


Revista Brasileira de Reumatologia

 Este é um artigo publicado em acesso aberto (Open Access) sob a licença Creative Commons Attribution Non-Commercial No Derivative, que permite uso, distribuição e reprodução em qualquer meio, sem restrições desde que sem fins comerciais, sem alterações e que o trabalho original seja corretamente citado. Fonte: http://www.scielo.br/scielo.php?script=sci_arttext&pid=S0482-50042015000300281&lng=en&nrm=iso&tlng=pt&ORIGINALLANG=pt. Acesso em: 10 abr. 2018.

REFERÊNCIA

MOTA, Licia Maria Henrique da et al. Safe use of biological therapies for the treatment of rheumatoid arthritis and spondyloarthritis. **Revista Brasileira de Reumatologia**, São Paulo, v. 55, n. 3, p. 281-309, maio/jun. 2015. Disponível em: <http://www.scielo.br/scielo.php?script=sci_arttext&pid=S0482-50042015000300281&lng=en&nrm=iso>. Acesso em: 10 abr. 2018. doi: <http://dx.doi.org/10.1016/j.rbr.2014.06.006>.



REVISTA BRASILEIRA DE REUMATOLOGIA

www.reumatologia.com.br



Review article

Safe use of biological therapies for the treatment of rheumatoid arthritis and spondyloarthritis



Licia Maria Henrique da Mota^{a,*}, Bóris Afonso Cruz^b, Claiton Viegas Brenol^c, Daniel Feldman Pollak^d, Geraldo da Rocha Castelar Pinheiro^e, Ieda Maria Magalhães Laurindo^f, Ivânio Alves Pereira^g, Jozélio Freire de Carvalho^h, Manoel Barros Bertoloⁱ, Marcelo de Medeiros Pinheiro^j, Max Victor Carioca Freitas^k, Nilzio Antônio da Silva^l, Paulo Louzada-Júnior^m, Percival Degrava Sampaio-Barrosⁿ, Rina Dalva Neubarth Giorgi^o, Rodrigo Aires Corrêa Lima^p, Luis Eduardo Coelho Andrade^q

^a Medicine School, Universidade de Brasília, Brasília, DF, Brazil

^b Instituto BIOCOR, Belo Horizonte, MG, Brazil

^c Department of Internal Medicine, Medicine School, Universidade Federal do Rio Grande do Sul, Porto Alegre, RS, Brazil

^d Escola Paulista de Medicina, Universidade Federal do Estado de São Paulo, São Paulo, SP, Brazil

^e Medical Sciences School, Universidade do Estado do Rio de Janeiro, Rio de Janeiro, RJ, Brazil

^f Medicine School, Universidade de São Paulo, São Paulo, SP, Brazil

^g Universidade do Sul de Santa Catarina, Florianópolis, SC, Brazil

^h Centro Médico Aliança, Salvador, BA, Brazil

ⁱ Medical Sciences School, Hospital de Clínicas, Universidade Estadual de Campinas, Campinas, SP, Brazil

^j Outpatient Clinic of Spondyloarthritis and Osteoporosis, Rheumatology Service, Escola Paulista de Medicina, Universidade Federal do Estado de São Paulo, São Paulo, SP, Brazil

^k Rheumatologist, Fortaleza, CE, Brazil

^l Medicine School, Universidade Federal de Goiás, Goiânia, GO, Brazil

^m Faculdade de Medicina de Ribeirão Preto, Universidade de São Paulo, Ribeirão Preto, SP, Brazil

ⁿ Rheumatology Service, Medicine School, Universidade de São Paulo, São Paulo, SP, Brazil

^o Diagnostics and Therapeutic Sector, Rheumatology Service, Hospital do Servidor Público Estadual de São Paulo, São Paulo, SP, Brazil

^p Teaching Hospital of Brasília, Hospital de Base do Distrito Federal, Brasília, DF, Brazil

^q Rheumatology Service, Escola Paulista de Medicina, Universidade Federal do Estado de São Paulo, São Paulo, SP, Brazil

ARTICLE INFO

Article history:

Received 25 June 2013

Accepted 30 June 2014

Available online 27 November 2014

ABSTRACT

The treatment of autoimmune rheumatic diseases has gradually improved over the last half century, which has been expanded with the contribution of biological therapies or immunobiopharmaceuticals. However, we must be alert to the possibilities of undesirable effects from the use of this class of medications. The Brazilian Society of Rheumatology (Sociedade Brasileira de Reumatologia) produced a document based on a comprehensive literature review on the safety aspects of this class of drugs, specifically with regard to the

* Corresponding author.

E-mail: liciamhmota@gmail.com (L.M.H. da Mota).

<http://dx.doi.org/10.1016/j.rbre.2014.06.006>

2255-5021/© 2014 Elsevier Editora Ltda. All rights reserved.

Keywords:

Rheumatoid arthritis
Spondyloarthritis
Biologicals
Immunobiologicals
Security

treatment of rheumatoid arthritis and spondyloarthritis. The themes selected by the participating experts, on which considerations have been established as the safe use of biological drugs, were: occurrence of infections (bacterial, viral, tuberculosis), infusion reactions, hematological, neurological, gastrointestinal and cardiovascular reactions, neoplastic events (solid tumors and hematologic neoplasms), immunogenicity, other occurrences and vaccine response. For didactic reasons, we opted by elaborating a summary of safety assessment in accordance with the previous themes, by drug class/mechanism of action (tumor necrosis factor antagonists, T-cell co-stimulation blockers, B-cell depleters and interleukin-6 receptor blockers). Separately, general considerations on safety in the use of biologicals in pregnancy and lactation were proposed. This review seeks to provide a broad and balanced update of that clinical and experimental experience pooled over the last two decades of use of immunobiological drugs for RA and spondyloarthritis treatment.

© 2014 Elsevier Editora Ltda. All rights reserved.

Segurança do uso de terapias biológicas para o tratamento de artrite reumatoide e espondiloartrites

R E S U M O

O tratamento das doenças reumáticas autoimunes sofreu uma progressiva melhora ao longo da última metade do século passado, que foi expandida com a contribuição das terapias biológicas ou imunobiológicas. No entanto, há que se atentar para as possibilidades de efeitos indesejáveis advindos da utilização dessa classe de medicações. A Sociedade Brasileira de Reumatologia (SBR) elaborou um documento, baseado em ampla revisão da literatura, sobre os aspectos relativos à segurança dessa classe de fármacos, mais especificamente no que diz respeito ao tratamento da artrite reumatoide (AR) e das espondiloartrites. Os temas selecionados pelos especialistas participantes, sobre os quais foram estabelecidas considerações quanto à segurança do uso de drogas biológicas, foram: ocorrência de infecções (bacterianas, virais, tuberculose), reações infusionais, reações hematológicas, neurológicas, gastrointestinais, cardiovasculares, ocorrências neoplásicas (neoplasias sólidas e da linhagem hematológica), imunogenicidade, outras ocorrências e reposta vacinal. Optou-se, por motivos didáticos, por se fazer um resumo da avaliação de segurança, de acordo com os tópicos anteriores, por classe de drogas/mecanismo de ação (antagonistas do fator de necrose tumoral, bloqueador da co-estimulação do linfócito T, depletor de linfócito B e bloqueador do receptor de interleucina-6). Em separado, foram tecidas considerações gerais sobre segurança do uso de biológicos na gravidez e na lactação. Esta revisão procura oferecer uma atualização ampla e equilibrada das experiências clínica e experimental acumuladas nas últimas duas décadas de uso de medicamentos imunobiológicos para o tratamento da AR e espondiloartrites.

© 2014 Elsevier Editora Ltda. Todos os direitos reservados.

Palavras-chave:

Artrite reumatoide
Espondiloartrites
Biológicos
Imunobiológicos
Segurança

Introduction

The treatment of autoimmune rheumatic diseases has gradually improved over the last half century, and has been expanded with the contribution of biological or immunobiological therapy (also called biological agents or disease-modifying drugs – DMD-biologicals). This entire process has been implicated in improving therapeutic outcomes and the quality of life, as well as in reducing the morbidity and mortality of patients.^{1,2}

Concomitantly, there has been a proportional strengthening of Rheumatology as a medical specialty. Such a scenario is very favorable and signals an auspicious perspective for individuals suffering from autoimmune rheumatic diseases. Monoclonal antibodies and recombinant molecules (or fusion

proteins), able to interfere with the signaling of cellular processes, multiply in a fast pace, and new therapeutic possibilities will be progressively added.³⁻⁵

However, as with any drug class, we must be alert to the possibility of undesirable effects from the use of immunobiological medicines – an aspect which becomes even more important, given the intense action of these molecules on various immunological processes of critical importance. Added to this is the fact that many of the targets of these molecules participate in multiple physiological processes, extending the range of possible effects of the respective inhibitors or antagonist drugs.

