition to HIV, viral hepatitis B and viral hepatitis C should be investigated prior to the use of biologic DMARDs. If those viral infections are present, biologic DMARDs should be avoided. In exceptional cases of infection by hepatitis C virus, biologic DMARDs can be used associated with the antiviral treatment.[175,176]

Specific infections, such as Chagas' disease, should be investigated in endemic regions. In addition, routine dental assessment and care are recommended before and during treatment, for the prevention and treatment of periodontal infections.[177]

BSR RECOMMENDATIONS FOR TREATING RHEUMATOID ARTHRITIS

Based on the above considerations and on the peculiar aspects of the Brazilian socioeconomic reality, the expert members of the Rheumatoid Arthritis Committee of the Brazilian Society of Rheumatology have proposed the recommendations summarized in Table 3 for treating patients diagnosed with RA.

Table 3
Recommendations of the Brazilian Society of Rheumatology for the treatment of rheumatoid arthritis

Recommendation 1: Before any type of treatment, patients should be instructed about their disease, and, particularly, about the possible evolution and prognosis. The treatment decision should be shared with patients.
Recommendation 2: Immediately after the diagnosis, a DMARD should be prescribed and the treatment should be adjusted aiming at achieving remission or low disease activity (according to CIDA) at frequent clinical assessments, within 30–90 days.
Recommendation 3: The treatment for RA should be conducted by a rheumatologist, who is the specialist with the greatest knowledge about the therapeutic options available, their indications and adverse effects.
Recommendation 4: The first-line treatment comprises synthetic DMARDs, such as MTX, LEF, and SSZ. The antimalarials HCQ and CQD are less effective and should be reserved for mild disease forms and with low erosive potential. CS or parenteral gold can be used on exceptional conditions.
Recommendation 5: MTX is the drug of choice for treating RA, but, if contraindicated and/or at the physician's discretion, other synthetic DMARDs can be used as first choice. Combinations of synthetic DMARDs can be prescribed, even as the first option, for established RA with predictors of poor prognosis.
Recommendation 6: Patients who failed to achieve a response, characterized as clinical remission or at least low disease activity (according to assessment by use of one of the CIDA) after at least two schemes of synthetic DMARDs, including at least one combination of synthetic DMARDs, should be assessed regarding the use of biologic DMARDs.
Recommendation 7: Exceptionally, for patients combining characteristics of worse prognosis and rapidly progressive disease, biologic DMARDs can be considered after one single scheme of synthetic DMARDs.
Recommendation 8: The use of anti-TNF agents (ADA, CERT, ETN, IFX, or GOL) is preferentially recommended as initial biologic therapy. However, in the presence of contraindications or in certain clinical situations, biologic therapy can be initiated with other biologic DMARDs, such as B lymphocyte depletion agents (RTX), T lymphocyte costimulation modulators (ABAT), and antibodies against the IL-6 receptor (TOCI).
Recommendation 9: After therapeutic failure to respond to the first biologic DMARD (anti-TNF or not), other biologic DMARDs (anti-TNF or not) can be used. It is up to the physician to choose the biologic DMARD to be used in patients who failed to respond to a biologic DMARD.
Recommendation 10: CF and AZA can be used in patients with severe extra-articular manifestations, such as vasculitis and/or lung involvement.
Recommendation 11: The intra-articular use of a corticoid is useful at any time during treatment. The oral use of a corticoid has a DMARD effect and improves the clinical response at the initial phase, but it should be used at low doses (< 15 mg/day of prednisone or equivalent) and for the shortest period of time necessary.
Recommendation 12: NSAIDs are useful to reduce the inflammatory process and pain, mainly at the initial phase of disease, but should always be prescribed in association with a DMARD.
Recommendation 13: At the beginning of the RA treatment, the patient should be preferably assessed monthly. Patients whose disease is under control can be assessed at longer intervals of up to three months.
Recommendation 14: Physical therapy, rehabilitation and occupational therapy are indicated from the patient's initial assessment onwards.
Recommendation 15: Surgical treatment, when properly and opportunely indicated, contributes to improve the function, motion, pain control, and quality of life of patients with RA.
Recommendation 16: It is recommended that patients be instructed to always consult with their physician before starting an alternative therapy (acupuncture, diet therapy, homeopathy, phytotherapy). The physician should assess whether the intended alternative treatment can induce any damage to the patient and instruct him/her not to replace traditional therapy for RA with the alternative therapy.
Recommendation 17: Patients should be educated regarding family planning, adequate time for pregnancy (based on disease activity and use of medications), and effective contraceptive methods for women on teratogenic drugs, such as MTX and LEF.
Recommendation 18: The active search for and adequate management of comorbidities (SAH, diabetes mellitus, dyslipidemia) should be performed, because comorbidities contribute to decrease the quality of life and increase the mortality of patients with RA.
Recommendation 19: Before initiating synthetic or biologic DMARDs, the patient's vaccination chart should be assessed, and the indicated vaccines should be administered, preferably prior to treatment with immunosuppressors or biologic agents, because the response to vaccine can be reduced.
Recommendation 20: Endemic-epidemic transmissible diseases in Brazil, such as tuberculosis infection, leprosy, malaria, Chagas' disease, schistosomiasis, yellow fever, dengue, filariasis, and helminth infections, should be assessed and properly treated in patients with RA.

CONCLUSIONS

This consensus aimed at elaborating recommendations for the treatment of RA in Brazil, considering the characteristics of the country, such as drug availability, socioeconomic level of the population, pharmacoeconomic aspects, and the occurrence of several endemic diseases.

Despite the recent publication of the North-American and European guidelines for the treatment of RA, it is worth reviewing the subject, considering specific aspects of the Brazilian reality. Thus, the finality of establishing consensual guidelines for treating RA in Brazil is to support Brazilian rheumatologists, by using the evidence obtained in scientific studies and the experience of an expert committee to homogenize the therapeutic approach of RA, within the Brazilian socioeconomic context, maintaining the physician's autonomy to indicate/choose between the therapeutic alternatives available.

Because of the rapid advance of knowledge in this science field, we suggest these recommendations be updated every two years.

Conflicts of interest:

