Use of biological therapies in rheumatoid arthritis management: a comparison between the main worldwide and Brazilian recommendations

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ABSTRACT

Introduction: Rheumatoid arthritis (RA) is a chronic systemic and progressive inflammatory disorder of the joints, which can result in deformity and functional disability. The diagnosis, treatment, and follow-up of patients with RA vary worldwide. The major societies of rheumatology, as well as governmental agencies in most countries, have tried to establish recommendations addressing diagnosis, treatment, and follow-up of RA. Despite the rapid advance in discovering new drugs, with increasingly efficient therapeutic responses, these recommendations have not been updated accordingly. Thus, efforts should be focused on standardizing the procedures established. Objective: Compare the main international recommendations for treatment of RA with the Brazilian protocols of the Brazilian Society of Rheumatology and Ministry of Health. **Methods:** The protocols of the following entities for treating RA were assessed: Brazilian Ministry of Health, Brazilian Society of Rheumatology, PANLAR/GLADAR, American College of Rheumatology, European League Against Rheumatism (EULAR), and Mexican College of Rheumatology. **Results:** Significant differences were identified between the several recommendations, especially regarding the criteria for beginning biological therapies, hierarchic sequence for using available biological drugs, and for suspending or switching them. **Conclusions:** The recommendations for treatment of RA should be more frequently updated. The worldwide standardization of criteria for elaborating recommendations would be of great value to provide similar guidance to rheumatologists in countries and regions throughout the world.

Keywords: consensus, rheumatoid arthritis, biological therapy.

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INTRODUCTION

Rheumatoid arthritis (RA) is a chronic systemic and progressive inflammatory disorder of yet unknown etiology, characterized by the symmetric involvement of small and large joints, which can result in joint deformity and functional disability.[1-3]

Rheumatoid arthritis has a worldwide distribution, affects all ethnicities, and is more frequently found among women than men (3:1). It has a prevalence ranging from 0.4% to 1.9% of the adult world population. In Brazil, the estimated prevalence is 0.46%. The disease usually begins between 20 and 60 years of age, with a peak incidence at the age of 45. Because RA affects adults in their productive years, with 50% of patients deemed unable to work after ten years of disease, it is considered a disease of socio-economic importance.[1,30,31]

The treatment of RA has evolved and changed quickly in the past couple of decades, with increasingly specific therapies aimed at neutralizing specific inflammatory mediators involved in the pathophysiology of disease. With the remarkable results of these target-specific therapies, RA treatment is no longer

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aimed only at improving symptoms, but at searching for disease remission. Several instruments and questionnaires, through which the patient's response to treatment can be quantified, have been used to assess disease activity. Their use has been fundamental in clinical studies, as they allow standardization of the results found.[6-8]

The American College of Rheumatology (ACR) criteria for improvement in RA (ACR20, ACR50, and ACR70) allow the quantification of clinical improvement by use of the following parameters: swollen and tender joint count; tests of inflammation blood markers; Health Assessment Questionnaire (HAQ) score; physician's global assessment of disease activity; and patient's global assessment of pain and disease activity. Improvement is expressed as percentages (20%, 50%, and 70%). On the other hand, the Disease Activity Score in 28 joints (DAS28) is an index that combines the analysis of swollen and tender joints, inflammation blood markers, and patient global assessment of the disease, providing information about disease activity at certain points. It allows the classification of RA as follows: disease remission, or mild, moderate, or intense activity. Other indices, with changes in certain variables, have the same purpose, and, besides DAS28, the most used are as follows: Simplified Disease Activity Index (SDAI), which, in addition to the swollen and tender joint count, patient's global assessment of disease activity, and C-reactive protein (CRP) level also uses the physician's global assessment of disease activity, and the Clinical Disease Activity Index (CDAI), which considers the same variables of the SDAI, except for CRP. The serial measurement of these indices throughout the follow-up of patients undergoing treatment also allows estimating the response to therapy. Other instruments of assessment include the ACR disease remission criteria, physician's visual analogue scale regarding disease activity, patient's visual analogue scale regarding pain and disease activity, HAQ, and 36-Item Short-Form Health Survey (SF-36).[5,9]

Another important advance in the initial assessment of patients with RA is defining which patients have a worse prognosis. Studies have reported the following factors of worse prognosis: a large number of affected joints; presence of extra-articular disease manifestations; positive serum rheumatoid factor (RF) or anti-cyclic citrullinated peptide antibody (anti-CCP); persistently high CRP levels; presence of bone erosions on imaging tests; poor result in quality of life questionnaires; and presence of HLA DR4. Thus, it is possible to establish a more aggressive therapeutic approach in the early stages of disease, preventing irreversible joint damage.[5]

