

2012 Brazilian Society of Rheumatology Consensus on the management of comorbidities in patients with rheumatoid arthritis

Ivânio Alves Pereira¹, Licia Maria Henrique da Mota², Boris Afonso Cruz³, Claiton Viegas Brenol⁴,
Lucila Stange Rezende Fronza⁵, Manoel Barros Bertolo⁶, Max Victor Carioca de Freitas⁷, Nilzio Antônio da Silva⁸,
Paulo Louzada-Junior⁹, Rina Dalva Neubarth Giorgi¹⁰, Rodrigo Aires Corrêa Lima¹¹, Geraldo da Rocha Castelar Pinheiro¹²

ABSTRACT

Objective: To elaborate recommendations of the Rheumatoid Arthritis Committee of the Brazilian Society of Rheumatology (SBR) to manage comorbidities in rheumatoid arthritis (RA). **Methods:** To review the literature and the opinions of the SBR RA Committee experts. **Results and conclusions:** Recommendations: 1) Early diagnosis and proper treatment of comorbidities are recommended; 2) The specific treatment of RA should be adapted to the presence of comorbidities; 3) Angiotensin-converting-enzyme inhibitors or angiotensin II receptor blockers are preferred to treat systemic arterial hypertension; 4) In patients diagnosed with rheumatoid arthritis and diabetes mellitus, the continuous use of a high cumulative dose of corticoids should be avoided; 5) Statins should be used to maintain LDL cholesterol levels under 100 mg/dL and the atherosclerotic index lower than 3.5 in patients with RA who have other comorbidities; 6) Metabolic syndrome should be treated; 7) Performing non-invasive tests to investigate subclinical atherosclerosis is recommended; 8) Greater surveillance for the early diagnosis of occult malignancy is recommended; 9) Preventive measures of venous thrombosis are suggested; 10) Bone densitometry is recommended in RA patients over the age of 50 years and in younger patients on corticoid therapy at a dose greater than 7.5 mg for over three months; 11) Patients with RA and osteoporosis should be instructed to avoid falls, to increase their dietary calcium intake and sun exposure, and to exercise; 12) Calcium and vitamin D supplementation is suggested. Bisphosphonates are suggested for patients with T score < -2.5 on bone densitometry; 13) A multidisciplinary team, with the active participation of a rheumatologist, is recommended to treat comorbidities.

Keywords: rheumatoid arthritis, comorbidities, arterial hypertension, diabetes mellitus, dyslipidemia.

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INTRODUCTION

Rheumatoid arthritis (RA) is a systemic autoimmune inflammatory disease whose major characteristic is the presence

of symmetric chronic polyarthritis of large and small joints. Despite its typical musculoskeletal involvement, RA is a systemic disease that may affect several organs, such as the lungs, eyes, and blood vessels. The condition causes a large

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Brazilian Society of Rheumatology - BSR.

1. Professor of the Discipline of Rheumatology, Universidade do Sul de Santa Catarina – UNISUL; Chief of the Rheumatology Service, Hospital Universitário, Universidade Federal de Santa Catarina – HU-UFSC

2. Collaborating Professor of Internal Medicine and of the Rheumatology Service, Medical School, Universidade de Brasília – FM-UnB; PhD in Medical Sciences, FM-UnB

3. Master in Epidemiology; Chief of the Rheumatology Service, BIOCOR Instituto

4. Adjunct Professor of the Department of Internal Medicine, Medical School, Universidade Federal do Rio Grande do Sul – UFRGS; Coordinator of the Rheumatoid Arthritis Outpatient Clinic of the Rheumatology Service, Hospital de Clínicas de Porto Alegre

5. Attending Physician of the Rheumatology Service, Hospital das Clínicas, Universidade Federal do Paraná – HC-UFPR; ex-fellow of the Rheumatology Service of the Hospital Geral AKH, Austria

6. Professor and Coordinator of the Discipline of Rheumatology, Medical Sciences School, Universidade Estadual de Campinas – Unicamp

7. Adjunct Professor of the Discipline of Immunology, Medical School, Universidade Federal do Ceará – FM-UFC

8. Full Professor of Rheumatology, Universidade Federal de Goiás – UFG

9. Professor with Habilitation Thesis (Associate), Medical School of Ribeirão Preto, Universidade de São Paulo – FMRP-USP

10. 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, Hospital Universitário de Brasília, Universidade de Brasília (UnB)

12. Adjunct Professor of the Medical Sciences School, Universidade do Estado do Rio de Janeiro – FCM-UERJ

Correspondence to: Ivânio Alves Pereira. Av. Rio Branco, 448 – sala 306. CEP: 88015-200. Florianópolis, SC, Brazil. E-mail: ivanioreumato@gmail.com

social and economic impact, considering the irreversible joint deformities and the significant decline in the patients' functional capacity.¹

In recent years, greater knowledge about the pathogenesis of RA and the recognition of therapeutic targets have allowed the use of the new disease-modifying antirheumatic drugs (DMARDs), including the biological DMARDs.^{2,3} In addition, new RA management strategies have been suggested, such as the use of DMARDs since the initial phase of the disease, more frequent assessments of patients, therapeutic changes or adjustments based on objective scores for assessing disease activity; and search for clinical remission or, when that is not possible, for low disease activity. Those management changes have resulted in improved prognosis for patients diagnosed with RA.⁴

Despite the noticeable advances in the treatment of RA, mortality among patients with RA continues higher than that of the general population, with no significant changes in recent years.⁵

Individuals diagnosed with RA have greater likelihood of having other diseases associated, such as those of autoimmune etiology,^{6,7} and comorbidities, such as systemic arterial hypertension (SAH), dyslipidemia, and diabetes mellitus (DM).⁸⁻¹⁴ The understanding and adequate management of the comorbidities of patients with RA are fundamental, because those diseases contribute to an increased cardiovascular risk and to the greater mortality observed in that group.¹⁵

The present study aimed at elaborating recommendations for the diagnosis and management of comorbidities in patients with RA, emphasizing the most frequent conditions. The purpose of this document is to synthesize the current position of the Brazilian Society of Rheumatology (SBR) on the topic, aiming at instructing the Brazilian physicians, especially rheumatologists, about the diagnosis and management of comorbidities in patients with RA in Brazil.

