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

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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.

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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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 ATPIII), 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-DRBI*02 and DRBI*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 review[87] 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-naive 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.

REFERENCES

1. McInnes IB, O'Dell JR. State-of-the-art: rheumatoid arthritis. Ann Rheum Dis 2010; 69(11):1898–906. [Erratum in: Ann Rheum Dis 2011; 70(2):399]
2. McInnes IB, Schett G. The pathogenesis of rheumatoid arthritis. N Engl J Med 2011; 365(23):2205–19.
3. Allaart CF, Huizinga TW. Treatment strategies in recent onset rheumatoid arthritis. Curr Opin Rheumatol 2011; 23(3):241–4.
4. Symmons DP. Rheumatoid arthritis: assessing disease activity and outcome. Clin Med 2010; 10(3):248–51.
5. Gonzalez A, Maradit Kremers H, Crowson CS, Nicola PJ, Davis JM 3rd, Therneau TM *et al*.. The widening mortality gap between rheumatoid arthritis patients and the general population. Arthritis Rheum 2007; 56(11):3583–7.
6. Hemminki K, Li X, Sundquist J, Sundquist K. Familial associations of rheumatoid arthritis with autoimmune diseases and related conditions. Arthritis Rheum 2009; 60(3):661–8.
7. Michou L, Rat AC, Lasbleiz S, Bardin T, Cornélis F. Prevalence and distribution of autoimmune diseases in 368 rheumatoid arthritis families. J Rheumatol 2008; 35(5):790–6.
8. Michaud K, Wolfe F. Comorbidities in rheumatoid arthritis. Best Pract Res Clin Rheumatol 2007; 21(5):885–906.
9. Crowson CS, Myasoedova E, Davis JM 3rd, Matteson EL, Roger VL, Therneau TM *et al*. Increased Prevalence of metabolic syndrome associated with rheumatoid arthritis in patients without clinical cardiovascular disease. J Rheumatol 2011; 38(1):29–35.
10. Chung CP, Oeser A, Solus JF, Avalos I, Gebretsadik T, Shintani A *et al*. Prevalence of the metabolic syndrome is increased in rheumatoid arthritis and is associated with coronary atherosclerosis. Atherosclerosis 2008; 196(2):756–63.
11. Steiner G, Urowitz MB. Lipid profiles in patients with rheumatoid arthritis: mechanisms and the impact of treatment. Semin Arthritis Rheum 2009; 38(5):372–81.
12. Solomon DH, Love TJ, Canning C, Schneeweiss S. Risk of diabetes among patients with rheumatoid arthritis, psoriatic arthritis and psoriasis. Ann Rheum Dis 2010; 69(12):2114–7.
13. van Halm VP, Peters MJ, Voskuyl AE, Boers M, Lems WF, Visser M *et al*. Rheumatoid arthritis versus diabetes as a risk factor for cardiovascular disease: a cross-sectional study, the CARRE Investigation. Ann Rheum Dis 2009; 68(9):1395–400.
14. Panoulas VF, Douglas KM, Milionis HJ, Stavropoulos-Kalinglou A, Nightingale P, Kita MD *et al*. Prevalence and associations of hypertension and its control in patients with rheumatoid arthritis. Rheumatology (Oxford) 2007; 46(9):1477–82.
15. Kitas GD, Gabriel SE. Cardiovascular disease in rheumatoid arthritis: state of the art and future perspectives. Ann Rheum Dis 2011; 70(1):8–14.
16. Gonzalez A, Maradit Kremers H, Crowson CS, Ballman KV, Roger VL, Jacobsen SJ *et al*. Do cardiovascular risk factors confer the same risk for cardiovascular outcomes in rheumatoid arthritis patients as in non-rheumatoid arthritis patients? Ann Rheum Dis 2008; 67(1):64–9.
17. Panoulas VF, Douglas KM, Stavropoulos-Kalinoglou A, Metsios GS, Nightingale P, Kita MD *et al*. Long-term exposure to medium-dose glucocorticoid therapy associates with hypertension in patients with rheumatoid arthritis. Rheumatology (Oxford) 2008; 47(1):72–5.
18. Alcorn N, Saunders S, Madhok R. Benefit-risk assessment of leflunomide: an appraisal of leflunomide in rheumatoid arthritis 10 years after licensing. Drug Saf 2009; 32(12):1123–34.