In addition to clinical and laboratory assessment, imaging exams have been useful for the follow-up of patients with RA. The structural changes of RA can be assessed by radiographs of hands and feet. In the early stage of the disease, soft tissue swelling and periarticular osteopenia can be observed. With disease progression, bone erosions and reduced articular space become evident. Several clinical studies have used the Sharp/van der Heijde radiological assessment of hands and feet, whose score considers the reduction in the articular space and the presence of bone erosions.[5,10]

Throughout the world, the diagnosis, treatment, and follow-up of patients with RA are quite variable, depending on several socio-economic and cultural factors. The major societies of rheumatology, as well as governmental agencies in most countries worldwide, have tried to establish consensus and protocols addressing criteria for RA diagnosis, treatment, and follow-up. However, with the rapid advance in discovering new drugs that provide increasingly efficient therapeutic responses, the access to new therapies has been made available neither uniformly nor quickly enough in different regions and countries.[11] Based on such difficulties, this study assessed some of the major recommendations about the treatment of RA throughout the world, and compared them with the Brazilian recommendations, aiming at improving the management and standardizing the treatment of patients with RA.

METHOD

The following recommendations were assessed: the Brazilian Ministry of Health Clinical Protocol and Therapeutic Guidelines for Treatment of RA, 2002;[12] Update of the Brazilian Consensus on the Diagnosis and Treatment of RA, 2007;[9] First Latin-American Position Paper on the Pharmacological Treatment of RA, 2006;[13] EULAR Recommendations for Management of RA with Synthetic and Biological Disease-modifying Antirheumatic Drugs, 2010;[5] the American College of Rheumatology 2008 Recommendations for the Use of Non-biologic and Biologic Disease-modifying Antirheumatic Drugs in RA;[14] and the Guías y Recomendaciones del Colegio Mexicano de Reumatología Para el Uso de Agentes Biológicos en Enfermos Reumáticos, 2006.[15]

All recommendations were compared, considering their method of elaboration and the following criteria in the use of biological therapies available for treating adults with RA:

- disease activity indices;
- disease activity level to recommend starting biological therapy;
- need for previous use of disease-modifying antirheumatic drugs (DMARDs);
- hierarchy for indicating the biological drug;

- criteria for switching biological drugs;
- time of biological drug use required to assess the response;
- possibility of altering the initially recommended dose or interval between doses;
- need for radiographic monitoring and its time interval;
- recommendation regarding the associated use of methotrexate;
- predicted biological drugs.

These data are shown in Table 1.

RESULTS

Methodologies adopted for each of the recommendations were as follows:

- Brazilian Ministry of Health, 2002.[12] The recommendation relied on advice from consultants, but neither their names nor the methodology are mentioned.
- Brazilian Society of Rheumatology, Update of the Brazilian Consensus on Diagnosis and Treatment of RA, 2007.[9] It was elaborated based on a consensual

Table 1
Summary of the recommendations for use of biological drugs in RA treatment in Brazil, Latin America, Europe, Mexico, and the United States of America

	Disease activity level for starting biological therapy	Previous use of DMARDs	Choice of biological drug	Switch of biological drugs	Index used for assessing response to treatment	Time required to assess response to treatment	Change in frequency or dose	Radiographic monitoring	Recommended combination with MTX	Predicted biological drugs
Brazil. Ministry of Health, 2002.[12]	Not specified	At least two, one of which, MTX	1st IFX, 2nd ADA or ETN (20% IFX)**	Not specified	Not specified	3 months	Not specified	After 6-12 months of treatment	Yes	IFX ADA ETN
Brazil. Brazilian Society of Rheumatology, 2007.[9]	Not specified	At least two, one of which, MTX	No preference (IFX, ADA, ETN, ABAT)	Not specified	DAS 28 SDAI CDAI	Not specified	Not specified	Annually or at the physician's discretion	Yes	ADA IFX ETN RTX ABAT
Latin-America. Pan-American League of Associations of Rheumatology, 2006.[13]	DAS28 >3.2	At least two, one of which, MTX, for a total of 24 weeks	No preference	Not specified	DAS28	8-12 weeks	Not specified	Not specified	Yes	IFX ADA ETN ANA RTX ABAT
EULAR, 2010[5]	High activity or presence of criteria of worse prognosis*	MTX isolated or in association (LEF, SSZ, or IM gold)	Anti-TNF (ADA, CERT, ETN, GOL, IFX)	TNFs, ABAT, TOCI, RTX	DAS, DAS28, SDAI, CDAI	3-6 months	Possible if remission > 12 months	Not specified	Yes	IFX ADA ETN GOL CERT ABAT TOCI RTX
American College of Rheumatology (ACR), 2008.[14]	High activity; 3-6 months of disease duration	MTX isolated or in association	Anti-TNF	Anti-TNF, ABAT, RTX	DAS 28 SDAI CDAI PAS	12 weeks	Not specified	Not specified	Yes	ETN IFX ADA ABAT RTX
Colegio Mexicano de Reumatologia, 2006.[15]	High activity; DAS28>5.8 for at least six weeks	At least two, one of which, MTX	Not specified	Not specified	DAS28	3 months	Not specified	Not specified	Yes	ETN IFX ANA RTX ABAT