METHOD OF ELABORATING THE RECOMMENDATIONS

The method of elaborating the recommendations includes a literature review and the opinion of expert members of the Rheumatoid Arthritis Committee of the SBR. The bibliographic research comprised publications of MEDLINE, SciELO, PubMed, and EMBASE databases up to February 2012. The recommendations were written and reassessed by all participants during multiple rounds of questionings and corrections conducted on the Internet.

Systemic arterial hypertension

Systemic arterial hypertension is one of the major modifiable risk factors for cardiovascular disease in patients with RA. It is an important and frequent pathology, associated with the development of subclinical atherosclerosis. Its prevalence is high, ranging from 53%–73%, according to some published studies.¹⁴⁻¹⁶ Panoulas et al.¹⁴ have found a 70.5% frequency of hypertensives in their sample, while Gonzalez et al.¹⁶ have reported a 52% frequency in the population studied. Despite that high frequency, SAH in RA has been less often diagnosed and treated (13.2% vs. 21%–23% in the population without RA).¹⁴⁻¹⁶

The mechanisms responsible for the appearance of SAH in patients with RA have not been clarified, but some classic factors, such as obesity, sedentary lifestyle, and use of medications, are associated with SAH in that population.¹⁵ The use of glucocorticoids for more than six months at a dose higher than 7.5 mg/day is associated with SAH in patients with RA.¹⁷ Similarly, an increase in blood pressure levels secondary to the use of leflunomide and cyclosporine can occur in patients with RA.¹⁸⁻²⁰ Factors inherent to the disease, such as the systemic inflammation of RA, might also contribute to the appearance of SAH in those patients. During its course, RA shows an increased expression of tumor necrosis factor alpha (TNF- α), interleukins (IL) 1 and 6, adhesion molecules, angiotensin II type 1 receptor, and endothelin, and a lower expression of nitric oxide; that unbalance might contribute to SAH.¹⁵

Regarding the treatment of RA, the use of non-steroidal anti-inflammatory drugs (NSAIDs) is known to attenuate the anti-hypertensive effect of diuretics, beta-blockers, angiotensin-converting enzyme inhibitors (ACEIs), and angiotensin II receptor blockers (ARBs).²¹ It is also worth noting that combining NSAIDs with diuretics and ACEIs or ARBs increases the likelihood of renal failure, especially in elderly patients or in those with conditions losing intravascular volume, such as liver cirrhosis, heart failure, hypoalbuminemia, and dehydration. Due to their beneficial effects at the endothelial level, and because they interfere less with the metabolism of carbohydrates and cause less dyslipidemia, ACEI and ARB, rather than beta-blockers and diuretics, are preferred to initiate the treatment of SAH in patients with RA.¹⁵ In the treatment of patients with RA and SAH, whenever possible, the concomitant use of NSAIDs and/or high doses of corticoids should be avoided.²²

Diabetes mellitus

The association between RA and insulin resistance has been well documented. However, there are few studies assessing the risk of patients with RA developing DM.^{12,23,24} A recent

study comparing 48,718 patients with RA, 40,346 patients with psoriasis or psoriatic arthritis, and 44,2033 controls has shown that patients with RA were at higher risk of developing type 2 DM as compared with controls (HR = 1.5; 95% CI 1.4–1.5).²³

Similarly, Han et al.²⁵ have shown that cardiovascular diseases and their risk factors, as well as type 2 DM, were more common among patients with RA. The use of corticoids in patients with RA is known to interfere negatively with the insulin sensitivity of patients with RA.²⁶ In addition, the treatment of the systemic inflammation of RA is known to be beneficial, especially with the use of hydroxychloroquine and anti-TNF.^{27–29}

Some studies have also shown that the prevalence of type 1 DM is higher in patients with RA, especially in the subgroup positive for the anti-cyclic citrullinated peptide (anti-CCP) antibody. That risk can be attributed to an allele shared by both diseases, acting like a common risk factor in the pathogenesis of both diseases. Liao et al.,³⁰ assessing 1,419 patients with RA, have shown that the presence of the PTPN22 allele is common to both RA and type 1 DM, relating to the coexistence of both diseases. However, the association was significant only for patients with RA positive for the anti-CCP antibody.