1. Has participated in clinical and/or experimental studies related to this consensus and sponsored by the pharmaceutical industry (PI) (Roche and Mantecorp); has received personal or institutional support from the PI (Abbott, AstraZeneca, MSD, Roche and Pfizer); has delivered speeches at events related to this consensus and sponsored by the PI (Abbott, AstraZeneca, Janssen, MSD, Mantecorp, Roche and Pfizer). Is a member of the Advisory Board for the PI or regulatory committees of scientific studies sponsored by the PI (AstraZeneca and MSD). Has elaborated scientific texts for periodicals sponsored by the PI (Abbott and Pfizer).
2. Has participated in clinical and/or experimental studies related to this consensus and sponsored by the PI (Roche); has received personal or institutional support from the PI (Abbott, BMS, Mantecorp, MSD, Novartis, Roche, Wyeth and Pfizer); has delivered speeches at events related to this consensus and sponsored by the PI (Abbott, MSD, Novartis, Roche and Wyeth).
3. Has participated in clinical and/or experimental studies related to this consensus and sponsored by the PI (BMS, Pfizer, Roche and Wyeth); has received personal or institutional support from the PI (Abbott, BMS, Mantecorp, MSD, Roche and Wyeth); has delivered speeches at events related to this consensus and sponsored by the PI (Abbott and Roche).
4. Has received personal or institutional support from the PI (Abbott, MSD, Janssen, Roche, BMS and Pfizer); has delivered speeches at events related to this consensus and sponsored by the PI (Abbott, MSD, Janssen, Roche, BMS and Pfizer). Is/was a member of the Advisory Board for the PI or regulatory committees of scientific studies sponsored by the PI (Pfizer, Abbott, MSD and BMS).
5. Has participated in clinical and/or experimental studies related to this consensus and sponsored by the PI (BMS, Pfizer and Roche); has received personal or institutional support from the PI (Abbott); has elaborated scientific texts for periodicals sponsored by the PI (Wyeth).
6. Has delivered speeches at events related to this consensus and sponsored by the PI (Abbott, Sanofi-Aventis and Pfizer).
7. Has received personal or institutional support from the PI (Abbott, MSD, Wyeth, Pfizer and Roche); has delivered speeches at events related to this consensus and sponsored by the PI (Abbott, MSD, Wyeth, Pfizer and Roche). Is/was a member of the Advisory Board for the PI or regulatory committees of scientific studies sponsored by the PI (Wyeth, MSD and AstraZeneca). Has elaborated scientific texts for periodicals sponsored by the PI (Abbott, Wyeth, BMS and AstraZeneca).
8. Has participated in clinical and/or experimental studies related to this consensus and sponsored by the PI (BMS and Roche); has received personal or institutional support from the PI (Roche, MSD, Wyeth/Pfizer and Abbott); has delivered speeches at events related to this consensus and sponsored by the PI (Roche, MSD, Janssen and Mantecorp).
9. The author declares no conflict of interest.
10. Has delivered speeches at events related to this consensus and sponsored by the PI (Roche and BMS). Is/was a member of the Advisory Board for the PI or regulatory committees of scientific studies sponsored by the FI (AstraZeneca).
11. Has participated in clinical and/or experimental studies related to this consensus and sponsored by the PI (Roche and Mantecorp); has received personal or institutional support from the PI (Lilly, Pfizer and Actelion); has delivered speeches at events related to this consensus and sponsored by the PI (Lilly, Pfizer and Actelion). Is/was a member of the Advisory Board for the PI or regulatory committees of scientific studies sponsored by the PI (MSD).
12. Has received personal or institutional support from the PI (Roche and Janssen-Cillag).

REFERENCES

REFERÊNCIAS

1. Alamanos Y, Voulgari PV, Drosos AA. Incidence and prevalence of rheumatoid arthritis, based on the 1987 American College of Rheumatology criteria: a systematic review. Semin Arthritis Rheum 2006; 36(3):182–8.
2. Marques-Neto JF, Gonçalves ET, Langen LFOB, Cunha MFL, Radominski S, Oliveira SM *et al*. Multicentric study of the prevalence of adult rheumatoid arthritis in Brazilian population samples. Rev Bras Reumatol 1993; 33:169–73.
3. Verstappen SM, van Albada-Kuipers GA, Bijlsma JW, Blaauw AA, Schenk Y, Haanen HC *et al*. A good response to early DMARD treatment of patients with rheumatoid arthritis in the first year predicts remission during follow up. Ann Rheum Dis 2005; 64(1):38–43.
4. Chehata JC, Hassell AB, Clarke SA, Mattey DL, Jones MA, Jones PW *et al*. Mortality in rheumatoid arthritis: relationship to single and composite measures of disease activity. Rheumatology 2001; 40(4):447–52.
5. da Mota LM, Cruz BA, Brenol CV, Pereira IA, Fronza LS, Bertolo MB *et al*. 2011. Consensus of the Brazilian Society of Rheumatology for diagnosis and early assessment of rheumatoid arthritis. Rev Bras Reumatol 2011; 51(3):199–219.
6. de Azevedo AB, Ferraz MB, Ciconelli RM. Indirect costs of rheumatoid arthritis in Brazil. Value Health 2008; 11(5):869–77.
7. McInnes IB, O'Dell JR. State-of-the-art: rheumatoid arthritis. Ann Rheum Dis 2010; 69(11):1898–906.