19. Robert N, Wong GW, Wright JM. Effect of cyclosporine on blood pressure. Cochrane Database Syst Rev 2010; (1):CD007893.
20. Atzeni F, Turiel M, Caporali R, Cavagna L, Tomasoni L, Sitia S *et al*. The effect of pharmacological therapy on the cardiovascular system of patients with systemic rheumatic diseases. Autoimmunity Rev 2010; 9(12):835–9.
21. White WB. Defining the problem of treating the patient with hypertension and arthritis pain. Am J Med 2009; 122(5 Suppl):S3–9.
22. Peters MJ, Symmons DP, McCarey D, Dijkmans BA, Nicola P, Kvien TK *et al*. EULAR evidence-based recommendations for cardiovascular risk management in patients with rheumatoid arthritis and other forms of inflammatory arthritis. Ann Rheum Dis 2010; 69(2):325–31.
23. Solomon DH, Massarotti E, Garg R, Liu J, Canning C, Schneeweiss S. Association between disease-modifying antirheumatic drugs and diabetes risk in patients with rheumatoid arthritis and psoriasis. JAMA 2011; 305(24):2525–31.
24. Tentolouris N, Arapostathi C, Voulgari C, Grammatikou S, Andrianakos A, Sfikakis PP. The effect of diabetes mellitus on the prevalence of rheumatoid arthritis: a case-control study. Diabet Med 2008; 25(8):1010–1.
25. Han C, Robinson DW Jr., Hackett MV, Paramore LC, Fraeman KH, Bala MV. Cardiovascular disease and risk factors in patients with rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis. J Rheumatol 2006; 33(11):2167–72.
26. Hoes JN, van der Goes MC, van Raalte DH, van der Zijl NJ, den Uyl D, Lems WF *et al*. Glucose tolerance, insulin sensitivity and β-cell function in patients with rheumatoid arthritis treated with or without low-to-medium dose glucocorticoids. Ann Rheum Dis 2011; 70(11):1887–94.
27. Wasko MC, Kay J, Hsia EC, Rahman MU. Diabetes mellitus and insulin resistance in patients with rheumatoid arthritis: risk reduction in a chronic inflammatory disease. Arthritis Care Res (Hoboken) 2011; 63(4):512–21.

28. Antohe JL, Bili A, Sartorius JA, Lester Kirchner H, Morris SJ, Dancea S *et al*. Diabetes risk in rheumatoid arthritis: Reduced incidence with anti-tumor necrosis factor- α therapy. Arthritis Care Res (Hoboken) 2012; 64(2):215–21.
29. Bili A, Sartorius JA, Kirchner HL, Morris SJ, Ledwich LJ, Antohe JL *et al*. Hydroxychloroquine use and decreased risk of diabetes in rheumatoid arthritis patients. J Clin Rheumatol 2011; 17(3):115–20.
30. Liao KP, Gunnarsson M, Källberg H, Ding B, Plenge RM, Padyukov L *et al*. Specific association of type 1 diabetes mellitus with anti-cyclic citrullinated peptide-positive rheumatoid arthritis. Arthritis Rheum 2009; 60(3):653–60.
31. Choy E, Sattar N. Interpreting lipid levels in the context of high-grade inflammatory states with a focus on rheumatoid arthritis: a challenge to conventional cardiovascular risk actions. Ann Rheum Dis 2009; 68(4):460–9.
32. White D, Fayez S, Doube A. Atherogenic lipid profiles in rheumatoid arthritis. N Z Med J 2006; 119(1240):U2125.
33. Nurmohamed MT. Atherogenic lipid profiles and its management in patients with rheumatoid arthritis. Vasc Health Risk Manag 2007; 3(6):845–52.
34. Myasoedova E, Crowson CS, Kremers HM, Fitz-Gibbon PD, Therneau TM, Gabriel SE. Total cholesterol and LDL levels decrease before rheumatoid arthritis. Ann Rheum Dis 2010; 69(7):1310–4.
35. Ghosh UC, Roy A, Sen K, Kundu AK, Saha I, Biswas A. Dyslipidaemia in rheumatoid arthritis in a tertiary care centre in Eastern India – a non-randomised trial. J Indian Med Assoc 2009; 107(7):427–30.