Security issues are important for the patient to attain a position of maximum possible well-being; such questions guide medical treatment since ancient times. With respect

to the use of immunobiological agents used in Rheumatology, the application of this premise can help in choosing the best option for each patient. With the advent of new therapies, the main questions from patients and physicians focus not only on the benefits and costs, but also on the safety of these medications. Thus, in addition to considering the mechanism of action and pharmacological peculiarities of each agent, including dosage, plasma and biological half-life and route of administration, as well as the opinion, adherence and the degree of understanding of the patient, the rheumatologist must weigh the major adverse events for each particular scenario.⁶

With these considerations in mind, the Brazilian Society of Rheumatology (*Sociedade Brasileira de Reumatologia/SBR*) deemed appropriate to elaborate a text on the safety aspects of this class of drugs. This document represents the consensus of the members of the Commission on Rheumatoid Arthritis (RA) of SBR and of several invited experts, including members of the SBR's Commission on Spondyloarthritis and other rheumatologists who attended the IV Forum on Biological Agents – Focus on Safety, sponsored by SBR.

Objective

The aim of this study was to provide a document representing the opinion of experts, based on extensive literature review on aspects relating to the safe use of immunobiological drugs in Rheumatology, specifically with regard to the treatment of RA and spondyloarthritis.

Method

The method of elaboration of this paper included a literature review, conducted by rheumatology experts, members of the Commission on RA of SBR and other invited experts, members of the Commission on Spondyloarthritis of SBR and participants of IV Forum on Biological Agents – Focus on Security, held on July 20/21, 2012, in São Paulo, Brazil. The bibliographical survey covered existing publications in MEDLINE, SciELO, PubMed and EMBASE up to February 2013. Recommendations were written and re-evaluated by all participants during multiple rounds of questioning and corrections made via the Internet.

The themes selected by the participating experts, about considerations given regarding the safety of the use of biological drugs in rheumatology, were: occurrence of infections (bacterial, viral, tuberculosis), infusion reactions, hematological, neurological, gastrointestinal and cardiovascular reactions, neoplastic events (solid tumors and hematological lineage neoplasms), immunogenicity, other occurrences and vaccine response. For didactic reasons, we opted by elaborating a summary of the safety assessment, in accordance with the previous themes, by drug class/mechanism of action and, separately, general considerations on safety in the use of biologicals in pregnancy and lactation.

Safety assessment by drug class/mechanism of action

Tumor necrosis factor antagonists (anti-TNF)

Tumor necrosis factor alpha (TNF α) is a proinflammatory cytokine that exerts multiple effects on different cell types and plays a critical role in the pathogenesis of chronic inflammatory diseases, such as RA, ankylosing spondylitis (AS), psoriatic arthritis (PA), and arthritis associated with inflammatory bowel diseases (enteropathic arthritis).⁷ TNF α exerts cytotoxic action on different types of lymphocytes, stimulating their apoptosis and that of endothelial cells. Currently, there are five different anti-TNF biological agents (also called TNF blockers) marketed: adalimumab (ADA), a 100% human monoclonal antibody; certolizumab (CERT) pegol, a Fab fragment of a humanized anti-TNF antibody with high affinity for TNF, conjugated with two molecules of polyethylene glycol (5–10% of animal protein); etanercept (ETN), a fusion protein composed of TNF soluble receptor plus Fc region of IgG; golimumab (GOL), another human monoclonal antibody; and infliximab (IFX), a chimeric monoclonal antibody (25–30% of animal protein).⁸ With the exception of IFX, a drug for intravenous (IV) use, the biological agents of anti-TNF class are drugs for subcutaneous (SC) use.

The biological agents of the anti-TNF class are prescribed where there is no response, or only an incomplete (partial) response was obtained, to basic conventional drugs, mainly methotrexate (MTX), both in RA^{9,10} and PA.^{11,12} On the other hand, in AS patients these biologicals may be prescribed after failure with continuous use of non-steroidal anti-inflammatory drugs (NSAIDs), in cases of predominantly axial disease, and after basic conventional drugs, in cases of peripheral disease.^{13,14}

Used in the treatment of RA for almost two decades, anti-TNF agents usually are used for at least five years in 60% of the patients, according to the Dutch Rheumatoid Arthritis Monitoring register.¹⁵ Its use for over a decade has not presented serious risks with respect to long-term safety in RA.¹⁶ The possibility of successive exchanges of biological agents in the long-term follow-up of patients with RA can bring questions about to what agent to impute beneficial or adverse effects.¹⁷

On the other hand, anti-TNF agents represent the only class of biological agents currently in proven use in AS. There are records of good response maintained in face of the use of IFX for eight years,¹⁸ ETN for four years,¹⁹ ADA for five years²⁰ and GOL for two years.²¹ There is no difference in efficacy among the various anti-TNF drugs in the treatment of AS. The sudden discontinuation of IFX, after a good sustained response for three years, led to relapse in more than 90% of the patients within a 1-year period.²² While anti-TNF maintenance is similar in AS and RA after one year of follow-up, the persistent use of anti-TNF in the long term is significantly longer in patients with AS.²³ Also in PA, anti-TNF agents maintain good response to treatment over time, with no deadline for discontinuation of these drugs.^{24–26}

Anti-TNF medications are contraindicated in pregnant or breastfeeding women, in patients with congestive heart failure (CHF) classes III and IV according to the New York Heart Association (NYHA), in the presence of active infection or at high risk for development of infections (chronic ulcer of

lower limbs, septic arthritis in the past 12 months), recurrent pulmonary infections, multiple sclerosis, and with current or previous diagnosis of neoplasia (less than five years). The patient should be carefully monitored, with assessment of possible emergence of signs of infection, that should be treated promptly and immediately.⁷⁻⁹

Infections

In the maintenance of any anti-TNF agent, both at the beginning of treatment and after years of medication, infection is the most frequent and important adverse event. Generally, these are usually bacterial or viral infections, mainly affecting the respiratory tract, skin, soft tissues and urinary tract.²⁷ The risk of hospitalization due to bacterial infection is twice as high in patients using anti-TNF than in patients in monotherapy with MTX; this risk increases four times when considering the first six months of treatment.²⁸

Most available data on the risk of infection in patients on biologic therapy concern the first anti-TNF agents: IFX, ETN and ADA. No definitive comparative studies were published. Meta-analyses and observational study assessments showed no significant difference in the incidence of infectious complications among different biological agents. Albeit with a shorter observation time, the current understanding is that the newer anti-TNF agents, e.g. GOL and CERT, are associated with the same risk of infection.²⁹

Although clinical trials have not shown significant increase versus placebo, meta-analyses, extension studies and post-marketing registries confirmed a higher risk of infection in patients with rheumatic diseases using biological agents. The relative risk (RR) for different forms of infection varies from 1.2 to 2.8 compared to synthetic or non-biological DMDs, e.g. MTX.^{29,30} Severe infections – defined as infections requiring hospitalization and/or IV antibiotics – and opportunistic infections such as tuberculosis and *Pneumocystis carinii* and fungal infections, also increased in patients on biologic therapy.³¹ The incidence of infectious complications do not increase with the progression of treatment and appears to be greatest in the first months of exposure to biological agents.^{27,31}

Variations in the spectrum of signs and symptoms associated with infection and atypical clinical presentations are common, and this requires a careful monitoring and clinical suspicion for a correct diagnosis.³⁰ Skin infections are among the most common adverse effects with the use of anti-TNF.²⁹ They account for about 20% of all infectious complications associated with TNF inhibitors, being second only to respiratory tract involvement.³⁰ Cellulitis of bacterial origin and herpes zoster virus infections are among the most common cutaneous infectious complications. Although infection by herpes zoster is more common in RA patients than in the general population, recent studies show an increased risk in users of immunobiological therapy.^{32,33}

As infectious complication, tuberculosis requires special attention. Considering that TNF plays a central role in the formation and maintenance of granuloma integrity, tuberculosis is an adverse event that should be potentially very frequent,³⁴ had it not been its systematic prevention, which should never be neglected. Most cases occur in the first months of treatment with anti-TNF and the frequencies of extra-pulmonary

tuberculosis and atypical presentations are higher in patients using anti-TNF agents.³⁵

Observational studies and meta-analyses sought to evaluate differences in the risk of tuberculosis among different anti-TNF agents, and the results are conflicting. The current understanding is that, if there is a difference, this would not be of clinical significance.³⁶ The risk of reactivation of tuberculosis appears to be lower with other biological agents, but there are no definitive data. That is why a screening exam for latent tuberculosis is in order, as well as its treatment in all patients that will depend on the use of biological agents.

Like other specialty societies, SBR recommends a screening for latent tuberculosis through epidemiology, chest imaging and tuberculin skin test (PPD).³⁷ When available, γ -interferon release *in vitro* assays (IGRA – interferon gamma release assay), e.g. Quantiferon® or Elispot®, can enhance the accuracy of a latent tuberculosis diagnosis.³⁸ Patients with evidence of latent tuberculosis should receive isoniazid for six months. During pregnancy there is a physiological state of immune suppression, which is important for the mother's relationship with fetal allogenic immunogenicity. At this point, the levels of progesterone increase, with consequent Th1 to Th2-response shift. Quantiferon® test depends on the integrity of the cellular immune response of Th1, and thus the performance of this test may be poorer during pregnancy. While possibly with clinical importance, to date there are no tests available for use in clinical practice allowing monitoring the onset and intensity of antibodies against anti-TNF drugs and other biologicals.