8. Klarenbeek NB, Kerstens PJ, Huizinga TW, Dijkmans BA, Allaart CF. Recent advances in the management of rheumatoid arthritis. BMJ 2010; 341:c6942.
9. Abourazzak F, El Mansouri L, Huchet D, Lozac'hmeur R, Hajjaj-Hassouni N, Ingels A *et al*. A. Long-term effects of therapeutic education for patients with rheumatoid arthritis. Joint Bone Spine 2009; 76(6):648–53.
10. Lovisi Neto BE, Jennings F, Barros Ohashi C, Silva PG, Natour J. Evaluation of the efficacy of an educational program for rheumatoid arthritis patients. Clin Exp Rheumatol 2009; 27(1):28–34.
11. Masiero S, Boniolo A, Wassermann L, Machiedo H, Volante D, Punzi L. Effects of an educational-behavioral joint protection program on people with moderate to severe rheumatoid arthritis: a randomized controlled trial. Clin Rheumatol 2007; 26(12):2043–50.
12. Niedermann K, de Bie RA, Kubli R, Ciurea A, Steurer-Stey C, Villiger PM *et al*. Effectiveness of individual resource-oriented joint protection education in people with rheumatoid arthritis. A randomized controlled trial. Patient Educ Couns 201; 82(1):42–8.
13. Lineker SC, Bell MJ, Badley EM. Evaluation of an inter-professional educational intervention to improve the use of arthritis best practices in primary care. J Rheumatol 2011; 38(5):931–7.
14. American College of Rheumatology Subcommittee on Rheumatoid Arthritis Guidelines. Guidelines for the management of rheumatoid arthritis: 2002 Update. Arthritis Rheum 2002; 46(2):328–46.
15. Katchamart W, Johnson S, Lin HJ, Phumethum V, Salliot C, Bombardier C. Predictors for remission in rheumatoid arthritis patients: A systematic review. Arthritis Care Res (Hoboken) 2010; 62(8):1128–43.
16. Ferraz-Amaro I, Machín S, Carmona L, González-Alvaro I, Díaz-González F; EMECAR study group. Pattern of use and safety of non-steroidal anti-inflammatory drugs in rheumatoid arthritis patients. A prospective analysis from clinical practice. Reumatol Clin 2009; 5(6):252–8.
17. Solomon DH, Rassen JA, Glynn RJ, Lee J, Levin R, Schneeweiss S. The comparative safety of analgesics in older adults with arthritis. Arch Intern Med 2010; 170(22):1968–76. [Erratum in: Arch Intern Med 2011; 171(5):403]
18. Chen YF, Jobanputra P, Barton P, Bryan S, Fry-Smith A, Harris G *et al*. Cyclooxygenase-2 selective non-steroidal anti-inflammatory drugs (etodolac, meloxicam, celecoxib, rofecoxib, etoricoxib, valdecoxib and lumiracoxib) for osteoarthritis and rheumatoid arthritis: a systematic review and economic evaluation. Health Technol Assess 2008; 12(11):1–278, iii.
19. van Everdingen AA, Jacobs JW, Siewertsz Van Reesema DR, Bijlsma JW. Low-dose prednisone therapy for patients with early rheumatoid arthritis: clinical efficacy, disease-modifying properties, and side effects: a randomized, double-blind, placebo-controlled clinical trial. Ann Intern Med 2002; 136(1):1–12.
20. Smolen JS, Landewé R, Breedveld FC, Dougados M, Emery P, Gaujoux-Viala C *et al*. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs. Ann Rheum Dis 2010; 69(6):964–75. [Erratum in: Ann Rheum Dis 2011; 70(8):1519]
21. Hoes JN, Jacobs JW, Verstappen SM, Bijlsma JW, Van der Heijden GJ. Adverse events of low- to medium-dose oral glucocorticoids in inflammatory diseases: a meta-analysis. Ann Rheum Dis 2009; 68(12):1833–8.
22. Dernis E, Ruyssen-Witrand A, Mouterde G, Maillefert JF, Tebib J, Cantagrel A *et al*. Use of glucocorticoids in rheumatoid arthritis – pratical modalities of glucocorticoid therapy: recommendations for clinical practice based on data from the literature and expert opinion. Joint Bone Spine 2010; 77(5):451–7.
23. Furst DE, Pangan AL, Harrold LR, Chang H, Reed G, Kremer JM *et al*. Greater likelihood of remission in rheumatoid arthritis patients treated earlier in the disease course: results from the Consortium of Rheumatology Researchers of North America registry. Arthritis Care Res (Hoboken) 2011; 63(6):856–64.
24. Lukas C, Combe B, Ravaud P, Sibilia J, Landew R, van der Heijde D. Favorable effect of very early disease-modifying antirheumatic drug treatment on radiographic progression in early inflammatory arthritis: Data from the Étude et Suivi des polyarthrites indifférenciées récentes (study and followup of early undifferentiated polyarthritis). Arthritis Rheum 2011; 63(7):1804–11.
25. Cronstein B. How does methotrexate suppress inflammation? Clin Exp Rheumatol 2010; 28(5 Suppl 61):S21–3.
26. Pincus T, Cronstein B, Braun J. Methotrexate – the anchor drug – an introduction. Clin Exp Rheumatol 2010; 28(5 Suppl 61):S1–2.
27. O'Dell JR, Haire CE, Erikson N, Drymalski W, Palmer W, Eckhoff PJ *et al*. Treatment of rheumatoid arthritis with methotrexate alone, sulfasalazine and hydroxychloroquine, or a combination of all three medications. N Engl J Med 1996; 334(20):1287–91.
28. Pereira IA, Cruz BA, Xavier RM, Pinheiro GRC, Titton DC, Giorgi RDN *et al*. National recommendations based on scientific evidence and opinions of experts on the use of methotrexate in rheumatic disorders, especially in rheumatoid arthritis: results of the 3E Initiative from Brazil. Rev Bras Reumatol 2009; 49(4):346–61.
29. Williams HJ, Ward JR, Dahl SL, Clegg DO, Willkens RF, Oglesby T *et al*. A controlled trial comparing sulfasalazine, gold sodium thiomalate, and placebo in rheumatoid arthritis. Arthritis Rheum 1988; 31(6):702–13.
30. Boers M, Verhoeven AC, Markusse HM, van de Laar MA, Westhovens R, van Denderen JC *et al*. Randomised comparison of combined step-down prednisolone, methotrexate and sulphasalazine with sulphasalazine alone in early rheumatoid arthritis. Lancet 1997; 350(9074):309–18. [Erratum in: Lancet 1998; 351(9097):220]
31. Rozman B. Clinical pharmacokinetics of leflunomide. Clin Pharmacokinet 2002; 41(6):421–30.
32. Scott DL, Smolen JS, Kalden JR, van de Putte LB, Larsen A, Kvien TK *et al*., European Leflunomide Study Group. Treatment of active rheumatoid arthritis with leflunomide: two year follow up of a double blind, placebo controlled trial versus sulfasalazine. Ann Rheum Dis 2001; 60(10):913–23.
33. Kalden JR, Scott DL, Smolen JS, Schattenkirchner M, Rozman B, Williams BD *et al*., European Leflunomide Study Group. Improved functional ability in patients with rheumatoid arthritis: longterm treatment with leflunomide versus sulfasalazina. European Leflunomide Study Group. J Rheumatol 2001; 28(9):1983–91.
34. Clark P, Casas E, Tugwell P, Medina C, Gheno C, Tenorio G *et al*. Hydroxychloroquine compared with placebo in rheumatoid arthritis. A randomized controlled trial. Ann Intern Med 1993; 119(11):1067–71.
35. A randomized trial of hydroxychloroquine in early rheumatoid arthritis: the HERA study. Am J Med 1995; 98(2):156–68.