36. Garciaa-Gómez C, Nolla JM, Valverde J, Gómez-Gerique JA, Castro MJ, Pintó X. Conventional lipid profile and lipoprotein(a) concentrations in treated patients with rheumatoid arthritis. J Rheumatol 2009; 36(7):1365–70.
37. Steiner G, Urowitz MB. Lipid profiles in patients with rheumatoid arthritis: mechanisms and the impact of treatment. Semin Arthritis Rheum 2009; 38(5):372–81.
38. Georgiadis AN, Papavasiliou EC, Lourida ES, Alamanos Y, Kostara C, Tselepis AD *et al*. Atherogenic lipid profile is a feature characteristic of patients with early rheumatoid arthritis: effect of early treatment – a prospective, controlled study. Arthritis Res Ther 2006; 8(3):R82.
39. Svenson KL, Lithell H, Hallgren R, Vessby B. Serum lipoprotein in active rheumatoid arthritis and other chronic inflammatory arthritides. II. Effects of anti-inflammatory and disease-modifying drug treatment. Arch Intern Med 1987; 147(11):1917–20.
40. Raynauld JP. Cardiovascular mortality in rheumatoid arthritis: how harmful are corticosteroids? J Rheumatol 1997; 24(3):415–6.
41. Wallace DJ, Metzger AL, Stecher VJ, Turnbull BA, Kern PA. Cholesterol-lowering effect of hydroxychloroquine in patients with rheumatic disease: reversal of deleterious effects of steroids on lipids. Am J Med 1990; 89(3):322–6.
42. van Halm VP, Nielen MM, Nurmohamed MT, van Schaardenburg D, Reesink HW, Voskuyl AE *et al*. Lipids and inflammation: serial measurements of the lipid profile of blood donors who later developed rheumatoid arthritis. Ann Rheum Dis 2007; 66(2):184–8.
43. Singh JA, Beg S, Lopez-Olivo MA. Tocilizumab for rheumatoid arthritis. Cochrane Database of Systematic Reviews. J Rheumatol 2011; 38(1):10–20.
44. Storage SS, Agrawal H, Furst DE. Description of the efficacy and safety of three new biologics in the treatment of rheumatoid arthritis. Korean J Intern Med 2010; 25(1):1–17.
45. Pollono EN, Lopez-Olivo MA, Lopez JA, Suarez-Almazor ME. A systematic review of the effect of TNF-alpha antagonists on lipid profiles in patients with rheumatoid arthritis. Clin Rheumatol 2010; 29(9):947–55.
46. McCarey DW, McInnes IB, Madhok R, Hampson R, Scherbakov O, Ford I *et al*. Trial of Atorvastatin in Rheumatoid Arthritis (TARA): double-blind, randomised placebo-controlled trial. Lancet 2004; 363(9426):2015–21.
47. Chatterjee Adhikari M, Guin A, Chakraborty S, Sinhamahapatra P, Ghosh A. Subclinical atherosclerosis and endothelial dysfunction in patients with early rheumatoid arthritis as evidenced by measurement of carotid intima-media thickness and flow-mediated vasodilatation: an observational study. Semin Arthritis Rheum 2012 41(5):669–75.
48. González-Juanatey C, Llorca J, González-Gay MA. Correlation between endothelial function and carotid atherosclerosis in rheumatoid arthritis patients with long-standing disease. Arthritis Res Ther 2011; 13(3):R101.
49. Pereira IA, Laurindo IM, Zimmermann AF, Werner Castro GR, Mello F, Borba EF. Single measurements of C-reactive protein and disease activity scores are not predictors of carotid atherosclerosis in rheumatoid arthritis patients. Acta Reumatol Port 2009; 34(1):58–64.
50. Chung CP, Oeser A, Raggi P, Gebretsadik T, Shintani AK, Sokka T *et al*. Increased coronary-artery atherosclerosis in rheumatoid arthritis: relationship to disease duration and cardiovascular risk factors. Arthritis Rheum 2005; 52(10):3045–53.
51. Maradit-Kremers H, Crowson CS, Nicola PJ, Ballman KV, Roger VL, Jacobsen SJ *et al*. Increased unrecognized coronary heart disease and sudden deaths in rheumatoid arthritis: a population-based cohort study. Arthritis Rheum 2005; 52(2):402–11.