Regarding the evaluation of Latent Tuberculosis Infection (LTBI) in patients who are already in use of some TNF blocker, the epidemiological investigation of contactants and/or re-exposure to mycobacteria should be done actively at every outpatient visit, in order to ensure an adequate surveillance of new cases. In the presence of a positive epidemiology, including personal, family and professional data, a reevaluation of LTBI is indicated.

In the case of PPD greater than or equal to 5 mm in patients with no prior treatment of LTBI before the use of anti-TNF agents, isoniazid must be initiated and maintained for six months. There is no need to discontinue TNF antagonists in asymptomatic patients. In those symptomatic patients, a proper expert evaluation is critical.

Assuming the lack of consistent scientific data on the necessity of repeating the tuberculin skin test (PPD), a booster test (PPD-Booster) and chest radiography in this setting, we do not recommend the practice of routine and/or annual investigation in asymptomatic patients and/or in the absence of convincing epidemiological data.

However, the rheumatologist may request a LTBI re-investigation in doubtful cases of clinical management, considering the local prevalence of tuberculosis, clinical data (alcoholism and malnutrition and other conditions associated with immunosuppression, for example) and socioeconomic conditions. This topic will be discussed in more detail in a specific document on the management of endemic diseases in patients with RA, now in production phase by SBR.

In the presence of hepatitis B and C infection, the use of anti-TNF should be avoided. In exceptional cases of hepatitis C virus infection, anti-TNF drugs can be used, with the associated antiviral treatment.³⁷

The treatment of other infectious diseases, including endemic/epidemic diseases in Brazil, such as leprosy, malaria, Chagas disease, esquistosomiasis, leishmaniasis, filariasis, dengue, yellow fever, fungal infections (blastomycosis, paracoccidioidomycosis, etc.), among others, will be discussed in a specific document by SBR.

Infusion reactions

Most skin reactions related to the administration of TNF inhibitors have mild to moderate intensity and do not require discontinuation of the drug.³⁹ The most common reactions are: erythema, urticaria, eczema or rash, which may, in turn, be accompanied by pain or edema.³⁹ While the appearance of rash has been described in approximately 6.9% of the patients on use of IFX,⁴⁰ injection site reactions were reported in 40% of the cases with ETN⁴¹ and in 15% of the cases with ADA.⁴² With respect to the new anti-TNFs, the incidence of reactions at the injection site appears to be lower: 2.3% with CERT⁴³ and 2.4% with GOL.⁴⁴

Hematological reactions

Changes such as thrombocytopenia, anemia (aplastic type) and pancytopenia are rarely reported during anti-TNF therapy, although some recommendations, such as the UK guidelines and the 2012 Consensus of the Brazilian Society of Rheumatology on Treatment of Rheumatoid Arthritis, suggest blood series monitoring.^{37,45} To date, 19 cases of thrombocytopenia were described in the literature in association with anti-TNF.⁴⁶ None of the cases was associated with significant clinical conditions or major bleeding. Moreover, leukopenia is a blood series abnormality that may be seen a little more commonly in some patients under anti-TNF therapy.⁴⁷ In this sense, a study involving 130 patients using IFX reported leucopenia in about 12% of the cases.⁴⁸ The possibility of marrow blockage or peripheral lysis has been evaluated, and it is suggested that this latter possibility is the most frequent.⁴⁹

The occurrence of neutropenia is defined as a neutrophil count below 1500/mm³ and the risk of infection is increased with neutropenia <1000/mm³. So far, neutropenia was reported in 111 patients using anti-TNF agents, most of them diagnosed with RA, and 96% were not in treatment with other immunosuppressive medication with potential to generate neutropenia. Most cases were using ESV (72.8%), followed by IFX (18.5%) and ADA (9%). One study showed that two important risk factors are a neutrophil count <4000/mm³ before the use of anti-TNF and a history of neutropenia due to synthetic DMDs. The presence of severe events accompanied by neutropenia has been reported in 6% of the cases, with no deaths associated.⁴⁶ Considering the data currently available, the conclusion is that the use of anti-TNF seems to be associated with lower risk of hematological changes, thrombocytopenia being a very rare event, and leucopenia due to neutropenia being the most frequent manifestation. As a routine, a cell blood count could be useful immediately before starting and during follow-up of patients in use of immunobiologicals.

Neurological reactions

To diagnose the neurological event associated with the use of biologic therapy, the following phenomena should be taken into account: the causal link between the use and the event,

observation of partial or complete improvement after drug withdrawal, relapse of symptoms after possible reintroduction of the biological agent, evidence of neurological involvement and, if possible, comparison with the expected incidence for the population.⁵⁰

Various neurological disorders have been described in patients on biologic therapy. Among them are: onset or exacerbation of multiple sclerosis, optic neuritis and various forms of demyelinating peripheral neuropathy. The prevalence of demyelinating disease induced by the use of biologicals, reported in randomized controlled trials and in post-marketing studies on autoimmune diseases (RA, juvenile idiopathic arthritis, spondyloarthritides and Crohn's disease) is estimated to be between 0.02% and 0.20%. A meta-analysis of these studies showed a prevalence of 0.05–0.20%. The cases are described mainly with the use of TNF α blockers (IFX, ETN and ADA) and with the greatest number of cases occurring with monoclonal antibodies.⁵¹ The mean elapsed time between the beginning of a biological DMD and the onset of symptoms was 7.5 months (range, 2–18 months) and with a favorable outcome after drug discontinuation and treatment in 66% of the cases.⁵¹

Demyelinating diseases of the central nervous system (CNS) showed less favorable outcomes. Multifocal leukoencephalopathy (MLE) exhibited greater correlation with natalizumab (taken away from the market due to this event) and, to a lesser extent, with alemtuzumab and alfalizumab, all not approved for use in the treatment of RA.⁵² By the time of preparation of this manuscript, MLE had been confirmed in a case of a patient diagnosed with RA in use of IFX.⁵³

Guillain-Barré syndrome is also described in patients with RA being treated with anti-TNFs and, as one of its causes, viral infection prior to the event must be remembered, since the risk of virus infection is increased when using these agents.⁵⁴

Two studies which evaluated the use of anti-TNF for multiple sclerosis treatment were discontinued due to exacerbation of the disease, suggesting the deleterious effect of these agents for this condition.^{55,56} An analysis by Fernández-Espartero et al., in Spain, comparing a systematic literature review (SLR) of case reports in the medical literature with the Spanish register of biological agents BIOBADASER (Spanish Registry of Biological Therapies in Rheumatic Diseases) and the pharmacovigilance system of Spain, FEDRA (Spanish Pharmacovigilance Database of Adverse Drug Reactions) failed to establish a clear association between the use of anti-TNF (IFX, ETN and ADA) for the treatment of rheumatic disorders and the occurrence of demyelinating disease.⁵⁷

Data from BIOBADASER, with an exposition of 13,075 patients/year with a diagnosis of RA, confirmed nine cases of demyelinating disease (22 suspected, unconfirmed, cases), with an incidence rate of 0.69 per 1000 patient-years (95% CI: 0.36–1.32). The incidence of multiple sclerosis in the Spanish population (0.022–0.038) was similar to the rate observed in patients who received anti-TNF (0.01–0.33).⁵⁷ Data from FEDRA described 10 cases of demyelinating diseases in RA patients treated with anti-TNF, and SLR found 31 case reports. The more frequent types of demyelination were: multiple sclerosis, optic neuritis and peripheral demyelinating disease. Among the rheumatic diseases studied, RA accounted for over 50% of the cases in the three analyses, with similar

distribution between gender and age and with an incidence rate lower than in PA (1.04/1000, 95% CI: 0.34–3.24) and AS (0.70/1000, 95% CI: 0.17–2.79). In BIOBADASER register, a longer time of anti-TNF exposition (mean, 1.44 years) and a lower recovery rate of demyelinating disease (43%) were observed.⁵⁷

The differences between these data and the apparent lack of association between the use of DMD for biological treatment of RA and the occurrence of demyelinating disease can be explained by a method bias for registration of cases in each of these studies, and by the difficulty of analysis of an appropriate control group.

In contrast, a study with a case-control design, using a database from a cohort of over 10,000 RA patients, suggested that anti-TNF agents were associated with an increased risk of approximately 30% for demyelinating events.⁵⁸

Regarding the measures employed for the treatment of neurological manifestations associated with anti-TNF, especially in cases of CNS manifestations and mononeuritis multiplex, the following conducts have been described (alone or in combination): high doses of oral- or pulse therapy corticosteroids, IV Ig, plasmapheresis, cyclophosphamide, azathioprine and cyclosporine A. Ig and pulse therapy with corticosteroids have been the most used methods. The exclusive practice of withdrawal of the biological agent used was also performed, in some cases with reversion or normalization of the clinical picture.⁵²

Before starting an anti-TNF, one should evaluate the possibility of previous neurological impairment through the history and physical examination in order to detect and treat previous neuropathy conditions. Neurological manifestations in RA are more frequent in elderly patients, in the disease with worse prognostic factors, and in the presence of comorbidities and other conditions potentially causing, or associated with, neuropathies. The use of anti-TNF agents is contraindicated in patients with demyelinating disease – especially in those with current or prior diagnosis of optic neuritis, demyelinating peripheral neuropathy and multiple sclerosis. In face of a suspicion of demyelinating disease, the anti-TNF medication should be immediately discontinued, seeking to establish whether there is a causal relationship between medication use and onset of symptoms. It is suggested that investigations be carried out and the right documentation be collected, depending on the type of neurological manifestation, in order to exclude the possibility of neurological disorders unrelated to the biological agent.