The continuous use of a high cumulative dose of corticoids to patients with concomitant RA and DM should be avoided, and strategies should be implemented for an effective control of the disease's systemic inflammation, considering that there is evidence suggesting a beneficial effect of the RA treatment on DM control.^{27–29}

Dyslipidemia

The dyslipidemia found in patients with RA is characterized by the presence of reduced levels of HDL-cholesterol (HDL) and an increased total cholesterol/HDL ratio (TC/HDL).^{31–34} The emergence of that pattern can precede the onset of RA articular manifestations and can be related to inflammatory changes secondary to the disease.^{33,34}

The levels of TC, and especially of HDL, are believed to decrease with disease activity, and that reduction might be related to the high levels of pro-inflammatory cytokines, such as TNF- α .^{31,33}

The treatment of RA itself is known to be able to interfere with the patients' lipid profile.^{35–38} The NSAIDs do not seem to affect lipid levels.³⁹ The effect of corticoids on the increase of TC and LDL levels have been widely documented, although their use in patients with RA has not been associated, so far, with increased cardiovascular risk.⁴⁰ Cyclosporine seems to have a deleterious effect on cholesterol levels, while antimalarials have a positive effect on reducing the serum levels of

TC and triglycerides.⁴¹ Treatment with other DMARDs and biologics, such as the drugs of the anti-TNF class, and mainly with the IL-6 receptor inhibitor (tocilizumab) have controlled inflammation and increased the previously reduced HDL and TC associated with inflammation, without interfering with the atherosclerotic index (TC/HDL), and without increasing clinical cardiovascular events so far.^{42–45}

It is worth noting that the use of statin group drugs has not only lipid lowering effects on patients with RA, but reduces the disease activity scores. The result of the ongoing Trial of Atorvastatin for the Primary Prevention of Cardiovascular Events in Rheumatoid Arthritis (TRACE RA) (<http://www.dgoh.nhs.uk/tracera>), which will involve 4,000 patients with RA, is awaited. That study will be able to define the role of statins in controlling inflammation and reducing the cardiovascular risk in patients with RA.⁴⁶

Atherosclerosis

Patients with RA have a higher prevalence of endothelial dysfunction,^{47,48} assessed by brachial ultrasound imaging, being that the first evidence of the beginning of the atherogenic process, in which arterial stiffness is found. Regarding the non-invasive tests that demonstrate the presence of subclinical atherosclerosis, studies have confirmed that carotid atherosclerosis with plaques is frequent,⁴⁹ as well as a higher coronary artery calcium score on computed tomographic angiography.⁵⁰

The prevalences of acute myocardial infarction (AMI) and congestive heart failure (CHF) are higher in patients with RA.^{51,52} Such conditions reduce survival and increase mortality of patients with RA. Regarding coronary artery disease, it is worth noting that angina symptoms are less frequent in patients with RA, and thus, those individuals often die suddenly or have silent myocardial infarction.⁵¹

Although the treatment of RA reduces the chance of myocardial infarction, especially with the use of methotrexate (MTX) and anti-TNF,^{53–55} it is worth noting that treating comorbidities, such as type 2 DM, dyslipidemia and SAH, in such patients is important.

In patients with RA, who have coronary artery disease, previous AMI or CHF, the indiscriminate and long-term use of NSAIDs, especially cyclooxygenase-2 selective NSAIDs, should be avoided, considering the greater mortality and the risk of hospitalization due to myocardial infarction and decompensated CHF. Of the NSAIDs, the risk of myocardial infarction, and other cardiovascular events seems to be lower with the use of naproxen.^{56,57}

Another aspect to be considered is smoking cessation in patients with RA. In addition to increasing the risk of

cardiovascular disease, smoking is known to increase the chances of genetically predisposed individuals developing RA, to increase the severity of articular manifestations, and to be associated with extra-articular manifestations of the disease.⁵⁸ Furthermore, smokers with RA have a lower clinical response to antirheumatic drugs, such as MTX, or to anti-TNF biologics.⁵⁹

Metabolic syndrome

Although there is no universally accepted definition, metabolic syndrome (MS) is characterized by the clustering of clinical manifestations that include central obesity, reduced levels of HDL, high levels of triglycerides, increased blood pressure and hyperglycemia. Currently, the most accepted definitions are those issued by the International Diabetes Federation (IDF), the National Cholesterol Education Program – Adult Treatment Panel III (NCEP ATP III), and the World Health Organization (WHO).^{60–62}

That syndrome represents an association of conditions having in common insulin resistance and increased abdominal fat, which are closely related to inflammation.⁶³ That relation to inflammation can justify the higher prevalence of MS in patients with RA,^{9,64–67} and the higher disease activity found in patients with RA who also have MS.^{66–68} Dessein et al.⁶⁹ have shown a 14%–19% prevalence of MS among patients with RA, and two other studies have not shown a greater prevalence of MS among patients with RA.^{68,70} The presence of MS in the population without RA has been associated with a greater chance of cardiovascular events and higher overall mortality.⁷¹

There were no studies assessing the higher prevalence of myocardial infarction or stroke associated with MS in the population with RA,⁷² but the presence of coronary artery calcification, which can be diagnosed in a test and increases the likelihood of a cardiovascular event, has been associated with MS in that population.⁶⁵ The role of the DMARDs in the prevalence of MS in patients with RA has not been defined, with disagreeing results regarding MTX. Toms et al.⁷³ have reported a lower prevalence of MS in elderly patients using MTX; on the other hand, a subanalysis of the CARRE Investigation has not confirmed those findings.¹³

Venous thrombosis and pulmonary embolism

Deep venous thrombosis (DVT) and pulmonary thromboembolism (PTE) stand out among noncardiac vascular events most likely to occur in RA.^{74,75} The incidence of those comorbidities can be associated with classic risk factors that affect the general population and with specific aspects of RA.^{74–76}

In general, the following findings contribute to increase the risk of thromboembolism: lower mobility consequent to joint lesions; hospitalizations with prolonged bed confinement; more advanced age of most arthritic patients; compression of the venous system adjacent to a joint with huge joint effusion; and obesity.⁷⁴