36. Marmor MF, Kellner U, Lai TY, Lyons JS, Mieler WF; American Academy of Ophthalmology. Revised recommendations on screening for chloroquine and hydroxychloroquine retinopathy. Ophthalmology 2011; 118(2):415–22.
37. Suarez-Almazor ME, Belseck E, Shea B, Homik J, Wells G, Tugwell P. Antimalarials for treating rheumatoid arthritis. Cochrane Database Syst Rev 2000; (4):CD000959.
38. Rau R, Herborn G, Menninger H, Sangha O. Radiographic outcome after three years of patients with early erosive rheumatoid arthritis treated with intramuscular methotrexate or parenteral gold. Extension of a one-year double-blind study in 174 patients. Rheumatology (Oxford) 2002; 41(2):196–204.
39. Lehman AJ, Esdaile JM, Klinkhoff AV, Grant E, Fitzgerald A, Canvin J; METGO Study Group. A 48-week, randomized, double-blind, double-observer, placebo-controlled multicenter trial of combination methotrexate and intramuscular gold therapy in rheumatoid arthritis: results of the METGO study. Arthritis Rheum 2005; 52(5):1360–70.
40. Caporali R, Conti F, Alivernini S, Atzeni F, Seriolo B, Cutolo M *et al*. Recommendations for the use of biologic therapy in rheumatoid arthritis: update from the Italian Society for Rheumatology I. Efficacy. Clin Exp Rheumatol 2011; 29(3 Suppl 66):S7–14.
41. Favalli EG, Caporali R, Sinigaglia L, Pipitone N, Miniati I, Montecucco C *et al*. Recommendations for the use of biologic therapy in rheumatoid arthritis: update from the Italian Society for Rheumatology II. Safety. Clin Exp Rheumatol 2011; 29(3 Suppl 66):S15–27.
42. Agênica Nacioanl de Vigilância Sanitária (ANVISA). Available from: http://portal.anvisa.gov.br/wps/portal/anvisa. [Acessed on November 2, 2011]
43. Markatseli TE, Papagoras C, Drosos AA. Prognostic factors for erosive rheumatoid arthritis. Clin Exp Rheumatol 2010; 28(1):114–23.
44. Visser K, Goekoop-Ruiterman YP, de Vries-Bouwstra JK, Ronday HK, Seys PE, Kerstens PJ *et al*. A matrix risk model for the prediction of rapid radiographic progression in patients with rheumatoid arthritis receiving different dynamic treatment strategies: post hoc analyses from the BeSt study. Ann Rheum Dis 2010; 69(7):1333–7.
45. Smolen JS, Aletaha D, Bijlsma JW, Breedveld FC, Boumpas D, Burmester G *et al*. Treating rheumatoid arthritis to target: recommendations of an international task force. Ann Rheum Dis 2010; 69(4):631–7.
46. Visser K, Katchamart W, Loza E, Martinez-Lopez JA, Salliot C, Trudeau J *et al*. Multinational evidence-based recommendations for the use of methotrexate in rheumatic disorders with a focus on rheumatoid arthritis: integrating systematic literature research and expert opinion of a broad international panel of rheumatologists in the 3E Initiative. Ann Rheum Dis 2009; 68(7):1086–93.
47. Momohara S, Inoue E, Ikari K, Yano K, Tokita A, Honjo Y *et al*. Comparison of characteristics and therapeutic efficacy in rheumatoid arthritis patients treated by rheumatologists and those treated by orthopedic surgeons under a team medicine approach at the same institute. Mod Rheumatol 2011 Jul 15. [Epub ahead of print]
48. Genovese MC, Cohen S, Moreland L, Lium D, Robbins S, Newmark R *et al*. Combination therapy with etanercept and anakinra in the treatment of patients with rheumatoid arthritis who have been treated unsuccessfully with methotrexate. Arthritis Rheum 2004; 50(5):1412–9.
49. Weinblatt M, Combe B, Covucci A, Aranda R, Becker JC, Keystone E. Safety of the selective costimulation modulator abatacept in rheumatoid arthritis patients receiving background biologic and nonbiologic disease-modifying antirheumatic drugs: A one-year randomized, placebo-controlled study. Arthritis Rheum 2006; 54(9):2807–16.
50. Kiely PD, Brown AK, Edwards CJ, O'Reilly DT, Ostör AJ, Quinn M *et al*. Contemporary treatment principles for early rheumatoid arthritis: a consensus statement. Rheumatology (Oxford) 2009; 48(7):765–72.
51. Hochberg MC, Tracy JK, Hawkins-Holt M, Flores RH. Comparison of the efficacy of the tumour necrosis factor alphablocking agents adalimumab, etanercept, and infliximab when added to methotrexate in patients with active rheumatoid arthritis. Ann Rheum Dis 2003; 62(suppl2):ii13–6.
52. Hetland ML, Christensen IJ, Tarp U, Dreyer L, Hansen A, Hansen IT *et al*. Direct comparison of treatment responses, remission rates, and drug adherence in patients with rheumatoid arthritis treated with adalimumab, etanercept, or infliximab: results from eight years of surveillance of clinical practice in the nationwide Danish DANBIO registry. Arthritis Rheum 2010; 62(1):22–32.
53. Goekoop-Ruiterman YP, de Vries-Bouwstra JK, Allaart CF, van Zeben D, Kerstens PJ, Hazes JM *et al*. Clinical and radiographic outcomes of four different treatment strategies in patients with early rheumatoid arthritis (the BeSt study): a randomized, controlled trial. Arthritis Rheum 2005; 52(11):3381–90.
54. van der Kooij SM, le Cessie S, Goekoop-Ruiterman YP, de Vries-Bouwstra JK, van Zeben D, Kerstens PJ *et al*. Clinical and radiological efficacy of initial vs delayed treatment with infliximab plus methotrexate in patients with early rheumatoid arthritis. Ann Rheum Dis 2009; 68(7):1153–8.
55. Breedveld FC, Weisman MH, Kavanaugh AF, Cohen SB, Pavelka K, van Vollenhoven R *et al*. The PREMIER study: A multicenter, randomized, double-blind clinical trial of combination therapy with adalimumab plus methotrexate versus methotrexate alone or adalimumab alone in patients with early, aggressive rheumatoid arthritis who had not had previous methotrexate treatment. Arthritis Rheum 2006; 54(1):26–37.
56. Emery P, Genovese MC, van Vollenhoven R, Sharp JT, Patra K, Sasso EH. Less radiographic progression with adalimumab plus methotrexate versus methotrexate monotherapy across the spectrum of clinical response in early rheumatoid arthritis. J Rheumatol 2009; 36(7):1429–41.
57. Emery P, Breedveld F, van der Heijde D, Ferraccioli G, Dougados M, Robertson D *et al*. Combination of Methotrexate and Etanercept in Early Rheumatoid Arthritis Trial Group. Two-year clinical and radiographic results with combination etanercept-methotrexate therapy versus monotherapy in early rheumatoid arthritis: a two-year, double-blind, randomized study. Arthritis Rheum 2010; 62(3):674–82.
58. Kekow J, Moots RJ, Emery P, Durez P, Koenig A, Singh A *et al*. Patient-reported outcomes improve with etanercept plus methotrexate in active early rheumatoid arthritis and the improvement is strongly associated with remission: the COMET trial. Ann Rheum Dis 2010; 69(1):222–5.
59. Smolen JS, Han C, van der Heijde DM, Emery P, Bathon JM, Keystone E *et al*.; Active-Controlled Study of Patients Receiving Infliximab for the Treatment of Rheumatoid Arthritis of Early Onset (ASPIRE) Study Group. Radiographic changes in rheumatoid arthritis patients attaining different disease activity states with methotrexate monotherapy and infliximab plus methotrexate: the impacts of remission and tumour necrosis factor blockade. Ann Rheum Dis 2009; 68(6):823–7.