The treatment should be individualized for each patient, depending on the severity and neurological manifestations, and pulse or high-dose corticosteroids, Ig, plasmapheresis, cyclophosphamide, azathioprine and cyclosporine A can be used. If re-introduction of a biological agent for control of RA activity is needed, the preference should be for a non-anti-TNF agent, such as rituximab (RTX) or abatecept (ABAT).

Gastrointestinal reactions

Gastrointestinal and hepatic manifestations associated with anti-TNF are uncommon.

Cardiovascular reactions

Rheumatic diseases of inflammatory nature are associated with high mortality, mostly from cardiovascular mortality.^{59,60} Several studies have found an increased occurrence of cardio-

vascular events in RA and AS, and this finding can be justified by the increase in inflammatory cytokines such as TNF, an accelerated atherosclerosis, endothelial dysfunction, use of other medications that cause cardiovascular morbidity and mortality, presence of traditional cardiovascular risk factors, and the genetic heritage of the individual.⁶¹

Diseases such as RA, AS and CHF have in common the presence of high levels of inflammatory cytokines, particularly TNF.⁶² In this sense, the attempt to treat CHF with anti-TNF appeared to be an alternative. However, the use of anti-TNF for the treatment of patients with heart failure (functional classes III and IV – NYHA) did not show benefit,⁶³ being associated with a large number of adverse events and deaths, leading to premature termination of these clinical studies.⁶⁴ In addition, some individuals with no previous history of heart disease developed CHF with this treatment; a complete reversion of this complication occurred with discontinuation of the anti-TNF agent.⁶⁵ This fact led to the termination of studies and put severe CHF as a contraindication to anti-TNF therapy. Thus, we had a dilemma: anti-TNF agents could improve, or possibly trigger or aggravate cardiovascular events in patients with RA? On one hand, it would be biologically plausible that the reduction in the inflammatory process through the use of anti-TNF agents would theoretically reduce the risk of heart failure. On the other hand, the anti-TNF agent could increase the risk of heart failure in patients with RA, just as occurred in the general population.⁶⁶ To try to solve this dilemma, in this topic we will analyze studies evaluating anti-TNF and cardiovascular events in RA, and not in other inflammatory rheumatic diseases, because, in addition of being strongly associated with cardiovascular events, RA is favored with the most robust published evidence. A global and individual analysis of the cardiovascular risk will be performed, taking into account myocardial infarction (MI), stroke and CHF.

The risk of the use of anti-TNF and cardiovascular events as a whole was assessed in seven studies involving RA patients, including a randomized controlled trial, four cohorts, one case-control study and one cross-sectional study. The general conclusion is that anti-TNF therapy reduces the incidence of cardiovascular events as a whole, with a decline of RR to 0.46 (95% CI: 0.25–0.85).^{67–71} Seven studies (one cohort, five case-control studies and one cross-sectional study) evaluated the risk of MI in patients with RA and found no differences between subjects receiving anti-TNF and the control group (treated with synthetic DMDs), although in those patients who had a good to moderate EULAR (European League Against Rheumatism) response after six months of treatment, a RR reduction of 64% (95% CI: 0.19–0.69%) was noted, compared with non-EULAR responders.^{72–78}

The risk of stroke with the use of anti-TNF was assessed in RA patients in four studies (one cohort, one case-control study and two cross-sectional studies). The conclusion of most of these studies is that TNF antagonists were not associated with a risk of stroke, and apparently in those individuals who responded to anti-TNF and to the continued use of these drugs for more than six months, the risk of stroke was reduced.⁷⁹

The occurrence of CHF during the use of anti-TNF in RA patients was assessed in six studies (five cohorts and one case-control study).^{80–85} The results of these studies were conflicting. Although the use of anti-TNF in elderly patients

may be associated with an increased risk of CHF,⁸⁴ in those patients aged less than 50 years the conclusion still is not final.

The general conclusion on this topic is that the use of anti-TNF in RA patients appears to be associated with less cardiovascular morbidity when the changes are evaluated together. However, the individual risk assessment of stroke, MI and CHF still has no definitive conclusions.

Solid neoplasms

It is speculated if the long-term use of biological DMDs could contribute to an increased risk of cancer in patients with inflammatory diseases. It is not yet clear whether the malignancy is a consequence of chronic inflammation, or of therapies used to treat inflammatory diseases such as RA.⁸⁶ Studies show that, in RA, there is a greater risk of certain malignancies, including lymphoma, lung cancer, non-melanoma skin cancer and possibly melanoma and leukemia. Current evidence suggests that this occurs due to uncontrolled inflammation and possibly to smoking.⁸⁶

Before the advent of biological DMDs, the incidence of solid cancers in patients diagnosed with RA mirrored what was seen in the general population, including lung, colorectal, skin, breast, prostate, bladder, ovary and pancreas neoplasms, and this scenario has not changed significantly since the introduction of new therapies.⁸⁷ Wolfe and Michaud observed in 13,001 patients from the National Databank for Rheumatic Diseases that the use of biologicals was not associated with an increased risk of solid tumors.⁸⁸

Skin tumors are among the possible manifestations associated with the use of anti-TNF agents. Evidence of an increased risk of non-melanoma carcinomata among patients treated with anti-TNF include one registry data meta-analysis, prospective observational studies and randomized trials.⁸⁸⁻⁹¹ The most common neoplasms are non-melanoma skin cancers, mainly basal cell carcinoma and, less frequently, squamous cell carcinoma.⁸⁹⁻⁹⁴ Cases of malignant melanoma, however, have also been described in patients using anti-TNF therapy.⁹⁵⁻¹⁰⁴ Although the exact role of these drugs in the development of melanomas is not well established, one should pay close attention to the appearance of pigmented lesions or changes in the characteristics of preexisting nevi.³⁹ When in doubt, in order to obtain a correct explanation of the picture, an histopathologic study of the lesion is recommended.

Regarding the recurrence of solid cancer after use of a biological agent, little is known due to the exclusion of these patients in their participation in clinical trials.¹⁰ In patients treated for solid cancer during more than five years, we can recommend the use of any biological agent. In patients under five years of treatment, RTX should be the biological choice. Thus, although no increased risk was observed for cancer, except for non-melanoma skin cancer⁸⁸⁻⁹¹ in patients using anti-TNF agents, surveillance for the occurrence of malignancies (including recurrence of solid tumors) in patients treated with TNF inhibitors remains appropriate.

Lymphomas

Since pre-biological times it is known that the estimated risk of a patient with RA developing lymphoma (especially non-Hodgkin's) is about two times higher than that for general

population.¹⁰⁵⁻¹⁰⁷ A Swedish case-control study showed that this risk is directly related to the intensity and duration of the inflammatory process.^{108,109}

TNF is known to have a role in surveillance against the development of neoplasia; therefore, its inhibition has been seen as a possible risk factor for the onset of tumors. On the other hand, coinciding with the beginning of anti-TNF therapy, the general way to treat this disease changed a lot. Over the past 15 years, much emphasis was given to early diagnosis and to a strict control of disease activity. This change could potentially reduce, for example, the risk for the onset of lymphoma. Nevertheless, one should not forget that, until recently, the anti-TNF therapy was restricted to patients refractory to traditional treatment, i.e., of long duration and with high inflammatory burden. Not surprisingly, therefore, that the data related to the risk of lymphoma associated with the use of anti-TNF therapy are conflicting.

In a recent meta-analysis involving 63 randomized clinical trials (RCTs) with 29,423 patients with RA, the risk of lymphoma among users of anti-TNF, compared with the risk of control subjects, was doubled (odds ratio [OR]=2.1; 95% CI: 0.55-8.4); however, this difference was not statistically significant. The authors of this meta-analysis point out that the limited number of patients and the reduced follow-up time of the RCTs limit the extrapolation of these data to the prolonged use of these drugs.¹¹⁰ In the analysis of the first cases of lymphoma among anti-TNF therapy users, half of them were diagnosed in the first eight weeks of treatment.¹¹¹ To date, there is no evidence of the emergence of an increasing risk of lymphoma related to the prolonged use of anti-TNF agents.^{86,112}

One SLR and a meta-analysis of observational studies and registries, also recently published, confirmed that, compared with the general population, patients treated with TNF inhibitors have an increased risk of lymphoma (standardized incidence ratio=2.55, 95% CI: 1.93-3.17).^{89,113-115} But when compared with RA patients treated with synthetic drugs, this increase in the risk for lymphoma was not observed (estimated risk = 1.11, 95% CI: 0.70-1.51).^{88,116,117}