Patients with RA have changes in the coagulation parameters and in the fibrinolytic system,⁷⁷ the most common findings being as follows: increased platelet count; increased platelet activation markers; and increased thrombin markers, such as thrombin-antithrombin complexes and prothrombin fragments. The increase in pro-inflammatory cytokines in RA is associated with high levels of fibrinogen, von Willebrand factor, and D-dimer.^{77,78}

Although the studies on the prevalence of DVT and PTE in RA have shown discordant results, an important study has reported that RA is a risk factor for DVT and PTE.^{75,79,80} That study has assessed the incidence of DVT and PTE in patients with RA hospitalized in the United States from 1979 to 2005. The results were as follows: 41,000 of 4,818,000 (0.85%) patients with RA had PTE, as compared with 3,366,000 of 891,055,000 (0.38%) patients without RA (RR = 2.25). Deep venous thrombosis occurred in 79,000 of 4,818,000 (1.64%) patients with RA as compared with 681,000 of 891,055,000 (0.86%) patients without RA (RR = 1.90). Regarding the impact of the different treatments used for RA, data from the British Society for Rheumatology Biologics Register have compared the incidence of DVT and PTE in 11,881 patients on anti-TNF and 3,673 on nonbiological DMARDs. Overall, no difference was observed in the incidence of DVT and PTE in the different groups (HR = 0.8; 95% CI: 0.5–1.5).⁸¹

A retrospective population-based study has compared data from 813 patients with RA with those of individuals without RA, cared for from January 1980 to December 2007. The authors have concluded that the incidence of DVT and PTE was greater in individuals with RA (HR = 3.6).⁷⁴ Thromboembolic events were associated with obesity (HR = 2.2), use of DMARDs (except for MTX and hydroxychloroquine) (HR = 1.9), use of biologics (HR = 2.7), use of acetylsalicylic acid (HR = 2.3), and recent arthroplasty (HR = 11.4). However, they were not associated with venous thromboembolism, positivity for the rheumatoid factor and the anti-CCP antibody, increased erythrocyte sedimentation rate, severity of RA, and presence of erosions or subcutaneous nodules.

Thus, there is discordance between the North-American study and the British Society for Rheumatology Biologics Register, in which no association of PTE/DVT and immunobiologics has been found.^{74,81}

The recommendations for the care of patients with RA should include preventive measures against PTE/DVT.

Malignancies

The occurrence of malignancies in patients with RA, either using DMARDs, especially biologics, or not, is of great interest, because of the great impact of those diseases on morbidity and mortality of patients with RA.

The results of studies of prevalence and relative risk as compared with a control population, and the role of the treatment of RA (including synthetic and biological DMARDs) in triggering malignancies are still controversial.^{82–88} Population studies for data collection from primary sources are required to widen the knowledge on the mechanisms of malignancy occurrence in patients with RA.

The mortality risk due to specific causes in hospitalized patients with RA has been quantified in a study based on a population cohort followed up for 20 years.⁸⁹ Among patients with RA, the risk of death increased due to the causes listed in all chapters of the International Classification of Diseases (ICD), except for the mental diseases. Specific causes of death in that group of patients included lung cancer [men: 1.4 (1.2–1.5); women: 1.6 (1.5–1.8)] and hematopoietic malignancies [men: 1.8 (1.4–2.3); women: 2.0 (1.7–2.3)]. Patients with RA, however, were less likely to die due to gastrointestinal tract malignancies [men: 0.82 (0.7–1.0); women: 0.8 (0.7–0.9)].

Hemminki et al.⁹⁰ have also reported a reduction in the risk of colon and rectal adenocarcinomas in patients with RA, suggesting that the underlying inflammatory mechanisms acting as risk factors in those patients could have been suppressed by the use of anti-inflammatory drugs.

The associated risk of four specific malignancies (lymphoma, and lung, colorectal and breast cancers) in patients with RA has been assessed in a meta-analysis.⁸² When compared with the general population, the standardized incidence ratio (SIR) estimates suggested that patients with RA had a two-fold increase in lymphoma risk (SIR 2.08; 95% CI 1.80–2.39) and a greater risk of Hodgkin than non-Hodgkin lymphoma. The risk of lung cancer was also increased (SIR 1.63; 95% CI 1.43–1.87). In contrast, a decrease in risk was observed for colorectal (SIR 0.77; 95% CI 0.65–0.9) and breast cancer (SIR 0.84; 95% CI 0.79–0.9). The SIR for all malignancies was 1.05 (95% CI 1.01–1.09). Thus, patients with RA seem to have a higher risk of lymphoma and lung cancer, and potentially lower risk of breast and colorectal cancer as compared with that of the general population.

Another study has followed 42,262 patients with RA up (with previous hospitalization) from 1980 to 2004 in Sweden.

SIR has been calculated for malignancies in patients with RA as compared with that of individuals without RA. Many malignancies, such as Hodgkin and non-Hodgkin lymphomas, skin cancer, and endocrine tumors (except for thyroid), have been more often diagnosed in patients with RA. Tumors of the colon, rectum and endometrium were decreased in patients with RA. Among patients hospitalized after 1999, SIRs for melanoma, squamous cell carcinoma, upper digestive tract cancer and leukemia were increased as compared with those of the previous periods.⁸⁴

The risk of the occurrence of non-Hodgkin lymphoma in patients with autoimmune diseases has been investigated in several studies and the results have been inconclusive. In a meta-analysis of cohort studies,⁸³ a greater risk of non-Hodgkin lymphoma has been reported in patients with RA (SIR 3.9; 95% CI 2.5–5.9). The random effects SIRs of non-Hodgkin lymphoma in patients with RA treated with synthetic DMARDs, cytotoxic drugs and biologics were 2.5 (95% CI 0.7–9.0), 5.1 (95% CI 0.9–28.6), and 11.5 (95% CI 3.7–26.9), respectively.