60. Emery P, Fleischmann RM, Moreland LW, Hsia EC, Strusberg I, Durez P *et al*. Golimumab, a human anti-tumor necrosis factor alpha monoclonal antibody, injected subcutaneously every four weeks in methotrexate-naive patients with active rheumatoid arthritis: twenty-four-week results of a phase III, multicenter, randomized, double-blind, placebo-controlled study of golimumab before methotrexate as first-line therapy for early-onset rheumatoid arthritis. Arthritis Rheum 2009; 60(8):2272–83.
61. Strand V, Mease P, Burmester GR, Nikaï E, Coteur G, van Vollenhoven R *et al*. Rapid and sustained improvements in health-related quality of life, fatigue, and other patient-reported outcomes in rheumatoid arthritis patients treated with certolizumab pegol plus methotrexate over 1 year: results from the RAPID 1 randomized controlled trial. Arthritis Res Ther 2009; 11(6):R170.
62. Smolen J, Landewé RB, Mease P, Brzezicki J, Mason D, Luijtens K *et al*. Efficacy and safety of certolizumab pegol plus methotrexate in active rheumatoid arthritis: the RAPID 2 study. A randomised controlled trial. Ann Rheum Dis 2009; 68(6):797–804.
63. van Vollenhoven RF, Ernestam S, Geborek P, Petersson IF, Cöster L, Waltbrand E *et al*. Addition of infliximab compared with addition of sulfasalazine and hydroxychloroquine to methotrexate in patients with early rheumatoid arthritis (Swefot trial): 1-year results of a randomised trial. Lancet 2009; 374(9688):459–66.
64. Bejarano V, Quinn M, Conaghan PG, Reece R, Keenan AM, Walker D *et al*. Effect of the early use of the anti-tumor necrosis factor adalimumab on the prevention of job loss in patients with early rheumatoid arthritis. Arthritis Rheum 2008; 59(10):1467–74.
65. Kimel M, Cifaldi M, Chen N, Revicki D. Adalimumab plus methotrexate improved SF-36 scores and reduced the effect of rheumatoid arthritis (RA) on work activity for patients with early RA. J Rheumatol 2008; 35(2):206–15.
66. van Vollenhoven RF, Cifaldi MA, Ray S, Chen N, Weisman MH. Improvement in work place and household productivity for patients with early rheumatoid arthritis treated with adalimumab plus methotrexate: work outcomes and their correlations with clinical and radiographic measures from a randomized controlled trial companion study. Arthritis Care Res (Hoboken) 2010; 62(2):226–34.
67. Furst DE, Schiff MH, Fleischmann RM, Strand V, Birbara CA, Compagnone D *et al*. Adalimumab, a fully human anti tumor necrosis factor-alpha monoclonal antibody, and concomitant standard antirheumatic therapy for the treatment of rheumatoid arthritis: results of STAR (Safety Trial of Adalimumab in Rheumatoid Arthritis). J Rheumatol 2003; 30(12):2563–71.
68. Nam JL, Winthrop KL, van Vollenhoven RF, Pavelka K, Valesini G, Hensor EM *et al*. Current evidence for the management of rheumatoid arthritis with biological disease-modifying anti-rheumatic drugs: a systematic literature review informing the EULAR recommendations for the management of RA. Ann Rheum Dis 2010; 69(6):976–86.
69. Kavanaugh A, Smolen JS, Emery P, Purcaru O, Keystone E, Richard L *et al*. Effect of certolizumab pegol with methotrexate on home and work place productivity and social activities in patients with active rheumatoid arthritis. Arthritis Rheum 2009; 61(11):1592–600.
70. Genovese MC, Bathon JM, Martin RW, Fleischmann RM, Tesser JR, Schiff MH *et al*. Etanercept versus methotrexate in patients with early rheumatoid arthritis: two-year radiographic and clinical outcomes. Arthritis Rheum 2002; 46(6):1443–50.
71. Maini R, St Clair EW, Breedveld F, Furst D, Kalden J, Weisman M *et al*. Infliximab (chimeric anti-tumour necrosis factor alpha monoclonal antibody) versus placebo in rheumatoid arthritis patients receiving concomitant methotrexate: a randomised phase III trial. ATTRACT Study Group. Lancet 1999; 354(9194):1932–9.
72. Keystone E, Genovese MC, Klareskog L, Hsia EC, Hall S, Miranda PC *et al*. Golimumab in patients with active rheumatoid arthritis despite methotrexate therapy: 52-week results of the GO-FORWARD study. Ann Rheum Dis 2010; 69(6):1129–35.
73. Singh JA, Wells GA, Christensen R, Tanjong Ghogomu E, Maxwell L, Macdonald JK *et al*. Adverse effects of biologics: a network meta-analysis and Cochrane overview. Cochrane Database Syst Rev 2011; (2):CD008794.
74. Curtis JR, Patkar N, Xie A, Martin C, Allison JJ, Saag M *et al*. Risk of serious bacterial infections among rheumatoid arthritis patients exposed to tumor necrosis factor alpha antagonists. Arthritis Rheum 2007; 56(4):1125–33.
75. Dixon WG, Symmons DP, Lunt M, Watson KD, Hyrich KL; British Society for Rheumatology Biologics Register Control Centre Consortium *et al*. Serious infection following anti-tumor necrosis factor alpha therapy in patients with rheumatoid arthritis: lessons from interpreting data from observational studies. Arthritis Rheum 2007; 56(9):2896–904.
76. Radstake TR, Svenson M, Eijsbouts AM, van den Hoogen FH, Enevold C, van Riel PL *et al*. Formation of antibodies against infliximab and adalimumab strongly correlates with functional drug levels and clinical responses in rheumatoid arthritis. Ann Rheum Dis 2009; 68(11):1739–45.
77. Bartelds GM, Wijbrandts CA, Nurmohamed MT, Stapel S, Lems WF, Aarden L *et al*. Anti-infliximab and anti-adalimumab antibodies in relation to response to adalimumab in infliximab switchers and anti-tumour necrosis factor naive patients: a cohort study. Ann Rheum Dis 2010; 69(5):817–21.
78. Maxwell LJ, Singh JA. Abatacept for rheumatoid arthritis: a Cochrane systematic review. J Rheumatol 2010; 37(2):234–45.
79. Westhovens R, Robles M, Ximenes AC, Nayiager S, Wollenhaupt J, Durez P *et al*. Clinical efficacy and safety of abatacept in methotrexate-naive patients with early rheumatoid arthritis and poor prognostic factors. Ann Rheum Dis 2009; 68(12):1870–7.
80. Bathon J, Robles M, Ximenes AC, Nayiager S, Wollenhaupt J, Durez P *et al*. Sustained disease remission and inhibition of radiographic progression in methotrexate-naïve patients with rheumatoid arthritis and poor prognostic factors treated with abatacept: 2-year outcomes. Ann Rheum Dis 2011; 70(11):1949–56.
81. Miller KL, Sawitzke AD, Doane J. Abatacept and serious respiratory infections in patients with previous lung disease. Clin Rheumatol 2008; 27(12):1569–71.
82. Cohen SB, Emery P, Greenwald MW, Dougados M, Furie RA, Genovese MC *et al*. Rituximab for rheumatoid arthritis refractory to anti-tumor necrosis factor therapy: Results of a multicenter, randomized, double-blind, placebo-controlled, phase III trial evaluating primary efficacy and safety at twenty-four weeks. Arthritis Rheum 2006; 54(9):2793–806.
83. Emery P, Deodhar A, Rigby WF, Isaacs JD, Combe B, Racewicz AJ *et al*. Efficacy and safety of different doses and retreatment of rituximab: a randomised, placebo-controlled trial in patients who are biological naive with active rheumatoid arthritis and an inadequate response to methotrexate (Study Evaluating Rituximab's Efficacy in MTX iNadequate rEsponders (SERENE)). Ann Rheum Dis 2010; 69(9):1629–35.