Immunogenicity

Anti-human chimeric antibodies (HACA) and human anti-human antibodies (HAHA) may occur with the use of any of the drugs in this class, but their effect on the effectiveness of therapy is unclear. The induction of antibodies against anti-TNF agents depends mainly on their structure. Chimeric molecules have a greater capacity to induce immunogenicity, compared with fully human drugs. Among anti-TNF agents, this phenomenon has been studied mainly in IFX users, especially in those with RA or Crohn's disease. The prevalence of anti-IFX antibodies in RA ranges from 12% to 44% and appears to be inversely related to serum levels and to the therapeutic response to medication. The use of ETN was associated with the development of anti-ETN antibodies in 0-18% of patients, without any apparent impact on the efficacy or on the occurrence of adverse events. Studies in patients with RA and with Crohn's disease show the presence of anti-ADA antibodies in 1-87% of patients. In 25 children with juvenile idiopathic arthritis, 8% had anti-ETN antibodies.^{118,119}

The methods more often used for the detection of HACA and HAHA are ELISA (Enzyme Linked Immuno Sorbent Assay)

and radioimmunoassay. The presence of anti-IFX antibodies in RA patients may suggest a poorer therapeutic response and an increased risk of infusion reaction. However, perhaps these same conclusions may not be observed in relation to anti-ADA and anti-ETN antibodies. Immunological tolerance to ADA and IFX may be increased with a concomitant use of immunomodulators such as MTX and azathioprine. There is no evidence in the literature of cross-reactivity of HACA and HAHA for the different anti-TNF agents.¹¹⁹

Other reactions

Among the manifestations not previously mentioned, those of dermatological origin are of special interest. Skin conditions described in anti-TNF inhibitor users may didactically be divided into: skin reactions related to their administration, skin infections, skin neoplasms (previously mentioned) and immune-mediated diseases.

Among the immune-mediated diseases, the onset of psoriasis has been described following the use of several drugs such as anti-malarials, anti-inflammatory drugs and beta-blockers.⁹⁷ In the case of association of psoriasis with the use of anti-TNF, the aspect that seems paradoxical is the onset of psoriatic skin lesions with the use of a drug indicated for their treatment. The prevalence of this phenomenon is varied, but according to some studies, it lies between 0.6% and 5.3%.^{98,99,120} The mean latency time between the start of the TNF inhibitor and the onset of skin lesions is 10 months; however, this time may vary from several days to several years.^{97,101-103} The three main types of psoriatic lesions observed are: pustular, about 56%; *en plaque*, in half of the cases; and guttate in about 12% of the cases.¹⁰⁴ In approximately 15% of the patients, more than one type of lesion is present.¹⁰⁴ The most characteristic clinical form associated with the use of TNF inhibitors is pustulosis palmoplantaris.¹⁰⁴

Initially, these lesions were considered as a hypersensitivity reaction to the drug. Subsequent histological studies, however, showed that the lesions were identical to those occurring in people with idiopathic psoriasis.^{102,120} In general, patients who develop this type of adverse effect had displayed a good response to anti-TNF, such that the appearance of the skin lesion affects negatively the effectiveness of the treatment.

Considering that most of the described cases of this association occurred in RA patients, we cannot forget that, from the beginning, it may be a case of PA, since in up to 15% of the patients with this illness the joint condition emerges before the skin condition. On the other hand, maybe this could be only the case of an association of two conditions that are not rare.¹⁰⁴ The coexistence of psoriasis and RA, however, is infrequent (about 2%), while the onset of psoriasis induced by TNF inhibitors occurs in about 3% of the patients with spondyloarthritides and in 2-5% of those with RA, an incidence much higher than expected.^{98,102,120}

Reports of cutaneous lupus,¹²¹⁻¹²⁴ alopecia areata,^{99,125-133} cutaneous vasculitis,¹³⁴⁻¹³⁸ vitiligo,^{135,139,140} relapsing polychondritis,¹⁴¹ polymyositis/dermatomyositis,^{142,143} localized scleroderma (morphea),¹⁴⁴⁻¹⁴⁶ granuloma annulare,^{135,147} lichen or lichenoid reaction,^{120,135,148} and pemphigus¹⁴⁹⁻¹⁵¹

were described with the use of TNF inhibitors. The cause and effect relationship of these associations, however, are not well established.

Vaccination response

Regarding vaccination, the response to influenza vaccine does not seem to be impaired in patients using anti-TNF agents, even when combined with MTX.¹⁵²⁻¹⁵⁴ However, an author showed a reduced response to this vaccine, when evaluating patients using IFX associated with MTX or ETN.¹⁵⁵ Similarly, a study conducted in Brazil, evaluating the H1N1 influenza vaccine, found, besides a good safety profile, a reduced serum protection in RA patients, regardless of disease activity. MTX was the only DMD associated with reduced response to the vaccine.¹⁵⁶ As for the pneumococcal vaccine, the use of MTX in isolation, or its use combined with some anti-TNFs (ADA, ETN and IFX), may decrease the effectiveness of the vaccine, while the use of these biologicals in isolation does not influence the vaccine response.^{153,155} Additionally, the use of anti-TNF could significantly reduce the response to hepatitis B vaccine.¹⁵⁷

Vaccines with live attenuated components should preferably be administered three to four weeks before initiation of immunosuppressive therapy, to ensure that viral replication finished before the alteration of the immune competence of the patient (in terms of drug use). Otherwise, under treatment, the vaccination should be delayed for at least the equivalent time of four half-lives of each anti-TNF drug.¹⁵⁸

T-cell co-stimulation blocker – ABAT

ABAT is a human fusion protein consisting of the extracellular domain of human CTLA-4 linked to the modified Fc portion of human immunoglobulin (Ig) G1. This drug inhibits T-cell activation for binding to CD80 and CD86, thereby blocking its interaction with CD28 (the co-stimulation receptor).¹⁵⁹ ABAT was approved in December 2005 by the Food and Drug Administration (FDA) for RA patients, both for therapeutic failure with synthetic, as biological, DMDs. In Brazil, the SBR Consensus (2012) on treatment of RA suggest that ABAT can be used in patients with active RA that failed with synthetic DMDs, preferably when these drugs were used in combination, or after the use of an anti-TNF. ABAT can be used preferably as monotherapy, or combined with a synthetic DMD.³⁷

A SLR on the use ABAT in RA patients pooled seven studies and 2908 patients. In this SLR, total adverse events were slightly more common with ABAT compared with placebo (RR=1.05, 95% CI: 1.01-1.08) and severe infections in 12 months were more common with ABAT versus control group (OR = 1.91, 95% CI: 1.07-3.42).¹⁶⁰ Pooled data from 4149 patients enrolled in several pivotal studies demonstrated that the incidence of serious adverse events (95% CI) with ABAT is very low, with gradual decrease at each year.^{161,162}

Regarding security of ABAT interaction with MTX or other DMDs, the extension of the AIM (Abatacept in Inadequate responders to Methotrexate) study showed efficacy and safety of ABAT combined with MTX.¹⁶³ The ASSURE (Abatacept Study of Safety in Use with Other RA Therapies) study also showed safety of combining ABAT with MTX and with hydroxychloroquine, sulfasalazine, leflunomide or azathioprine.¹⁶⁴

Infections

ABAT is contraindicated in patients with active infections, including skin ulcers, infected prostheses, and in catheter users.¹⁶⁵ The risk of serious infection is reported in 2.9% with ABAT versus 1.9% for placebo.¹⁶⁴ The combination with other biologicals increases the risk (serious infection 5.8% versus 1.6%).¹⁶⁴ ABAT does not increase *Mycobacterium tuberculosis* infection, and only nine cases of tuberculosis in 4149 patients treated over time (12, 132 patient-years) have been reported.¹⁶² A study with mice demonstrated the safety of this drug in relation to tuberculosis infection.¹⁶⁶ In this study, chronic *M. tuberculosis* infection was caused in C57BL/6 mice. After four months of induced infection, mice were treated with different biological agents for up to 16 weeks in three different groups (one group with ABAT and the other two with anti-TNF or placebo). In mice treated with placebo and ABAT, tuberculosis control was maintained, with 100% of survival after 16 weeks of treatment. Mice treated with anti-TNF had 100% of mortality at nine weeks, with weight loss and increased bacterial load in the lungs, lymph nodes and spleen. Thus, it was concluded that ABAT did not exacerbate the infection with *M. tuberculosis* in mice.¹⁶⁶

As for those patients who initiated their treatment with other biological agents, screening tests for hepatitis B and C must be performed before the start of ABAT.¹⁶¹

Infusion reactions

The infusion reactions with ABAT are rare, with 3.9/100 patient-years in six studies reviewed involving 3755 patients.¹⁶² The most common symptoms are dizziness, nausea, headache and hypertension. Severe hypersensitivity reactions are rare (0.4% versus 0.2% with placebo).^{162,167}

Hematological reactions

To date, no studies evaluating hematological changes and ABAT in rheumatic diseases were published.

Neurological reactions

To date, no reports of peripheral neuropathy or CNS involvement associated with the use of ABAT were published.