52. Nicola PJ, Maradit-Kremers H, Roger VL, Jacobsen SJ, Crowson CS, Ballman KV*et al*. The risk of congestive heart failure in rheumatoid arthritis: a population-based study over 46 years. Arthritis Rheum 2005; 52(2):412–20.
53. Westlake SL, Colebatch AN, Baird J, Kiely P, Quinn M, Choy E *et al*. The effect of methotrexate on cardiovascular disease in patients with rheumatoid arthritis: a systematic literature review. Rheumatology (Oxford) 2010; 49(2):295–307.
54. Westlake SL, Colebatch AN, Baird J, Curzen N, Kiely P, Quinn M *et al*. Tumour necrosis factor antagonists and the risk of cardiovascular disease in patients with rheumatoid arthritis: a systematic literature review. Rheumatology (Oxford) 2011; 50(3):518–31.
55. Barnabe C, Martin BJ, Ghali WA. Systematic review and meta-analysis: anti-tumor necrosis factor α therapy and cardiovascular events in rheumatoid arthritis. Arthritis Care Res (Hoboken) 2011; 63(4):522–9.
56. Gislason GH, Rasmussen JN, Abildstrom SZ, Schramm TK, Hansen ML, Fosbøl EL *et al*. Increased mortality and cardiovascular morbidity associated with use of nonsteroidal anti-inflammatory drugs in chronic heart failure. Arch Intern Med 2009; 169(2):141–9.
57. Solomon DH, Glynn RJ, Rothman KJ, Schneeweiss S, Setoguchi S, Mogun H *et al*. Subgroup analyses to determine cardiovascular risk associated with nonsteroidal anti-inflammatory drugs and coxibs in specific patient groups. Arthritis Rheum 2008; 59(8):1097–104.
58. Söderlin M, Petersson I, Bergman S, Svensson B; BARFOT study group. Smoking at onset of rheumatoid arthritis (RA) and its effect on disease activity and functional status: experiences from BARFOT, a long-term observational study on early RA. Scand J Rheumatol 2011; 40(4):249–55.

59. Saevarsdottir S, Wedrén S, Seddighzadeh M, Bengtsson C, Wesley A, Lindblad S *et al.* Patients with early rheumatoid arthritis who smoke are less likely to respond to treatment with methotrexate and tumor necrosis factor inhibitors: observations from the Epidemiological Investigation of Rheumatoid Arthritis and the Swedish Rheumatology Register cohorts. Arthritis Rheum 2011; 63(1):26–36.
60. Alberti KG, Zimmet P, Shaw J. Metabolic syndrome – a new world-wide definition. A Consensus Statement from the International Diabetes Federation. Diabet Med 2006; 23(5):469–80.
61. Executive Summary of The Third Report of The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, And Treatment of High Blood Cholesterol In Adults (Adult Treatment Panel III) JAMA 2001; 285(19):2846–97.
62. Grundy SM, Cleeman JI, Daniels SR, Donato KA, Eckel RH, Franklin BA *et al*. Diagnosis and management of the metabolic syndrome: an American Heart Association/National Heart, Lung, and Blood Institute Scientific Statement. [Executive summary]. Circulation 2005; 112(17):e285–e290.
63. Santos MJ, Fonseca JE. Metabolic syndrome, inflammation and atherosclerosis – the role of adipokines in health and in systemic inflammatory rheumatic diseases. Acta Reumatol Port 2009; 34(4):590–8.
64. Chung CP, Oeser A, Solus JF, Avalos I, Gebretsadik T, Shintani A *et al*. Prevalence of the metabolic syndrome is increased in rheumatoid arthritis and is associated with coronary atherosclerosis.Atherosclerosis 2008; 196(2):756–63.
65. Sidiropoulos PI, Karvounaris SA, Boumpas DT. Metabolic syndrome in rheumatic diseases: epidemiology, pathophysiology, and clinical implications. Arthritis Res Ther 2008; 10(3):207.