84. Keystone E, Emery P, Peterfy CG, Tak PP, Cohen S, Genovese MC *et al*. Rituximab inhibits structural joint damage in patients with rheumatoid arthritis with an inadequate response to tumour necrosis factor inhibitor therapies. Ann Rheum Dis 2009; 68(2):216–21.
85. Popa C, Leandro MJ, Cambridge G, Edwards JC. Repeated B lymphocyte depletion with rituximab in rheumatoid arthritis over 7 years. Rheumatology (Oxford) 2007; 46(4):626–30.
86. Chatzidionysiou K, Lie E, Nasonov E, Lukina G, Hetland ML, Tarp U *et al*. Highest clinical effectiveness of rituximab in autoantibody-positive patients with rheumatoid arthritis and in those for whom no more than one previous TNF antagonist has failed: pooled data from 10 European registries. Ann Rheum Dis 2011; 70(9):1575–80.
87. Jones G, Sebba A, Gu J, Lowenstein MB, Calvo A, Gomez-Reino JJ *et al*. Comparison of tocilizumab monotherapy versus methotrexate monotherapy in patients with moderate to severe rheumatoid arthritis: the AMBITION study. Ann Rheum Dis 2010; 69(1):88–96.
88. Campbell L, Chen C, Bhagat SS, Parker RA, Östör AJ. Risk of adverse events including serious infections in rheumatoid arthritis patients treated with tocilizumab: a systematic literature review and meta-analysis of randomized controlled trials. Rheumatology (Oxford) 2011; 50(3):552–62.
89. Singh JA, Beg S, Lopez-Olivo MA. Tocilizumab for rheumatoid arthritis: a Cochrane systematic review. J Rheumatol 2011; 38(1):10–20.
90. Gout T, Östör AJ, Nisar MK. Lower gastrointestinal perforation in rheumatoid arthritis patients treated with conventional DMARDs or tocilizumab: a systematic literature review. Clin Rheumatol 2011; 30(11):1471–4.
91. Suarez-Almazor ME, Spooner C, Belseck E. Azathioprine for treating rheumatoid arthritis. Cochrane Database Syst Rev 2000; (4):CD001461.
92. Suarez-Almazor ME, Belseck E, Shea B, Wells G, Tugwell P. Cyclophosphamide for treating rheumatoid arthritis. Cochrane Database Syst Rev 2000; (4):CD001157.
93. Wells G, Haguenauer D, Shea B, Suarez-Almazor ME, Welch VA, Tugwell P. Cyclosporine for rheumatoid arthritis. Cochrane Database Syst Rev 2000; (2):CD001083.
94. Stein CM, Pincus T, Yocum D, Tugwell P, Wells G, Gluck O *et al*. Combination treatment of severe rheumatoid arthritis with cyclosporine and methotrexate for forty-eight weeks: an open-label extension study. The Methotrexate-Cyclosporine Combination Study Group. Arthritis Rheum1997; 40(10):1843–51.
95. Knevel R, Schoels M, Huizinga TW, Aletaha D, Burmester GR, Combe B *et al*. Current evidence for a strategic approach to the management of rheumatoid arthritis with disease-modifying anti-rheumatic drugs: a systematic literature review informing the EULAR recommendations for the management of rheumatoid arthritis. Ann Rheum Dis 2010; 69(6):987–94.
96. Katchamart W, Trudeau J, Phumethum V, Bombardier C. Methotrexate monotherapy versus methotrexate combination therapy with non-biologic disease modifying anti-rheumatic drugs for rheumatoid arthritis. Cochrane Database Syst Rev 201014; (4):CD008495.
97. Scott DL, Wolfe F, Huizinga TW. Rheumatoid arthritis. Lancet 2010; 376(9746):1094–108.
98. Suarez-Almazor ME, Belseck E, Shea B, Wells G, Tugwell P. Sulfasalazine for rheumatoid arthritis. Cochrane Database Syst Rev 2000; (2):CD000958.
99. Osiri M, Shea B, Robinson V, Suarez-Almazor M, Strand V, Tugwell P *et al*. Leflunomide for treating rheumatoid arthritis. Cochrane Database Syst Rev 2003; (1):CD002047.
100. Hamilton J, McInnes IB, Thomson EA, Porter D, Hunter JA, Madhok R *et al*. Comparative study of intramuscular gold and methotrexate in a rheumatoid arthritis population from a socially deprived area. Ann Rheum Dis 2001; 60(6):566–72.
101. van der Heijde DM, van Riel PL, Nuver-Zwart IH, van de Putte LB. Sulphasalazine versus hydroxychloroquine in rheumatoid arthritis: 3-year follow-up. Lancet 1990; 335(8688):539–53.
102. Svensson B, Boonen A, Albertsson K, van der Heijde D, Keller C, Hafström I. Low-dose prednisolone in addition to the initial disease-modifying antirheumatic drug in patients with early active rheumatoid arthritis reduces joint destruction and increases the remission rate: a two-year randomized trial. Arthritis Rheum 2005; 52(11):3360–70.54.
103. Kremer JM, Genovese MC, Cannon GW, Caldwell JR, Cush JJ, Furst DE *et al*. Concomitant leflunomide therapy in patients with active rheumatoid arthritis despite stable doses of methotrexate. A randomized, double-blind, placebo-controlled trial. Ann Intern Med 2002; 137(9):726–33.
104. Titton DC, Silveira IG, Louzada-Junior P, Hayata AL, Carvalho HM, Ranza R *et al*. Brazilian biologic registry: BiobadaBrasil implementation process and preliminary results. Rev Bras Reumatol 2011; 51(2):152–60.
105. Salliot C, Finckh A, Katchamart W, Lu Y, Sun Y, Bombardier C *et al*. Indirect comparisons of the efficacy of biological anti-rheumatic agents in rheumatoid arthritis in patients with an inadequate response to conventional disease-modifying anti-rheumatic drugs or to an anti-tumour necrosis factor agent: a meta-analysis. Ann Rheum Dis 2011; 70(2):266–71.
106. Malottki K, Barton P, Tsourapas A, Uthman AO, Liu Z, Routh K *et al*. Adalimumab, etanercept, infliximab, rituximab and abatacept for the treatment of rheumatoid arthritis after the failure of a tumour necrosis factor inhibitor: a systematic review and economic evaluation. Health Technol Assess 2011; 15(14):1–278.
107. O'Mahony R, Richards A, Deighton C, Scott D. Withdrawal of disease-modifying antirheumatic drugs in patients with rheumatoid arthritis: a systematic review and meta-analysis. Ann Rheum Dis 2010; 69(10):1823–6.
108. Grigor C, Capell H, Stirling A, McMahon AD, Lock P, Vallance R *et al*. Effect of a treatment strategy of tight control for rheumatoid arthritis (the TICORA study): a single-blind randomised controlled trial. Lancet 2004; 364(9430):263–9.
109. Deighton C, OMahony R, Tosh J, Turner C, Rudolf M. Guideline Development Group. Management of rheumatoid arthritis: summary of NICE guidance. BMJ 2009; 338:b702.
110. Vliet Vlieland TP. Rehabilitation of people with rheumatoid arthritis. Best Pract Res Clin Rheumatol 2003; 17(5):847–61.
111. Garber CE, Blissmer B, Deschenes MR, Franklin BA, Lamonte MJ, Lee IM *et al*. American College of Sports Medicine. American College of Sports Medicine position stand. Quantity and quality of exercise for developing and maintaining cardiorespiratory, musculoskeletal, and neuromotor fitness in apparently healthy adults: guidance for prescribing exercise. Med Sci Sports Exerc 2011; 43(7):1334–59.
112. Baillet A, Payraud E, Niderprim V-A, Nissen MJ, Allenet B, François P *et al*. A dynamic exercise program to improve patients' disability in rheumatoid arthritis: a prospective randomized controlled trial. Rheumatology 2009; 48(4):10–415.