Gastrointestinal reactions

Liver enzyme changes are mild and rare in patients treated with ABAT (0.1–1% of patients) and thus have little clinical value. It appears that the combination with MTX, NSAIDs, corticosteroids, sulfasalazine and leflunomide does not increase the occurrence of hepatotoxicity.¹⁶¹

Cardiovascular reactions

Regarding the increased cardiovascular risk in patients with RA, studies have shown that the use of ABAT determines no greater risk.^{161,162} Cardiovascular disease does not contraindicate the use of ABAT and this drug does not interact with cardiovascular drugs, nor with the use of oral anticoagulants.¹⁶²

Neoplasms

Solid neoplasms and lymphomas

The risk of malignancies, e.g., non-melanoma skin cancer, lung cancer, colorectal cancer and breast cancer, for ABAT

users is comparable with the risk for RA patients in use of synthetic DMDs.¹⁶² One study analyzed seven clinical trials with 4134 patients versus RA patients from five cohorts (41,529 RA patients, with a mean follow-up between 1.8 and 9.3 years). In the population treated with ABAT, a lymphoma rate similar to that in different cohorts of RA was found, with a standardized incidence rate = 0.89 (95% CI: 0.36–2.15).¹⁶⁸

Regarding the risk of lymphoma and other hematological diseases, double-blind and open studies involving 4149 patients treated with ABAT (11,658 patient-years) showed hematologic malignancy occurring only in 0.13/100 patient-years (similar to RA), but just as with anti-TNF biologicals, the use of ABAT should be avoided in patients who had lymphoma over the past five years.¹⁶¹

Immunogenicity

Unlike what was observed with the use of anti-TNF biological DMDs, antinuclear antibodies (ANA) and anti-DNA did not become positive over time in patients treated with ABAT.¹⁶² There appears that the formation of HACA and HAHA using ABAT does not occur.

Other events

The use of ABAT is contraindicated in patients with signs of chronic obstructive pulmonary disease (COPD), because of the exacerbation of dyspnea and an increased occurrence of infections.³⁷ Studies were published on the occurrence of psoriasiform rash,¹⁶⁹ as well as lupus-like syndrome and Sjögren syndrome,¹⁷⁰ possibly in association with the use of ABAT.

The risk of development of autoimmune events with the use of ABAT, based on pooled data of 4149 patients and 12,132 patient-years, showed rare cases of cutaneous psoriasis (OR = 0.60), Sjögren's syndrome (OR = 0.26) and vasculitis (OR = 0.34).¹⁶²

Vaccination response

Regarding vaccination in RA patients in use of ABAT, a sub-analysis of the ARRIVE (Abatacept Researched in RA Patients with an Inadequate anti-TNF response to Validate Effectiveness) study evaluated the efficacy and safety of influenza vaccination in 20 patients.¹⁷¹ A total of 55%, 50% and 35% of the patients developed vaccine response to H1N1, H3N2 and influenza B virus strains, respectively. A study in Brazil investigated the humoral response to vaccination against H1N1 flu virus in 11 RA patients treated with MTX in combination with ABAT.¹⁷² Only 9% of the patients treated with the combination of MTX and ABAT achieved seroprotection, compared with 58% of patients treated only with MTX and with 70% of healthy individuals. Schiff et al. investigated the response to anti-pneumococcal vaccine in 21 patients with RA treated with ABAT in a sub-analysis of the ARRIVE study.¹⁷³ Of these 21 patients, 81% exhibited immune response to at least one serotype.¹⁷³

B-cell depletion drug – RTX

RTX is a monoclonal antibody directed against lymphocytes CD20+ in patients with RA in moderate to severe

activity, with treatment failure to an anti-TNF agent.^{37,174} RTX is used preferably in combination with MTX, and may be prescribed in association with other DMDs. RTX has a better therapeutic response in patients with positive serology for rheumatoid factor (RF) and/or anti-cyclic citrullinated peptide (anti-CCP) antibodies.¹⁷⁵ Individuals with good response to treatment may be subjected to a new course of RTX if the disease is reactivated in a time interval <6 months.¹⁷⁶

In a meta-analysis that included 938 patients treated with RTX and unresponsive or intolerant to synthetic DMDs or anti-TNF agents followed during 24–48 weeks, it was observed that the incidence of adverse effects in all systems was not higher than in those patients treated with placebo (RR: 1.062, 95% CI: 0.912–1.236, $p=0.438$). With regard to the number of patients who experienced at least one serious adverse event, no significant difference between those treated with RTX and placebo was observed (RR: 0.855, 95% CI: 0.622–1.174, $p=0.333$).¹⁷⁷ The long-term safety after multiple infusions of RTX was also analyzed in a recent publication.¹⁷⁸ Submitted data are pooled from eight RCTs and two open-label extension studies, including a total of 3194 patients who received up to 17 courses of RTX over 9.5 years (4418 patient-years). The percentage of infections and serious adverse events remained stable over time and after multiple infusions.¹⁷⁸

RTX is contraindicated in patients with hypersensitivity to this drug or to other murine proteins, with active infection and severe heart failure.¹⁷⁹

Infections

With regard to infections, a meta-analysis that included 745 patients treated with RTX in three RCTs found that there was no increased risk for serious infections compared with placebo.¹⁸⁰

In the aforementioned study by van Vollenhoven et al.¹⁷⁸ the percentage of serious infections was 3.94/100 patient-years (3.26/100 patient-years in patients observed for more than five years) and was comparable to that for the placebo group associated with MTX (3.79/100 patient-years). A decrease in Ig levels was observed from four months, after at least one course of RTX, but the clinical significance of this is uncertain. The subgroup of patients with low IgG levels showed a higher risk of serious infections compared to patients who never presented this finding, but the risk of infection was already increased in these patients, even before the onset of IgG level decrease. IgG levels must be measured prior to treatment with RTX and monitored over time.¹⁷⁹ Low levels of IgM were not associated with an increased risk of infection.

Regarding tuberculosis, RTX is approved for patients who do not respond or are intolerant to anti-TNF. Thus, most patients who used RTX have been pre-selected for latent tuberculosis in clinical trials and in daily practice. With that in mind, reactivation of tuberculosis was not observed, despite the package insert recommending a search for latent tuberculosis before starting the medication.^{36,181}

Regarding hepatitis B and C, experts recommend that serology for hepatitis B should be performed prior to initiation of treatment with RTX.¹⁷⁹ Reactivation has been documented in

both negative and positive patients to hepatitis B virus surface antigen (HBsAg),^{182,183} emphasizing the need to investigate not only HBsAg, but also other antibodies against core antigen (HbcAg – hepatitis B core antigen) to identify a positive state of carrier. The negativity for HBsAg (also with negativity for anti-HBs antibodies) identifies the group of patients requiring vaccination prior to immunosuppressive therapy. A search for hepatitis B virus DNA (HBV-DNA) is not indicated as screening tool, but for investigation of viral load and response in chronic infection established by hepatitis B. Although there is variation among currently existing recommendations, it is generally considered that those HbsAg-and/or anti-Hbc-positive patients should be treated prophylactically. The treatment of occult infection by hepatitis B virus with anti-Hbc-positive in isolation remains uncertain: in such patients, HBV DNA could be determined, and then prophylaxis could be considered, with close patient monitoring. Routine evaluation for hepatitis C should also be considered.^{184–189}

Infusion reactions

The most frequent adverse events are infusion reactions, which occur in 30–40% of the patients during the first infusion and about in 10% at second infusion.¹⁹⁰ In most cases, the reactions are of mild to moderate intensity. Severe cases requiring drug discontinuation occur in less than 1% of treated patients.¹⁷⁹ Sixty minutes before each RTX infusion, the patient must be treated with IV methylprednisolone 100 mg, acetaminophen 1 g and antihistamines, to reduce severity and frequency of infusion reactions.¹⁹⁰

Hematological reactions

The effect on B lymphocytes with depletion of these cells is expected, and is part of the action mechanism of this drug. However, a significant reduction in total lymphocyte count is not expected. The safety of B-cell depletion after multiple infusions of RTX, especially related to the cumulative risk of serious infections and malignancies, is not fully established in patients with RA.¹⁷⁸ Hematologic adverse events have not been shown to be relevant in long-term studies.^{178,191}

Neurological reactions

To date, six cases of MLE were reported in patients with RA treated with RTX.^{178,179} Most cases had long-term RA and were users of multiple immunosuppressants. The number of reported cases of MLE in patients diagnosed with RA in use of RTX confers a risk of 0.4/100,000 patient-years, slightly increased compared to the general population (0.2/100,000) and lower than that observed in patients with systemic lupus erythematosus (4/100,000).⁵³ Thus, although the occurrence is considered rare (1:20,000) due to the high morbidity and mortality of the condition, clinical surveillance for this diagnosis is recommended in this patient population.

To date, no reports of peripheral neuropathy associated with the use of RTX were published.

Gastrointestinal reactions

Increases in gastrointestinal adverse events after exposure to RTX have not been observed.^{178,192}

Cardiovascular reactions

Increased risk of acute MI over time in patients treated with RTX has not been observed.¹⁷⁸

Neoplasms

Solid neoplasms and lymphomas

Increased risk of solid or hematological malignancies over time in patients treated with RTX with an observational period of approximately 10 years has not been observed.¹⁷⁸

Immunogenicity

Safety data from long-term RCTs on RA patients indicate that 11% (273/2578) of the patients exposed to RTX develop HACA.¹⁹¹ HACA-positive patients did not show a higher number of infusion reactions during the second course of RTX, compared with HACA-negative patients.