66. Pereira RM, de Carvalho JF, Bonfa E. Metabolic syndrome in rheumatological diseases. Autoimmun Rev 2009; 8(5):415–9.
67. da Cunha V, Brenol C, Brenol J, Fuchs S, Arlindo E, Melo I *et al*. Metabolic syndrome prevalence is increased in rheumatoid arthritis patients and is associated with disease activity. Scand J Rheumatol 2012; 41(3):186–91.
68. Karvounaris SA, Sidiropoulos PI, Papadakis JA, Spanakis EK, Bertsias GK, Kritikos HD *et al.* Metabolic syndrome is common among middle-to-older aged Mediterranean patients with rheumatoid arthritis and correlates with disease activity: a retrospective, cross-sectional, controlled, study. Ann Rheum Dis 2007; 66(1):28–33.
69. Dessein PH, Tobias M, Veller MG. Metabolic syndrome and subclinical atherosclerosis in rheumatoid arthritis. J Rheumatol 2006; 33(12):2425–32.
70. La Montagna G, Cacciapuoti F, Buono R, Manzella D, Mennillo GA, Arciello A *et al.* Insulin resistance is an independent risk factor for atherosclerosis in rheumatoid arthritis. Diab Vasc Dis Res 2007; 4(2):130–5.
71. Mottillo S, Filion KB, Genest J, Joseph L, Pilote L, Poirier P *et al*. The metabolic syndrome and cardiovascular risk a systematic review and meta-analysis. J Am Coll Cardiol 2010; 56(14):1113–32.
72. da Cunha VR, Brenol CV, Brenol JC, Xavier RM. Rheumatoid arthritis and metabolic syndrome. Rev Bras Reumatol 2011; 51(3):260–8.
73. Toms TE, Panoulas VF, John H, Douglas KM, Kitas GD. Methotrexate therapy associates with reduced prevalence of the metabolic syndrome in rheumatoid arthritis patients over the age of 60 – more than just an anti-inflammatory effect? A cross sectional study. Arthritis Res Ther 2009; 11(4):R110.
74. Bacani AK, Gabriel SE, Crowson CS, Heit JA, Matteson EL. Noncardiac vascular disease in rheumatoid arthritis: increase in venous thromboembolic events? Arthritis Rheum 2012; 64(1):53–61.
75. Matta F, Singala R, Yaekoub AY, Najjar R, Stein PD. Risk of venous thromboembolism with rheumatoid arthritis. Thromb Haemost 2009; 101(1):134–8.
76. Aksu K, Donmez A, Keser G. Inflammation-induced thrombosis: mechanisms, disease associations and management. Curr Pharm Des 2012; 18(11):1478–93.
77. Undas A, Gissel M, Kwasny-Krochin B, Gluszko P, Mann KG, Brummel-Ziedins KE. Thrombin generation in rheumatoid arthritis: dependence on plasma factor composition. Thromb Haemost 2010; 104(2):224–30.
78. Bisoendial RJ, Levi M, Tak PP, Stroes ES. The prothrombotic state in rheumatoid arthritis: an additive risk factor for adverse cardiovascular events. Semin Thromb Hemost 2010; 36(4):452–7.
79. Mameli A, Barcellona D, Marongiu F. Rheumatoid arthritis and thrombosis. Clin Exp Rheumatol 2009; 27(5):846–55.
80. Liang KP, Liang KV, Matteson EL, McClelland RL, Christianson TJ, Turesson C. Incidence of noncardiac vascular diseasein rheumatoid arthritis and relationship to extraarticular disease manifestations. Arthritis Rheum 2006; 54(2):642–8.
81. Davies R, Galloway JB, Watson KD, Lunt M, Symmons DP, Hyrich KL; BSRBR Control Centre Consortium, British Society for Rheumatology Biologics Register. Venous thrombotic events are not increased in patients with rheumatoid arthritis treated with anti-TNF therapy: results from the British Society for Rheumatology Biologics Register. Ann Rheum Dis 2011; 70(10):1831–4.
82. 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.
83. Zintzaras E, Voulgarelis M, Moutsopoulos HM. The risk of lymphoma development in autoimmune diseases: a meta-analysis. Arch Intern Med 2005; 165(20):2337–44.
84. Hemminki K, Li X, Sundquist K, Sundquist J. Cancer risk in hospitalized rheumatoid arthritis patients. Rheumatology (Oxford) 2008; 47(5):698–701.