113. de Jong Z, Munneke M, Zwinderman AH, Kroon HM, Jansen A, Ronday KH *et al*. Is a long-term high-intensity exercise program effective and safe in patients with rheumatoid arthritis? Results of a randomized controlled trial. Arthritis Rheum 2003; 48(9):2415–24.
114. Munneke M, de Jong Z, Zwinderman AH, Ronday HK, van Schaardenburg D, Dijkmans BA *et al*. Effect of a high-intensity weight-bearing exercise program on radiologic damage progression of the large joints in subgroups of patients with rheumatoid arthritis. Arthritis Rheum 2005; 53(3):410–7.
115. Robinson V, Brosseau L, Casimiro L, Judd M, Shea B, Wells G *et al*. Thermotherapy for treating rheumatoid arthritis. Cochrane Database Syst Rev 2002; (2):CD002826.
116. Brosseau LU, Pelland LU, Casimiro LY, Robinson VI, Tugwell PE, Wells GE. Electrical stimulation for the treatment of rheumatoid arthritis. Cochrane Database Syst Rev 2002; (2):CD003687.
117. Brosseau L, Judd MG, Marchand S, Robinson VA, Tugwell P, Wells G *et al*. Transcutaneous electrical nerve stimulation (TENS) for the treatment of rheumatoid arthritis in the hand. Cochrane Database Syst Rev 2003; (3):CD004377.
118. Brosseau L, Robinson V, Wells G, Debie R, Gam A, Harman K *et al*. Low level laser therapy (Classes I, II and III) for treating rheumatoid arthritis. Cochrane Database Syst Rev 2005; (4):CD002049.
119. Meireles SM, Jones A, Jennings F, Suda AL, Parizotto NA, Natour J. Assessment of the effectiveness of low-level laser therapy on the hands of patients with rheumatoid arthritis: a randomized double-blind controlled trial. Clin Rheumatol 2010; 29(5):501–9.
120. Vliet Vlieland TP, van den Ende CH. Nonpharmacological treatment of rheumatoid arthritis. Curr Opin Rheumatol 2011; 23(3):259–64.
121. Hand C, Law M, McColl MA. Occupational therapy interventions for chronic diseases: a scoping review. Am J Occup Ther 2011; 65(4):428–36.
122. Vliet Vlieland TP. Non-drug care for RA – is the era of evidence-based practice approaching? Rheumatology 2007; 46(9):1397–404.
123. Veehof MM, Taal E, Heijnsdijk-Rouwenhorst LM, van de Laar MA. Efficacy of wrist working splints in patients with rheumatoid arthritis: a randomized controlled study. Arthritis Rheum 2008; 59(12):1698–704.
124. Boonen A, Matricali GA, Verduyckt J, Taelman V, Verschueren P, Sileghem A *et al*. Orthopaedic surgery in patients with rheumatoid arthritis: a shift towards more frequent and earlier non-joint-sacrificing surgery. Ann Rheum Dis 2006; 65(5):694–5.
125. Kapetanovic MC, Lindqvist E, Saxne T, Eberhardt K. Orthopaedic surgery in patients with rheumatoid arthritis over 20 years: prevalence and predictive factors of large joint replacement. Ann Rheum Dis 2008; 67(10):1412–6.
126. Dos Santos MF, Furtado RN, Konai MS, Castiglioni ML, Marchetti RR, Silva CP *et al*. Effectiveness of radiation synovectomy with Yttrium-90 and Samarium-153 particulate hydroxyapatite in rheumatoid arthritis patients with knee synovitis: a controlled, randomized, double-blinded trial. Clin Rheumatol 2011; 30(1):77–85.
127. Macfarlane GJ, El-Metwally A, De Silva V, Ernst E, Dowds GL, Moots RJ; on behalf of the Arthritis Research UK Working Group on Complementary and Alternative Medicines. Evidence for the efficacy of complementary and alternative medicines in the management of rheumatoid arthritis: a systematic review. Rheumatology (Oxford) 2011; 50(9):1672–83.
128. Mazzantini M, Talarico R, Doveri M, Consensi A, Cazzato M, Bazzichi L *et al*. Incident comorbidity among patients with rheumatoid arthritis treated or not with low-dose glucocorticoids: a retrospective study. J Rheumatol 2010; 37(11):2232–6.
129. Myasoedova E, Davis JM 3rd, Crowson CS, Gabriel SE. Epidemiology of rheumatoid arthritis: rheumatoid arthritis and mortality. Curr Rheumatol Rep 2010; 12(5):379–85.
130. Nurmohamed MT. Atherogenic lipid profiles and its management in patients with rheumatoid arthritis. Vasc Health Risk Manag 2007; 3(6):845–52.
131. Smitten AL, Simon TA, Hochberg MC, Suissa S. A meta-analysis of the incidence of malignancy in adult patients with rheumatoid arthritis. Arthritis Res Ther 2008; 10(2):R45.
132. Geborek P, Jacobsson LT, Lindblad S, Lysholm J, Rantapää-Dahlqvist S, Saxne T *et al*. Risks of solid cancers in patients with rheumatoid arthritis and after treatment with tumour necrosis factor antagonists. Ann Rheum Dis 2005; 64(10):1421–6.
133. Mikuls TR. Co-morbidity in rheumatoid arthritis. Best Pract Res Clin Rheumatol 2003; 17:729–52.
134. Bongartz T, Nannini C, Medina-Velasquez YF, Achenbach SJ, Crowson CS, Ryu JH *et al*. Incidence and mortality of interstitial lung disease in rheumatoid arthritis: a population-based study. Arthritis Rheum 2010; 62(6):1583–91.
135. Sokka T, Abelson B, Pincus T. Mortality in rheumatoid arthritis: 2008 update. Clin Exp Rheumatol 2008; 26(5 Suppl 51):S35–61.
136. Mielants H, Van den Bosch F. Extra-articular manifestations. Clin Exp Rheumatol 2009; 27(4 Suppl 55):S56–61.
137. Szodoray P, Varoczy L, Szegedi G, Zeher M. Autologous stem cell transplantation in autoimmune and rheumatic diseases: from the molecular background to clinical applications. Scand J Rheumatol 2010; 39(1):1–11.
138. Kobelt G. Health economic issues in rheumatoid arthritis. Scand J Rheumatol 2006; 35(6):415–25.
139. Schoels M, Wong J, Scott DL, Zink A, Richards P, Landewé R *et al*. Economic aspects of treatment options in rheumatoid arthritis: a systematic literature review informing the EULAR recommendations for the management of rheumatoid arthritis. Ann Rheum Dis 2010; 69(6):995–1003.
140. Finckh A, Bansback N, Marra CA, Anis AH, Michaud K, Lubin S *et al*. Treatment of very early rheumatoid arthritis with symptomatic therapy, disease-modifying anti-rheumatic drugs, or biologic agents: a cost-effectiveness analysis. Ann Intern Med 2009; 151(9):612–21.
141. Welsing PM, Severens JL, Hartman M, van Riel PL, Laan RF. Modeling the 5-year cost effectiveness of treatment strategies including tumor necrosis factor-blocking agents and leflunomide for treating rheumatoid arthritis in the Netherlands. Arthritis Rheum 2004; 51(6):964–73.
142. Monteiro RDC, Zanini AC. Cost analysis of drug therapy in rheumatoid arthritis. Revista Brasileira de Ciências Farmacêuticas 2008; 44(1):25–33.
143. Kielhorn A, Porter D, Diamantopoulos A, Lewis G. UK cost-utility analysis of rituximab in patients with rheumatoid arthritis that failed to respond adequately to a biologic disease-modifying anti-rheumatic drug. Curr Med Res Opin 2008; 24(9):2639–50.
144. Vera-Llonch M, Massarotti E, Wolfe F, Shadick N, Westhovens R, Sofrygin O *et al*. Cost-effectiveness of abatacept in patients with moderately to severely active rheumatoid arthritis and inadequate response to tumor necrosis factor-alpha antagonists. J Rheumatol 2008; 35(9):1745–53.
145. Ferraz MB, de Soarez PC, Riera R, Ciconelli RM. Diagnosis and therapeutical management offered to rheumatoid arthritis patients in Brazil – rheumatologists' answers from an assessment questionnaire. Acta Reumatol Port 2009; 34(1):44–51.