Other events

Few cases of psoriasiform conditions have been reported after RTX infusion for the treatment of rheumatic diseases or other indications. A series of three cases was described in two patients with RA and in one with SLE, requiring specific treatment for psoriasis and RTX discontinuation.¹⁹²

Pulmonary manifestations were identified in a systematic review study with 121 cases of interstitial lung disease. Only nine of these patients had indication of RTX for treatment of rheumatic diseases, including three cases of RA, one of them in association with Castleman's disease. In this review, the interstitial lung disease was considered as a rare event, but with potential for morbidity and mortality. All cases had imaging (radiographs and/or computed tomography) findings. Pulmonary function tests, when performed, showed a deficit of diffusion capacity and a restrictive respiratory pattern.¹⁹³

In a series of 43 patients with autoimmune diseases, in two cases of patients with systemic lupus erythematosus, and in one case of primary Sjögren's syndrome, mild fever type reactions, arthralgia, rash, and urticaria-like lesions were observed; and in one case the medication had to be discontinued.¹⁹⁴ We did not find similar reports in patients with RA or spondyloarthritides. There are case reports of serum sickness, with the appearance of mild to moderate disease after infusion of RTX.¹⁹⁵

Vaccination response

The use of RTX is associated with a reduced response to both T-cell independent and T-cell dependent vaccines.¹⁵⁸ There is evidence to suggest a compromised response to anti-pneumococcal and influenza vaccines, when administered to patients receiving RTX.^{179,196,197} The response to influenza vaccine (also including A and H1N1 vaccines) is also particularly compromised when the vaccine is administered early, four to eight weeks after administration of RTX. Thus, influenza and pneumococcal vaccines must be applied before starting RTX, or six months after the 1st infusion and four weeks before the next dose.^{158,179} High-risk patients for contracting tetanus and treated with RTX within the last 24 weeks should use passive immunization with tetanus Ig. Hepatitis B

is another vaccine that should be administered before the use of RTX.¹⁷⁹

Interleukin-6 (IL-6) receptor blocker – tocilizumab (TOCI)

TOCI is a humanized monoclonal antibody directed against the receptor of IL-6, including soluble and plasma membrane-bound fractions, and able to blocking their cellular actions. TOCI is not only used in the treatment of RA activity in combination with MTX or other DMD, but also as monotherapy and in patients with an inadequate response to MTX or other DMDs, or to TNF blockers.³⁷ In general, monitoring should be continuous for all adverse events related to TOCI. However, some of them are more related to the initiation of treatment and tend to present a subsequent reduction in the frequency of occurrence, such as infusion reactions and changes in lipid and liver transaminases' plasma concentrations.

The data on TOCI safety profile were pooled from 24-week randomized, placebo-controlled clinical trials (RPCCTs) considered pivotal for registration and approval of this drug, but also from longer-term studies, including results of registry trials and post-marketing surveillance studies, particularly of FDA and EMEA (European Medicines Evaluation Agency).

Infections

Like other immunobiological agents, TOCI should not be used in patients with active infection by any pathogen, including bacteria, viruses, fungi and parasites.^{198,199} Traditionally, C-reactive protein (CRP) is used as a biomarker for tracking infections. However, CRP is not useful for TOCI users, since a significant reduction in plasma concentration of CRP occurs after using that agent. So far, there is no evidence demonstrating the ability of TOCI in suppressing febrile response. Recent Cochrane meta-analysis, including 8 RPCCTs, showed an infection risk 1.2 times greater for patients treated with TOCI versus those using synthetic DMDs,^{36,200} in accordance with data previously published by the Nishimoto group.²⁰¹ However, this risk does not increase with time of exposure, showing a major event rate ranging from four to six per 100,000 patient-years,²⁰² even if combined with other synthetic DMDs.²⁰³

Unlike TNF blockers, TOCI did not increase the risk of TbL reactivation.²⁰⁴ However, a screening for LTBI is still recommended before and during use of immunobiological agents, especially in endemic areas. In Japan, there was no increase in the number of cases of disease caused by non-tuberculous mycobacteria.²⁰⁵

Recent evidence revealed no increase in the rate of surgical wound infection in patients with RA in use of TOCI after undergoing total knee or hip arthroplasty.²⁰⁶ The suspension of TOCI at least for four weeks before the procedure is recommended. After pooling retrospectively information on infectious conditions occurring after orthopedic surgery (arthroplasty) in the period 1999–2010, Momohara et al. observed more delay for surgical wound healing (20/122, 16.4%) than infections (3/122,

2.45%) in the TOCI group, especially when the surgical procedure involved the foot and the column.²⁰⁷

Regarding B and C viral hepatitis, the data obtained from studies are still preliminary, since these patients were excluded from RPCCTs. At the moment, TOCI should not be used in this clinical setting.^{204,208}

As for opportunistic infections, the rate is low, ranging from 0.2 to 0.3 for every 100,000 patient-years. Fungal infections are the most reported.²⁰³

Infusion reactions

These are rare events with TOCI and can be minimized by slowing the rate of IV infusion and/or by administration of premedication with corticosteroids. Severe anaphylactic reactions and the need for permanent discontinuation of TOCI are quite rare.

Hematological reactions

Studies with small numbers of participants have shown that one of the major hematologic adverse events related to TOCI is neutropenia.²⁰⁹ The mechanism responsible is still not well known, but it appears to be related to a direct immunological role or to IL-6 receptor blockage in these cells.

In general, the neutropenia is transient and of low intensity, and does not increase the risk of infection per se. More severe or prolonged cases require reducing the dose of medication to 4 mg/kg infusion; if the problem is not resolved, the medication should be permanently discontinued.²¹⁰

Neurological reactions

There is only one case report of peripheral neuropathy related to the use of TOCI.²¹⁰

Gastrointestinal reactions

Elevations of liver enzymes may occur in 8–10% of the patients, regardless of synthetic DMDs, as with other cytokine blockers. These elevations are usually mild and transient, and do not increase the risk of irreversible hepatocellular injury.²¹¹ When the treatment is initiated, monitoring the patient every four to eight weeks is recommended, and then every three to six months. Persistent elevations suggest the need for a more comprehensive investigation into other causes, besides a dose reduction and discontinuation of medication.²⁰³

Some cases of intestinal (especially colonic) perforation have been reported in patients using TOCI. One hypothesis to explain this finding is the possibility of subclinical diverticulitis. Thus, an anamnesis directed for previous history of colonic diverticular disease and diverticulitis is recommended. This risk increases with concomitant use of corticosteroids and NSAIDs; therefore, these medications should be used sparingly in this scenario.²⁰³

Cardiovascular reactions

No consistent clinical studies were published evaluating cardiovascular events as primary outcomes, with use of TOCI in patients with rheumatic diseases. However, Schiff et al., when assessing over eight thousand patients from RPCCTs with RA using TOCI, observed low incidence of AMI (0.25/100 patient-years) and stroke (0.19/100 patient-year) and no increase with a longer exposure to the drug (2006–2010).²⁰³

Neoplasms

Solid neoplasms and lymphomas

After reviewing data from 63 RPCCTs with more than 29,000 patients with RA, no increased risk of solid or hematological malignancies was observed in the first 24 weeks, when compared with a control group treated with synthetic DMDs.¹¹⁰

In the longer term, register data have not been published so often, when compared with TNF blockers' data. However, in the light of current knowledge, it seems that there is no higher risk of neoplasia among patients using TOCI, compared with what was observed in the control group.²¹²

Immunogenicity

Taking into consideration that this is an immunobiological agent, TOCI have antigenic potential, although immunogenic reports published are scarce. The ability of formation of HAHA neutralizing antibodies, including intensity, isotype, specificity and kinetics, has been studied, but the frequency is much lower than that reported for TNF blockers.²¹³

Other events

There are some anecdotal cases or case reports of patients who developed other unexpected adverse reactions after TCZ, including skin (ulcers, necrotizing fasciitis)²¹⁴ and mucosal (persistent aphthous ulcerations in the oral mucosa) conditions,²¹⁵ as well as ocular (bilateral retinopathy with hemorrhage and cotton-wool infiltrates),²¹⁶ and lung (organizing pneumonia and exacerbation of interstitial conditions) events.^{217,218}

Just as observed with TNF antagonists, some initial cases (de novo) of psoriasis and uveitis have been reported after IL-6 blockade, emphasizing paradoxical events that may occur also with the use of this medication.^{219–221}

Vaccination response

To date, only few studies on vaccine response in patients treated with TOCI were published. Two studies demonstrated an adequate safety and efficacy profile (seroprotection and seroconversion) for influenza vaccine in patients with RA, regardless of MTX²²² and systemic onset juvenile idiopathic arthritis.²²³ In addition, no exacerbation of the joint scenario in these patients was observed. Regarding other vaccines and immunizations, there are no data on the safety and efficacy profile.

Table 1 presents the main adverse events resulting from treatment with biological DMDs for RA and spondyloarthritides.

Biologicals, pregnancy and lactation

Some rheumatic diseases for which biological DMDs are indicated, such as RA, affect disproportionately females,²²⁴ including patients of childbearing age, when pregnancy can occur in a planned or unplanned way.