DMARDs: disease-modifying anti-rheumatic drugs; MTX: methotrexate; LEF: leflunomide; SSZ: sulfasalazine; IFX: infliximab; ADA: adalimumab; ETN: etanercept; ABAT: abatacept; TOCI: tocilizumab; CERT: certolizumab; GOL: golimumab; ANA: anakinra; RTX: rituximab; DAS28: disease activity score - 28 joints; DAS44: disease activity score - 44 joints; CDAI: clinical disease activity index; SDAI: simplified disease activity index; PAS: patient activity scale; EULAR: European League Against Rheumatism.

* Criteria for worse prognosis: high rheumatoid factor or anti-CCP titers; persistently high disease activity level; number of inflamed joints or increased concentration of acute-phase reactants (erythrocyte sedimentation rate or C-reactive protein); early articular erosions.

** Adalimumab and etanercept could only be indicated in up to 20% of patients on infliximab.

meeting with the participation of 16 rheumatologists of the Brazilian Society of Rheumatology. The text was based on the study carried out by SBR representatives, published in the *Revista Brasileira de Reumatologia* in 2004, in addition to the experience of rheumatologists, and was complemented by bibliographic review. The managements were classified according to the degree of recommendation and strength of evidence (A, B, C, and D), based on the experience of experts and complemented by bibliographic review. The due date of the next review was not specified.

- PANLAR 2006, First Latin-American Position Paper on the Pharmacological Treatment of RA, 2006.[13] An executive committee, named by the PANLAR committees of epidemiology, RA, and radiology held a meeting at Lisbon, in May 2003. The objective was to establish a task force to develop a Latin-American consensus on the management of RA. The participants discussed the problems found in the region and the availability of adequate treatment for RA, which resulted in the elaboration of guidelines for clinical practice. The secondary objective was to disclose the conclusions and recommendations of the consensus, as well as the participating countries.
- EULAR Recommendations for the Management of RA with Synthetic and Biological Disease-modifying Antirheumatic Drugs, 2010.[5] These recommendations relied on expert committees in areas of rheumatology, infectology, and health economics, and one patient, and involved 12 European countries and the United States. The following sources were used as database: PubMed, EMBASE, Medline, Cochrane library, and recent abstracts prior to 2009. The review comprised meta-analyses, systematic reviews, randomized and controlled trials (RCTs), non RCTs and observational registries, including data records. Categorization of levels of evidence and degree of recommendation were used according to the standards of the Oxford Center for Evidence-Based Medicine. Agreement between participants was also considered. The works began in December 2008 and ended in June 2009, and a due date for reviewing the recommendations was not established. The recommendations were subdivided into the following five areas: synthetic DMARDs (isolated or combined use) without glucocorticoids; glucocorticoid isolated or combined with synthetic DMARDs; biological DMARDs; treatment strategies; and economic data.
- American College of Rheumatology 2008 Recommendations for the Use of Non-biologic and Biologic Disease-Modifying Antirheumatic Drugs in RA, 2008.[14] A systematic review of the literature was carried out using the following sources: PubMed, EMBASE, SCOPUS, Web of Science, and International Pharmaceutical Abstracts (IPA). The evidence originating from different clinical situations was compiled and submitted to a group of experts, and the factors related to disease prognosis, such as degree of functional limitation, presence of extra-articular disease, positivity for RF and/or anti-CCP antibodies and/or bone erosions on radiography were considered significant. Subsequently, the strength of evidence was attributed to each final recommendation using the American College of Cardiology methods as follows: 1) level of evidence A, data obtained from multiple RCTs or meta-analyses; 2) level of evidence B, data obtained from a single RCT or non RCTs; 3) level of evidence C, data obtained from expert consensus, case-studies, or standardized managements. Periodic review of the recommendations is suggested, depending on the availability of new therapies, new evidence, changes in the risk/benefit ratio of treatments and changes in policies that define the resources available for health care.
- *Guías y Recomendaciones del Colegio Mexicano de Reumatología Para el Uso de Agentes Biológicos en Enfermos Reumáticos,* 2006.[15] A group of experts elaborated the methodology, and the major criterion for choosing the members was the number of prescriptions. Information was shared through electronic media, using a previously elaborated questionnaire, and afterwards the experts met for discussion and drafting the final document. Analysis of results used the Delphi technique, and the minimum percentage of agreement between experts was 80%. Other consensus statements, such as the Guide of the British Society of Rheumatology for the use of anti-TNF alpha in patients with RA, were used as reference. Review due date was recommended in two years.