Data from the Swedish Early Arthritis Registry (symptom duration < 1 year) have shown that, before the diagnosis of RA, no increase in the risk of lymphoma (RR 0.67 [95% CI 0.37–1.23]) or other malignancies (RR 0.78 [95% CI 0.70–0.88]) was observed. Within the first ten years after the diagnosis of RA, the HR for developing lymphomas was 1.75 (95% CI 1.04–2.96). Those findings indicate that, in general, the risk of lymphoma is increased in the first decade after the diagnosis of RA.⁹¹

The pathogenesis of the occurrence of solid or hematopoietic malignancies in patients with RA is not known. The deregulation of the immune system in autoimmune diseases could lead to cancer, and there is definitive evidence relating some autoimmune mechanisms to the occurrence of malignancies.⁹⁰

A significant association of HLA-DRB1*02 and DRB1*03 has been found with the likely occurrence of malignancies (OR 5.2 and 9.9, respectively), independently of the family history of RA and cancer or the clinical RA activity. Thus, HLA class II alleles seem to be associated with the occurrence of malignancies in patients with RA.⁹²

Despite the lack of previously published formal recommendations, the Rheumatoid Arthritis Committee of the SBR recommends that, during the clinical follow-up of patients with RA, the clinician be permanently aware of any symptom that might suggest malignancy, because of its increased risk, especially in patients with severe forms and on biological DMARDs. The investigation for malignancies in patients with

RA should follow the same protocol of patients without RA, aiming at early diagnosis, and should include screening tests.

Biological DMARDs have been used for the treatment of RA for over one decade. Since then, the still incomplete understanding of their effects and of the inhibited pathways raises questions about the safety profile of those drugs, including the risk of cancer.⁸⁸

Regarding the anti-TNF agents, TNF is known to play an important role in inflammation and can affect the control of tumor growth.⁸⁹

The information available so far has not allowed stating precisely the most common types of tumors, the patients on biological DMARDs at risk for developing cancer, and the time of the possible occurrence of the tumor. Data that can be analyzed originate from meta-analyses of randomized controlled studies and observational studies, including the registries of biologics.⁸⁹

Data from the German Biologics Register RABBIT, a prospective cohort study, were used to investigate the risk of new or recurring malignancies in patients with RA on biologics as compared with other synthetic DMARDs. No significant differences were found in the incidence of malignancies in patients exposed or not to treatment with anti-TNF and anti-IL1. The same applies to the risk of recurring malignancies. The authors have suggested, however, that the results require being validated in larger cohorts.⁹³

A recent systematic literature review⁸⁷ has included all randomized, double-blind, placebo-controlled studies assessing patients with initial RA who began anti-TNF therapy without the previous use of DMARD (including MTX), in a total of 2,183 patients on biologic therapy and 1,236 patients on MTX. No significant difference regarding the occurrence of malignancies was observed between patients on anti-TNF and controls. The authors have concluded that the risk of malignancies seems not to be increased in patients early diagnosed and not receiving previous treatment with MTX or other DMARD.

The safety of anti-TNF in patients with RA has also been assessed by calculating the estimated risk in meta-analyses with and without adjustment to exposure.⁹⁴ Eighteen randomized studies involving 8,808 patients with RA have been included (mean treatment time of 0.8 year). The treatment with the recommended doses of anti-TNF has not increased the risk of death (RR 1.39; 95% CI 0.74–2.62), of lymphoma (RR 1.26; 95% CI 0.52–3.06), of non-melanoma skin cancer (RR 1.27; 95% CI 0.67–2.42), or the compound endpoint of non-cutaneous malignancies plus melanomas (RR 1.31; 95% CI 0.69–2.48).

In a meta-analysis comprising studies that had included patients with RA using etanercept (ETP) for at least 12

weeks,⁹⁵ 3,316 patients have been assessed, of whom 2,244 received ETP (2,484 person-years of follow-up) and 1,072, control therapy (1,051 person-years). Malignancies have been diagnosed in 26 patients in the ETP group [incidence rate (IR) 10.47/1,000 person-years] and in seven patients in the control group (IR 6.66/1,000 person-years). The HR was 1.84 (95% CI 0.79–4.28) for the ETP group as compared with the control group. In that analysis, the occurrence of malignancies was greater in patients treated with ETP, although the results were not statistically significant.

To determine the short-term and medium-term malignancy risks in patients with RA and using anti-TNF, data from the following entities have been assessed and crossed: the Swedish Biologics Register (ARTIS); the Swedish registers of RA; and the Swedish Cancer Register. In the first six years of anti-TNF therapy, no elevation in the malignancy risk has been observed.⁹⁶

Another aspect to consider is the occurrence of cancer in patients with RA and previous history of malignancy treated with anti-TNF. Data from the British Society for Rheumatology Biologics Register have evidenced 293 patients with previous diagnosis of malignancies in a total of 14,000 patients with RA. The malignancy IRs were compared in 177 patients with RA treated with anti-TNF and 117 patients treated with synthetic DMARDs, all of whom had a previous diagnosis of malignancy. The malignancy IRs were 25.3 events/1,000 person-years in the anti-TNF cohort and 28.3/1,000 person-years in the synthetic DMARD cohort, generating an IR adjusted for age and gender of 0.58 (95% CI 0.23–1.43) for the cohort treated with anti-TNF as compared with the cohort treated with DMARDs. The authors have concluded that the way British rheumatologists select patients with RA and previous malignancies for biological therapy does not increase the occurrence of malignancies.⁹⁷ Those data, however, should not be interpreted as indicative of the safety of the anti-TNF therapy for patients with RA and previous malignancies.