146. Cavalcanti FS. Management of rheumatoid diseases: the Brazilian perspective. Rheumatology (Oxford) 2010; 49(12):2231–2.
147. Hazes JM, Coulie PG, Geenen V, Vermeire S, Carbonnel F, Louis E *et al*. Rheumatoid arthritis and pregnancy: evolution of disease activity and pathophysiological considerations for drug use. Rheumatology (Oxford) 2011; 50(11):1955–68.
148. Kuriya B, Hernández-Díaz S, Liu J, Bermas BL, Daniel G, Solomon DH. Patterns of medication use during pregnancy in rheumatoid arthritis. Arthritis Care Res 2011; 63(5):721–8.
149. Abarientos C, Sperber K, Shapiro DL, Aronow WS, Chao CP, Ash JY. Hydroxychloroquine in systemic lupus erythematosus and rheumatoid arthritis and its safety in pregnancy. Expert Opin Drug Saf 2011; 10(5):705–14.
150. Partlett R, Roussou E. The treatment of rheumatoid arthritis during pregnancy. Rheumatol Int 2011; 31(4):445–9.
151. Thompson AE, Bashook PG. Rheumatologists recommended patient information when prescribing methotrexate for rheumatoid arthritis. Clin Exp Rheumatol 2010; 28(4):539–45.
152. Bengtsson C, Kapetanovic MC, Källberg H, Sverdrup B, Nordmark B, Klareskog L *et al*.; EIRA Study Group. Common vaccinations among adults do not increase the risk of developing rheumatoid arthritis: results from the Swedish EIRA study. Ann Rheum Dis 2010; 69(10):1831–3.
153. Ribeiro AC, Guedes LK, Moraes JC, Saad CG, Aikawa NE, Calich AL *et al*. Reduced seroprotection after pandemic H1N1 influenza adjuvant-free vaccination in patients with rheumatoid arthritis: implications for clinical practice. Ann Rheum Dis 2011; 70(12):2144–7.
154. Heijstek MW, Ott de Bruin LM, Bijl M, Borrow R, van der Klis F, Koné-Paut I *et al*. EULAR recommendations for vaccination in paediatric patients with rheumatic diseases. Ann Rheum Dis 2011; 70(10):1704–12.
155. Scheinberg M, Guedes-Barbosa LS, Mangueira C, Rosseto EA, Mota L, Oliveira AC *et al*. Yellow fever revaccination during infliximab therapy. Arthritis Care Res (Hoboken) 2010; 62(6):896–8.
156. Mota LM, Oliveira AC, Lima RA, Santos-Neto LL, Tauil PL. Vaccination against yellow fever among patients on immunosuppressors with diagnoses of rheumatic diseases. Rev Soc Bras Med Trop 2009; 42(1):23–7.
157. Barreto ML, Teixeira MG, Bastos FI, Ximenes RA, Barata RB, Rodrigues LC. Successes and failures in the control of infectious diseases in Brazil: social and environmental context, policies, interventions, and research needs. Lancet 2011; 377(9780):1877–89.
158. Lima I, Santiago M. Antibodies against cyclic citrullinated peptides in infectious diseases – a systematic review. Clin Rheumatol 2010; 29(12):1345–51.
159. Mody GM, Cardiel MH. Challenges in the management of rheumatoid arthritis in developing countries. Best Pract Res Clin Rheumatol 2008; 22(4):621–41.
160. Wallis RS. Biologics and infections: lessons from tumor necrosis factor blocking agents. Infect Dis Clin North Am 2011; 25(4):895–910.
161. Askling J, Fored CM, Brandt L, Baecklund E, Bertilsson L, Coster L *et al*. Risk and case characteristics of tuberculosis in rheumatoid arthritis associated with tumor necrosis factor antagonists in Sweden. Arthritis Rheum 2005; 52(7):1986–92.
162. Dixon WG, Watson K, Lunt M, Hyrich KL, Silman AJ, Symmons DP. Rates of serious infection, including site-specific and bacterial intracellular infection, in rheumatoid arthritis patients receiving anti-tumor necrosis factor therapy: results from the British Society for Rheumatology Biologics Register. Arthritis Rheum 2006; 54(8):2368–76.
163. Ellerin T, Rubin RH, Weinblatt ME. Infections and anti-tumor necrosis factor alpha therapy. Arthritis Rheum 2003; 48(11):3013–22.
164. Gomez-Reino JJ, Carmona L, Valverde VR, Mola EM, Montero MD. Treatment of rheumatoid arthritis with tumor necrosis factor inhibitors may predispose to significant increase in tuberculosis risk: a multicenter active-surveillance report. Arthritis Rheum 2003; 48(8):2122–7.
165. Sociedade Brasileira de Pneumologia e Tisiologia. III Diretrizes em Tuberculose da SBPT. J Bras Pneumol 2009; 35(10):1018–48.
166. Tubach F, Salmon D, Ravaud P, Allanore Y, Goupille P, Bréban M *et al*. Risk of tuberculosis is higher with anti-tumor necrosis factor monoclonal antibody therapy than with soluble tumor necrosis factor receptor therapy: The three-year prospective French Research Axed on Tolerance of Biotherapies registry. Arthritis Rheum 2009; 60(7):1884–94.
167. Callado MR, Lima JR, Nobre CA, Vieira WP. Low prevalence of reactive PPD prior to infliximab use: comparative study on a population sample of Hospital Geral de Fortaleza. Rev Bras Reumatol 2011; 51(1):40–52.
168. Ponce de Leon D, Acevedo-Vasquez E, Alvizuri S, Gutierrez C, Cucho M, Alfaro J *et al*. Comparison of an interferon-gamma assay with tuberculin skin testing for detection of tuberculosis (TB) infection in patients with rheumatoid arthritis in a TB-endemic population. J Rheumatol 2008; 35(5):776–81.
169. Bocchino M, Matarese A, Bellofiore B, Giacomelli P, Santoro G, Balato N *et al*. Performance of two commercial blood IFN-gamma release assays for the detection of Mycobacterium tuberculosis infection in patient candidates for anti-TNF-alpha treatment. Eur J Clin Microbiol Infect Dis 2008; 27(10):907–13.
170. Kowada A. Cost effectiveness of interferon-gamma release assay for tuberculosis screening of rheumatoid arthritis patients prior to initiation of tumor necrosis factor-α antagonist therapy. Mol Diagn Ther 2010; 14(6):367–73.
171. Machado A Jr, Emodi K, Takenami I, Finkmoore BC, Barbosa T, Carvalho J *et al*. Analysis of discordance between the tuberculin skin test and the interferon-gamma release assay. Int J Tuberc Lung Dis 2009; 13(4):446–53.
172. Smieja MJ, Marchetti CA, Cook DJ, Smaill FM. Isoniazid for preventing tuberculosis in non-HIV infected persons. Cochrane Database Syst Rev 2000; (2):CD001363.
173. Pineda NI, Pereira SM, Matos ED, Barreto ML. Quimioprofilaxia na prevenção da tuberculose. J Bras Pneumol 2004; 30(4):485–95.
174. Fonseca JE, Lucas H, Canhão H, Duarte R, Santos MJ, Villar M *et al*. Grupo de Estudos de Artrite Reumatoide da Sociedade Portuguesa de Reumatologia; Comissão de Tuberculose da Sociedade Portuguesa de Pneumologia. Recommendations for the diagnosis and treatment of latent and active tuberculosis in patients with inflammatory joint diseases treated with tumour necrosis factor alpha inhibitors. Acta Reumatol Port 2006; 31(3):237–45.
175. Cabrera Villalba SR, Victoria Hernández Miguel M, Sanmartí Sala R. How does one manage patients with rheumatoid arthritis and positive serology to hepatitis B, hepatitis C, human immunodeficiency virus? Reumatol Clin 2011; 7(3):203–7.
176. Roux CH, Brocq O, Breuil V, Albert C, Euller-Ziegler L. Safety of anti-TNF-alpha therapy in rheumatoid arthritis and spondylarthropathies with concurrent B or C chronic hepatitis. Rheumatology (Oxford) 2006; 45(10):1294–7.
177. Detert J, Pischon N, Burmester GR, Buttgereit F. The association between rheumatoid arthritis and periodontal disease. Arthritis Res Ther 2010; 12(5):218.