DISCUSSION

Important differences were found between the different treatment recommendations, such as the choice of methodology adopted for their elaboration. The most recent guides (ACR 2008 and EULAR 2010) have chosen the systematic review of the literature to support the recommendations elaborated by experts. The older recommendations have been mainly based on the opinion of experts and consultants.

Although disease activity indices have been widely recommended as indicators for the use of these new therapies,

as well as for treatment follow-up, the Brazilian Ministry of Health protocol and the Brazilian Society of Rheumatology consensus have not specified at which disease activity level these therapies should be initiated. However, all these entities, except for the Brazilian Ministry of Health, have based the indication of therapy on one of these indices, the DAS28 being the most frequently recommended.

The Brazilian Ministry of Health protocol specifies infliximab as the first drug to be used, while adalimumab and etanercept can only be indicated in up to 20% of the patients using infliximab. The justification for this limitation is not mentioned. The EULAR recommends as the first biological drug any of the anti-TNFs, justifying this indication mainly because of their proved safety, in addition to the fact that these drugs have been used for treatment of RA for the longest time.

Switching biological drugs and the sequence or criteria for choosing the next agent were only discussed in EULAR 2010, in which the replacement by another anti-TNF or other class of biological drug is allowed, but no definition of hierarchy is provided. The change in dose intervals or dose variation according to weight has also only been mentioned in EULAR 2010, which suggests 12 months after remission. Changes in the interval and dose due to refractoriness have been mentioned in no consensus statement.

The Mexican guide provides criteria for drug suspension due to therapeutic failure, which occurs when a 1.2-score reduction in the DAS28 is not achieved, or when a reduction in the index to less than 3.2 is not achieved after three months treatment with the biological drug.

All recommendations have suggested the previous use of methotrexate isolated or associated with other non-biological DMARDs when indicating the use of a biological drug. Regarding the time required to assess treatment response, most guides recommend at least 12 weeks.

Radiographic monitoring is recommended by the Brazilian Ministry of Health and the Brazilian Society of Rheumatology Consensus, with an assessment time of at least 6 months and maximum of 12 months. The other consensuses do not specify such a requirement, or the period.

The indicated biological agents vary greatly, reflecting the diversity of authorization and availability criteria of the regulatory agencies in different countries and regions worldwide. Currently, the only consensus that gathers all drugs already approved by the major regulatory agencies is the EULAR 2010.

The societies of rheumatology and health care managers need to more frequently and quickly update the recommendations for RA treatment, as the scientific evolution has rapidly modified the treatment of disease and is obviously far from finished. So far, the new options have not achieved the total control of RA in all cases studied.[16-27]

The delay in updating the recommendations benefits neither patients with RA, who fail to have access to efficient treatment options, nor health care managers, who are deprived from more strict criteria for beginning, replacing, following up, and even suspending the use of these new therapies, which are expensive.[11] It is worth noting that, so far, the association of biological therapies is formally contraindicated. Thus, the incorporation of new high-cost technologies, but similar to the already existing drugs, would not result in higher cost, but in more options in the search for the major objective, which is remission of rheumatoid disease and prevention of articular damage.

The establishment of worldwide criteria guiding common principles in RA treatment, such as the beginning of biological therapy, hierarchic definition of choosing and switching different classes of biological drugs, and follow-up and drug suspension strategies, considering the importance of respecting the regional characteristics and health systems of each country, would provide uniform recommendations, thus standardizing decision making by rheumatologists.

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