The 2008 edition of the WHO Classification of Tumors of Hematopoietic and Lymphoid tissues recognizes a new diagnostic entity termed “other iatrogenic immunodeficiency-associated lymphoproliferative disorders”, highlighting lymphomas arising in patients treated with immunosuppressive agents for autoimmune disorders.⁹⁸

The role of anti-TNF therapy and lymphoma risk in patients with RA remains unclear. Wong et al.⁹⁸ have published a meta-analysis of all randomized controlled clinical trials describing patients diagnosed with RA receiving anti-TNF therapy. The adjusted overall rates were 0.36 lymphoma per 1,000 person-years in patients who did not receive anti-TNF therapy vs. 1.65 lymphomas per 1,000 person-years in patients who received

anti-TNF therapy. The corresponding 95% CI for that rate difference was (-0.214, 2.79). The adjusted rate difference was 1.29 lymphomas per 1,000 person-years (95% CI 0.21–2.3; $P=0.093$). Thus, there is a suggestion of increased lymphomas in the group treated with anti-TNF, with the predominant subset being B-cell lymphomas. Since the occurrence of lymphoma is a rare event, there was no statistical significance.

In another meta-analysis performed aiming at assessing the risk of malignancies in patients with RA treated with anti-TNF in clinical practice (prospective observational studies), the estimated risk for tumors in all sites was 0.95 (95% CI 0.85–1.05).⁹⁹ In patients previously diagnosed with malignancies, a higher risk of tumor recurrence or of new diagnoses of malignancy was observed. That risk was not increased by exposure to anti-TNF. Results of four studies in that meta-analysis have suggested that patients treated with anti-TNF would have a significantly higher risk of developing non-melanoma skin cancer (1.45, 95% CI 1.15–1.76). In addition, patients had a higher risk of developing melanoma, the pooled estimate being 1.79 (95% CI 0.92–2.67). The pooled estimate for the risk of lymphoma was 1.11 (95% CI 0.70–1.51). That systematic review has shown that anti-TNF therapies do not increase the risk of malignancies, particularly of lymphoma. However, that class of drugs seems to increase the risk of skin cancer, including melanoma.

Using data from the ARTIS, the Swedish Cancer Register, pre-existing RA cohorts and cross-linkage with other national health and census registers, a Swedish RA cohort ($n = 67,743$) was assembled and patients who began anti-TNF therapy between 1998 and July 2006 ($n = 6,604$) were identified. A general population comparator ($n = 471,024$) was also assembled, the incidence of lymphomas from 1999 to 2006 being assessed and compared in those individuals. Of the 6,604 patients with RA treated with anti-TNF, 26 malignant lymphomas were observed during 26,981 person-years of follow-up, corresponding to a RR of 1.35 (95% CI 0.82–2.11) vs. anti-TN-naïve patients with RA (336 lymphomas during 365,026 person-years) and RR of 2.72 (95% CI 1.82–4.08) vs. the general population comparator (1,568 lymphomas during 3,355,849 person-years). Patients with RA beginning anti-TNF therapy in 1998–2001 accounted for the entire increase in lymphoma risk vs. the two comparators. However, RR has not significantly varied with time since the beginning of the first treatment or with the accumulated duration of treatment, or with the type of anti-TNF agent. In conclusion, as used in the routine care against RA, the anti-TNF agents are not associated with any major further increase in the already elevated lymphoma occurrence in RA. Changes in the selection of patients for treatment may influence the observed risk.¹⁰⁰

Data on the role of biological DMARDs other than anti-TNF agents in the occurrence of malignancies in patients with RA are scarcer.

To obtain information on the occurrence of malignancies in patients with RA being treated with abatacept (ABT), data from the ABT clinical development program were compared with those of other patients with RA and of the general population. A total of 4,134 patients with RA treated with ABT in seven different trials and 41,529 patients with RA treated with synthetic DMARDs in five observational cohorts were included in the study. In the ABT-treated patients, the 51 malignancies, excluding non-melanoma skin cancer and including seven cases of breast cancer, two cases of colorectal cancer, 13 cases of lung cancer, and five cases of lymphoma observed were not greater than the range of cases found in the five observational cohorts. The SIR comparing patients with RA with the general population was consistent with that reported in the literature. In conclusion, the IR of total malignancy (breast, colorectal and lung cancers and lymphoma) in the ABT clinical development program was consistent with that of a population with RA not using ABT, although data require further monitoring.¹⁰¹

To determine the real-life conditions of safety of treatment with rituximab (RTX) in patients with RA regarding malignancies, analysis of safety data from a cohort of patients with RA who received at least one course of RTX was performed. Patients with RA and previously diagnosed with malignancies were followed up and compared with the group of patients with no history of malignancy. The study selected 186 patients with RA. The mean follow-up was 22.3 ± 15 months, corresponding to a follow-up of 346 patient-years of RTX exposure, of whom, 24 patients (12.9%) had a history of malignancy. Five cancers were diagnosed during follow-up as follows: four new malignancies (one prostate, one breast, one colon and one cervical cancer) and one recurrence of breast cancer. The overall malignancy rate was 1.45/100 patient-years (95% CI 0.19–2.70), comparable to those of the previously studied DMARD-treated cohorts. No new hematopoietic malignancy was reported, and the six cases of lymphoma that had been in remission prior to RTX therapy remained under follow-up. Thus, although based on a small number of malignancy cases observed, and despite selection bias (12.9% of prior malignancies in RXT-treated patients), that observational study has suggested that RTX does not increase the risk of malignancies in patients with RA.¹⁰²

Up to 70% of the cancer diagnoses were made by non-oncologist physicians, evidencing the importance of those professionals in disease control. Because RA is a condition associated with the occurrence of malignancies *per se* or

resulting from its treatment, rheumatologists should be aware of suspected symptoms. It is worth noting that constant surveillance is the only way to obtain proper diagnostic and therapeutic managements, and promptness in diagnosing and conducting the case is the only way to assure a reduction in morbidity and mortality due to malignancies.