85. Kim YJ, Shim JS, Choi CB, Bae SC. Mortality and incidence of malignancy in Korean patients with rheumatoid arthritis. J Rheumatol 2012; 39(2):226–32.
86. Bongartz T, Sutton AJ, Sweeting MJ, Buchan I, Matteson EL, Montori V. Anti-TNF antibody therapy in rheumatoid arthritis and the risk of serious infections and malignancies: systematic review and meta-analysis of rare harmful effects in randomized controlled trials. JAMA 2006; 295(19):2275–85.
87. Thompson AE, Rieder SW, Pope JE. Tumor necrosis factor therapy and the risk of serious infection and malignancy in patients with early rheumatoid arthritis: a meta-analysis of randomized controlled trials. Arthritis Rheum 2011; 63(6):1479–85.
88. Askling J. The risk of malignancies in RA patients treated with biologics. Z Rheumatol 2010; 69(9):774–9.
89. Thomas E, Symmons DP, Brewster DH, Black RJ, Macfarlane GJ. National study of cause-specific mortality in rheumatoid arthritis, juvenile chronic arthritis, and other rheumatic conditions: a 20 year followup study. J Rheumatol 2003; 30(5):958–65.
90. Hemminki K, Liu X, Ji J, Sundquist J, Sundquist K. Autoimmune disease and subsequent digestive tract cancer by histology. Ann Oncol 2012; 23(4)927–33.

91. Hellgren K, Smedby KE, Feltelius N, Baecklund E, Askling J. Do rheumatoid arthritis and lymphoma share risk factors? A comparison of lymphoma and cancer risks before and after diagnosis of rheumatoid arthritis. Arthritis Rheum 2010; 62(5):1252–8.
92. Miranda-Duarte A, Kraus-Weisman A, Granados J, Vill AR. Human leukocyte antigens class II genes are associated with cancer development in the autoimmune rheumatic diseases. Rev Invest Clin 2011; 63(3):236–43.
93. Strangfeld A, Hierse F, Rau R, Burmester GR, Krummel-Lorenz B, Demary W *et al*. Risk of incident or recurrent malignancies among patients with rheumatoid arthritis exposed to biologic therapy in the German biologics register RABBIT. Arthritis Res Ther 2010; 12(1):R5.
94. Leombruno JP, Einarson TR, Keystone EC. The safety of anti-tumour necrosis factor treatments in rheumatoid arthritis: meta and exposure-adjusted pooled analyses of serious adverse events. Ann Rheum Dis 2009; 68(7):1136–45.
95. Bongartz T, Warren FC, Mines D, Matteson EL, Abrams KR, Sutton AJ. Etanercept therapy in rheumatoid arthritis and the risk of malignancies: a systematic review and individual patient data meta-analysis of randomised controlled trials. Ann Rheum Dis 2009; 68(7):1177–83.
96. Askling J, van Vollenhoven RF, Granath F, Raaschou P, Fored CM, Baecklund E *et al*. Cancer risk in patients with rheumatoid arthritis treated with anti-tumor necrosis factor alpha therapies: does the risk change with the time since start of treatment? Arthritis Rheum 2009; 60(11):3180–9.
97. Dixon WG, Watson KD, Lunt M, Mercer LK, Hyrich KL, Symmons DP *et al*. Influence of anti-tumor necrosis factor therapy on cancer incidence in patients with rheumatoid arthritis who have had a prior malignancy: results from the British Society for Rheumatology Biologics Register. Arthritis Care Res (Hoboken). 2010; 62(6):755–63. [Erratum in: Arthritis Care Res (Hoboken) 2010; 62(10):1514.]
98. Wong AK, Kerkoutian S, Said J, Rashidi H, Pullarkat ST. Risk of lymphoma in patients receiving antitumor necrosis factor therapy: a meta-analysis of published randomized controlled studies. Clin Rheumatol 2012; 31(4):631–6.
99. Mariette X, Matucci-Cerinic M, Pavelka K, Taylor P, van Vollenhoven R, Heatley R *et al*. Malignancies associated with tumour necrosis factor inhibitors in registries and prospective observational studies: a systematic review and meta-analysis. Ann Rheum Dis 2011; 70(11):1895–904.