Osteoporosis

Osteoporosis and fractures are common comorbidities in patients with RA, being part of the natural course of the disease. Although osteoporosis in RA has been extensively studied for the past years, it has been rarely addressed in clinical guidelines, its management often being given less attention in the care of arthritic patients. The relevance of this issue is reflected in the high prevalence of those comorbidities, which can affect more than half of the patients with RA.¹⁰³ Consequently, the risk of fractures is greater than that of the general population. In a retrospective study with more than 30,000 patients with RA, the risk of hip and spine fractures was approximately twice that observed in the general population, and almost three times greater in patients on glucocorticoids.¹⁰⁴ In addition, almost 20% of female patients with RA can have new fractures in five years.¹⁰⁵

The pathogenesis of RA explains the imbalance between bone production and resorption. The disease has an increased production of cytokines, such as IL-1, IL-6, TNF- α , and transforming growth factor-beta, which stimulate inflammation and are involved in osteoclast activation and differentiation.¹⁰⁶ Those cytokines regulate the expression of the receptor activator of nuclear factor kappa- β ligand (RANKL), and, consequently, osteoprotegerin (OPG), which are major mediators of bone remodeling.¹⁰⁷ In addition to the RANK-RANKL-OPG pathway, Th17 lymphocytes seem to play an important role in bone resorption through the selective production of pro-inflammatory cytokines. Evidence suggests that Th17 lymphocytes have osteoclastogenic effects on murine models and accelerate bone loss in inflammatory diseases.^{107,108}

Rheumatoid arthritis is an independent risk factor for bone fracture.¹⁰⁹ In the management of patients with RA, traditional risk factors, such as advanced age, history of previous fracture, corticotherapy, family history of hip fracture, low body weight, smoking, and alcohol abuse, should be assessed. Other clinical conditions that cause bone mass loss, such as hypogonadism, early menopause, and inflammatory bowel disease, should also be documented in the clinical assessment. The characteristics of the disease related to low bone mineral density are as follows: elevated HAQ (Health Assessment Questionnaire); functional classes III and IV; long-term disease; high activity

scores; elevated inflammatory tests; and corticotherapy.¹¹⁰ They should be identified and minimized. Another independent risk factor for bone mass loss is sedentary lifestyle. Beginning physical activity can also reduce the risk of osteopenia and bone mass loss.^{111–113}

Brazilian guidelines for assessment, prevention and treatment of osteoporosis in patients with RA are urgently needed. In the initial assessment, bone densitometry should be indicated for all patients over the age of 50 years. Bone mineral density should also be evaluated in patients under 50 years with an additional risk factor, such as history of fracture and corticotherapy (dose ≥ 7.5 mg of prednisone/day for more than three months).¹¹³ In patients with established osteoporosis, the following should be assessed: alkaline phosphatase; TSH; protein electrophoresis; and serum vitamin D. Regarding the non-pharmacological management, the following measures should be taken for all patients: to practice impact exercises; to prevent falls; to stop smoking; to increase sun exposure; and to avoid alcohol abuse. Special attention should be paid to patients on corticotherapy, in addition to calcium prescription (1,200–1,500 mg/day) and vitamin D supplementation.¹¹⁴ Regarding the pharmacological management, treatment with bisphosphonates should be preferentially indicated for all patients with a T score < -2.5 on bone densitometry, and for those on corticotherapy with a T score < -1.0 .^{113,114}

RECOMENDATIONS OF THE BRAZILIAN SOCIETY OF RHEUMATOLOGY FOR THE MANAGEMENT OF COMORBIDITIES IN PATIENTS DIAGNOSED WITH RHEUMATOID ARTHRITIS

Based on the previous considerations, the expert members of the Rheumatoid Arthritis Committee of the SBR have proposed the recommendations summarized in Table 1 for managing comorbidities in patients diagnosed with RA.

CONCLUSIONS

Recommendations for the early diagnosis and proper treatment of RA have been proposed in our consensus documents and are fundamental for improving the clinical outcomes of RA.^{115,116} Similarly, understanding and managing comorbidities, such as osteoporosis, SAH, DM, dyslipidemia, MS, and atherosclerosis, are of great importance to reduce the disease-related morbidity and mortality and improve the patients' quality of life. Being aware of the signs and symptoms that might suggest the presence of malignancy at an initial phase is important to improve the prognosis of comorbidities. Pharmacological

and non-pharmacological measures to prevent venous thrombosis should be taken for patients with RA, considering their increased risk for that complication.

The multidisciplinary follow-up of patients with RA and comorbidities difficult to control is suggested to determine a better clinical response to those associated pathologies.

Table 1

Recommendations of the Brazilian Society of Rheumatology for the management of comorbidities in patients diagnosed with rheumatoid arthritis

Recommendation 1: The early diagnosis and proper treatment of comorbidities, such as systemic arterial hypertension, diabetes mellitus, dyslipidemia, metabolic syndrome, and atherosclerosis are of great importance in the management of patients with rheumatoid arthritis, because they reduce disease-related morbidity and mortality and improve the patients' quality of life.

Recommendation 2: The specific treatment of rheumatoid arthritis should be adapted to the presence of comorbidities, using, whenever possible, drugs that control comorbidities.

Recommendation 3: Because of the beneficial effects on the endothelium, and because they interfere less with the metabolism of carbohydrates and cause less dyslipidemia, angiotensin-converting-enzyme inhibitors or angiotensin II receptor blockers are preferred to begin the treatment of systemic arterial hypertension in patients with rheumatoid arthritis, rather than beta-blockers and diuretics. In the treatment of patients with concomitant rheumatoid arthritis and systemic arterial hypertension, whenever possible, the continuous and joint use of anti-inflammatory agents and/or high doses of glucocorticoid should be avoided.

Recommendation 4: In patients diagnosed with rheumatoid arthritis and diabetes mellitus, the continuous use of a high cumulative dose of corticoids should be avoided. Strategies for an effective control of the systemic inflammation of rheumatoid arthritis should be implemented, because this seems to help control diabetes mellitus.

Recommendation 5: The occurrence of dyslipidemia in rheumatoid arthritis increases the risk of cardiovascular morbidity and mortality. Appropriate treatment should start early. Statins should be used to maintain LDL cholesterol levels under 100 mg/dL and the atherosclerotic index lower than 3.5 in patients with rheumatoid arthritis who have other comorbidities that increase even further the risk for a cardiovascular event (such as systemic arterial hypertension, diabetes mellitus and/or dyslipidemia), and in those with evidence of subclinical atherosclerotic disease, such as the presence of atheroma plaques in the carotid arteries.

Recommendation 6: The presence of metabolic syndrome in the population without rheumatoid arthritis is associated with a higher likelihood of cardiovascular events and higher overall mortality. All the components of that condition, such as central obesity, reduced HDL cholesterol levels, high triglyceride levels, increased arterial blood pressure, and hyperglycemia, should be properly treated.

Recommendation 7: Considering the high prevalence of atherosclerosis in rheumatoid arthritis, and its accelerated and silent course, non-invasive tests to investigate subclinical atherosclerosis are recommended in patients with rheumatoid arthritis and comorbidities. Ultrasound imaging of the carotid arteries of patients over the age of 50 years and with rheumatoid arthritis is suggested to measure the intima-media thickness and investigate atheroma plaques.

Recommendation 8: Greater surveillance of signs and symptoms that might indicate an early diagnosis of occult malignancy in patients with rheumatoid arthritis is recommended to the rheumatologist, considering the greater prevalence of solid malignancies and lymphoma.

Recommendation 9: Pharmacological and non-pharmacological preventive measures, such as the use of unfractionated or low-molecular-weight heparin, should be considered in hospitalized patients with rheumatoid arthritis, because thromboembolic complications are more frequent in those patients.

Recommendation 10: Bone densitometry is recommended in rheumatoid arthritis patients over the age of 50 years and in younger patients on corticoid therapy at a dose greater than 7.5 mg for over three months.

Recommendation 11: Patients with rheumatoid arthritis and osteoporosis should be instructed to avoid falls, to increase their dietary calcium intake and sun exposure, and to exercise.

Recommendation 12: Calcium and vitamin D supplementation is suggested to patients with rheumatoid arthritis on corticoids for more than three months, or to those who have other concomitant risk factors for fractures. Bisphosphonates are suggested for patients with T score < -2.5 on bone densitometry, or < -1.0 in the presence of other risk factors for osteoporosis.

Recommendation 13: A multidisciplinary team, with the active participation of a rheumatologist, is recommended to treat the comorbidities of difficult control in patients with rheumatoid arthritis.

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2012 Brazilian Society of Rheumatology Consensus on the management of comorbidities in patients with rheumatoid arthritis

[Rev Bras Reumatol 2012; 52(4):474-495]

Ivânio Alves Pereira, Licia Maria Henrique da Mota, Boris Afonso Cruz, Claiton Viegas Brenol,
Lucila Stange Rezende Fronza, Manoel Barros Bertolo, Max Victor Carioca de Freitas, Nilzio Antônio da Silva,
Paulo Louzada-Junior, Rina Dalva Neubarth Giorgi, Rodrigo Aires Corrêa Lima, Geraldo da Rocha Castelar Pinheiro

In Page 474, where it reads:

Rheumatology Service and Endocrinology Service of the Sabin Laboratório de Análises Clínicas; Hospital
Universitário de Brasília – HUB.

It should read:

Brazilian Society of Rheumatology - BSR.

In Page 476, where it reads:

Treatment with other DMARDs and biologics, such as the drugs of the anti-TNF class, and mainly with the
IL-6 receptor inhibitor (tocilizumab) have controlled inflammation and increased the previously reduced TC/
HDL associated with inflammation, without interfering with the atherosclerotic index, and without increasing
clinical cardiovascular events so far.⁴²⁻⁴⁵

It should read:

Treatment with other DMARDs and biologics, such as the drugs of the anti-TNF class, and mainly with the
IL-6 receptor inhibitor (tocilizumab) have controlled inflammation and increased the previously reduced
HDL and TC associated with inflammation, without interfering with the atherosclerotic index (TC/HDL),
and without increasing clinical cardiovascular events so far.⁴²⁻⁴⁵

In page 493:

Discount the reference below:

47. Peters MJ, Nurmohamed MT, Kitas GD, Sattar N. Statin treatment of rheumatoid arthritis: comment on
the editorial by Ridker and Solomon. *Arthritis Rheum* 2010; 62(1):302-3.

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