100. Askling J, Baecklund E, Granath F, Geborek P, Fored M, Backlin C *et al*. Anti-tumour necrosis factor therapy in rheumatoid arthritis and risk of malignant lymphomas: relative risks and time trends in the Swedish Biologics Register. Ann Rheum Dis 2009; 68(5):648–53.
101. Simon TA, Smitten AL, Franklin J, Askling J, Lacaille D, Wolfe F *et al*. Malignancies in the rheumatoid arthritis abatacept clinical development programme: an epidemiological assessment. Ann Rheum Dis 2009; 68(12):1819–26.
102. Slimani S, Lukas C, Combe B, Morel J. Rituximab in rheumatoid arthritis and the risk of malignancies: report from a French cohort. Joint Bone Spine 2011; 78(5):484–7.
103. Forsblad D'Elia H, Larsen A, Waltbrand E, Kvist G, Mellström D, Saxne T *et al*. Radiographic joint destruction in postmenopausal rheumatoid arthritis is strongly associated with generalized osteoporosis. Ann Rheum Dis 2003; 62(7):617–23.
104. van Staa TP, Geusens P, Bijlsma JW, Leufkens HG, Cooper C. Clinical assessment of the long-term risk of fracture in patients with rheumatoid arthritis. Arthritis Rheum 2006; 54(10):3104–12.
105. Vis M, Haavardsholm EA, Bøyesen P, Haugeberg G, Uhlig T, Hoff M *et al*. High incidence of vertebral and non-vertebral fractures in the OSTRA cohort study: a 5-year follow-up study in postmenopausal women with rheumatoid arthritis. Osteoporos Int 2011; 22(9):2413–9.
106. Edwards CJ, Williams E. The role of interleukin-6 in rheumatoid arthritis-associated osteoporosis. Osteoporos Int 2010; 21(8):1287–93.
107. Daoussis D, Andonopoulos AP, Liossis SN. Wnt pathway and IL-17: novel regulators of joint remodeling in rheumatic diseases. Looking beyond the RANK-RANKL-OPG axis. Semin Arthritis Rheum 2010; 39(5):369–83.
108. Yuan FL, Li X, Lu WG, Zhao YQ, Li CW, Li JP *et al*. Type 17 T-helper cells might be a promising therapeutic target for osteoporosis. Mol Biol Rep 2012; 39(1):771–4.
109. Kanis JA, Borgstrom F, De Laet C, Johansson H, Johnell O, Jonsson B *et al*. Assessment of fracture risk. Osteoporos Int 2005; 16(6):581–9.
110. Broy SB, Tanner SB; FRAX® Position Development Conference Members. Official Positions for FRAX® clinical regarding rheumatoid arthritis from Joint Official Positions Development Conference of the International Society for Clinical Densitometry and International Osteoporosis Foundation on FRAX®. J Clin Densitom 2011; 14(3):184–9.
111. Tourinho TF, Capp E, Brenol JC, Stein A. Physical activity prevents bone loss in premenopausal women with rheumatoid arthritis: a cohort study. Rheumatol Int 2008; 28(10):1001–7.
112. de Jong Z, Munneke M, Lems WF, Zwinderman AH, Kroon HM, Pauwels EK *et al*. Slowing of bone loss in patients with rheumatoid arthritis by long-term high-intensity exercise: results of a randomized, controlled trial. Arthritis Rheum 2004; 50(4):1066–76.
113. Papaioannou A, Morin S, Cheung AM, Atkinson S, Brown JP, Feldman S *et al.*; Scientific Advisory Council of Osteoporosis Canada. 2010 clinical practice guidelines for the diagnosis and management of osteoporosis in Canada: summary. CMAJ 2010; 182(17):1864–73.
114. Grossman JM, Gordon R, Ranganath VK, Deal C, Caplan L, Chen W *et al*. American College of Rheumatology 2010 recommendations for the prevention and treatment of glucocorticoid-induced osteoporosis. Arthritis Care Res (Hoboken) 2010; 62(11):1515–26.
115. Mota LMH, 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.
116. da Mota LM, Cruz BA, Brenol CV, Pereira IA, Rezende-Fronza LS, Bertolo MB *et al*. 2012 Brazilian Society of Rheumatology Consensus for the treatment of rheumatoid arthritis. Rev Bras Reumatol 2012; 52(2):152–74.

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

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

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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.