The use of medications during the conception, pregnancy and lactation periods causes great anxiety for the pregnant patient and also for her physician, who must prescribe these

Table 1 – Main adverse events resulting from the use of disease-modifying drugs (DMD) for the treatment of rheumatic diseases.

Drugs (mechanism of action)	Infections	Infusion reactions	Hematological reactions	Neurological reactions	Gastrointestinal reactions	Cardiovascular reactions	Solid neoplasms	Hematological neoplasms	Immunogenicity	Other occurrences	Vaccine response
Anti-TNF (adalimumab – ADA, certolizumab – CERT, etanercept – ETN, golimumab – GOL, infliximab – IFX) ^a	Infections, bacterial or viral, are the most frequent and important adverse events arising from the use of anti-TNF, mainly affecting the respiratory tract, skin, soft tissues and urinary tract. ²⁷ The risk of hospitalization caused by bacterial infection is two times higher in the patient using anti-TNF than in patients on MTX alone; this risk increases four times when considering the first six months of treatment. ⁴⁸ Since TNF plays a central role in the formation and maintenance of the granuloma, tuberculosis is an adverse event that potentially should be very frequent, if it had not been for its systematic prevention, which should never be neglected. ^{34–36} In the presence of infection by hepatitis B and C viruses, the use of anti-TNF should be avoided. In exceptional cases of infection by hepatitis C virus, anti-TNF drugs can be used with the associated antiviral treatment. ³⁷	Most skin reactions related to the administration of TNF inhibitors have mild to moderate intensity, and do not require discontinuation of the drug. ³⁹ The most common reactions are: erythema, urticaria and eczema or rash, which may, in turn, be accompanied by pain or edema. ³⁹ While the appearance of rash has been described in approximately 6.9% of the patients receiving IFX, ⁴⁰ reactions were reported in 40% of the cases with ETN ⁴¹ and 15% with ADA. ⁴² With the new anti-TNF antibodies, the incidence of injection site reactions appears to be smaller: 2.3% with CERT ⁴³ and 2.4% with GOL. ⁴⁴	The use of anti-TNF agents seems to be associated with low risk of hematological changes, thrombocytopenia being a very rare event, and leucopenia caused by a severe neutropenia being the most frequent manifestation. ^{37,45–49} As a routine, the cell blood count could be useful immediately before start of immunobiological agents and through the follow-up of these patients.	Neurological manifestations have been described in patients using anti-TNF therapy, including with exacerbation or onset of multiple sclerosis, Guillain-Barré syndrome, multifocal leukoencephalopathy (MLE), optic neuritis and various forms of demyelinating peripheral neuropathy. The prevalence of demyelinating disease induced by the use of anti-TNF is estimated between 0.02% and 0.20%. The use of anti-TNF therapy is contraindicated in patients with a demyelinating disease such as optic neuritis, peripheral demyelinating neuropathy and multiple sclerosis. On suspicion of a demyelinating disease, discontinue anti-TNF immediately and seek to establish the causal link between the use and the symptoms. Undertake a research and proper documentation, depending on the type of neurological manifestation. Treatment should be individualized for each patient, depending on the severity of the clinical picture. ^{50–58}	Gastrointestinal and hepatic manifestations associated with the use of anti-TNF are unusual.	The use of anti-TNF in RA appears to be associated with lower cardiovascular morbidity when the manifestations are jointly evaluated; however, the individual assessment of the risk of stroke, myocardial infarction (MI) and congestive heart failure (CHF) still has no definitive conclusions. CHF class II or IV (New York Heart Association – NYHA) is a contraindication for prescribing anti-TNF drugs. ^{59–85}	While no increased risk for neoplasia was observed (except for non-melanoma skin cancer) in patients using anti-TNF agents, surveillance for the occurrence of malignancies (including recurrence of solid tumors) in patients treated with TNF inhibitors remains appropriate. ^{86–104}	Compared with the general population, patients treated with TNF inhibitors have an increased risk of lymphoma. However, when compared with patients with RA treated with conventional drugs, no increased risk for lymphoma and other hematologic malignancies was observed. ^{105–117}	HACA (human anti-chimeric antibodies) and HAHA (human anti-human antibodies) can occur with all drugs of this class, but their effect on the effectiveness of therapy is unclear. The induction of production of antibodies against anti-TNF α agents depends mainly on its structure. Chimeric drugs have a greater capacity to induce immunogenicity compared to fully human drugs. ^{118,119} The immunological tolerance to ADA and IFX may be increased with concomitant use of immunomodulators, such as methotrexate and azathioprine. There is no evidence in the literature that HACA and HAHA cross-react with the different anti-TNF agents. ¹²⁵	Dermatological manifestations described in users of anti-TNF inhibitors include skin reactions related to its administration, skin infections, skin cancer and immune-mediated diseases, such as psoriasis, ^{97–99,101–104} cutaneous lupus, ^{121–124} alopecia areata, ^{99,125–133} cutaneous vasculitis, ^{134–138} vitiligo, ^{135,139,140} relapsing polychondritis, ¹⁴¹ polymyositis/dermatomyositis, ^{142,143} localized scleroderma (morphea), ^{144–146} granuloma annulare, ^{135,147} lichen or lichenoid reaction ^{120,135,148} and pemphigus. ¹⁴⁹	The response to influenza vaccine does not appear to be impaired in patients using anti-TNF agents, even when combined with MTX. ^{152–154} A study conducted in Brazil and that evaluated the vaccine against H1N1 influenza, found, besides a good safety profile, reduced serum protection in patients with RA independently of disease activity. MTX was the only DMD associated with reduced response to the vaccine. ¹⁵⁶ As for the pneumococcal vaccine, the use of MTX in isolation or combined with some anti-TNFs (ADA, ETN and IFX), may decrease the effectiveness of the vaccine, while the isolated use of these biologicals does not influence the vaccine response. ^{153,155} Additionally, the use of anti-TNF can significantly reduce the vaccine response against hepatitis B. ¹⁵⁷ Vaccines with live attenuated components should preferably be given three to four weeks before initiation of immunosuppressive therapy, to ensure that viral replication has finished before the change of the patient's immune competence (in terms of drug use). Otherwise, under treatment, the vaccination should be delayed for at least the equivalent time of four half-lives of each anti-TNF drug. ¹⁵⁸

Table 1 (Continued)

Drugs (mechanism of action)	Infections	Infusion reactions	Hematological reactions	Neurological reactions	Gastrointestinal reactions	Cardiovascular reactions	Solid neoplasms	Hematological neoplasms	Immunogenicity	Other occurrences	Vaccine response
Abatacept (ABAT)	<p>ABAT is contraindicated in patients with active infections, including skin ulcers, with infected prostheses, or in those using a catheter. Risk of serious infection is reported in 3% with ABAT versus 1.9% with placebo.^{164,165}</p> <p>The use of ABAT do not increase <i>Mycobacterium tuberculosis</i> infection.^{162,166}</p> <p>As for patients who initiate other biological agents, screening tests for hepatitis B and C must be made before the use of ABAT.¹⁶¹</p>	<p>The infusion reactions with ABAT are most common symptoms are dizziness, nausea, headache, systemic hypertension, hypotension and dyspnea. Severe hypersensitivity reactions are rare (0.4% versus 0.2% with placebo).^{162,167}</p>	<p>Hematologic manifestations related to the use of ABAT are rare.</p>	<p>To date, there are no reports of peripheral neuropathy or central nervous system disease associated with the use of ABAT.</p>	<p>Liver enzyme abnormalities are mild, occurring only rarely with ABAT (0.1-1% of patients), and thus of little clinical value. The combination with MTX, NSAIDs, corticosteroids, sulfasalazine and leflunomide does not increase hepatotoxicity.¹⁶¹</p>	<p>Regarding the increased cardiovascular risk of RA patients, studies show that the use of ABAT does not determine higher risk. Cardiovascular disease does not use of ABAT, and contraindicate the use of ABAT, and interact with cardiovascular drugs or with oral anticoagulation.^{161,162}</p>	<p>The risk of other malignancies, e.g. non-melanoma skin cancer, lung cancer, colorectal cancer and breast cancer, with ABAT is comparable with RA patients using synthetic DMD.^{162,168}</p>	<p>Regarding the risk of lymphoma and other blood diseases, double-blind studies with 4149 patients treated with ABAT (11,658 patient-years) showed hematologic malignancy in only 0.13/100 patient-years (similar to RA), but as with the use of anti-TNF biological agents, the use of ABAT should be avoided in patients with lymphoma over the past five years.¹⁶¹</p>	<p>Different from that observed with the use of anti-TNF biological DMDs, the antinuclear factor (ANA) and anti-DNA did not show positivity over time in patients treated with ABAT.¹⁶²</p> <p>Apparently no formation of HACA and HAMA occurred with the use of abatacept.</p>	<p>The use of ABAT is contraindicated in patients with a diagnosis of chronic obstructive pulmonary disease (COPD) due to exacerbation of dyspnea and increased occurrence of infections.³⁷ There are reports of occurrence of psoriasisiform rash¹⁶⁹ and lupus-like syndrome and Sjögren syndrome.¹⁷⁰</p> <p>possibly in combination with the use ABAT. The risk of development of autoimmune events with the use of ABAT, based on the accumulated data of 4149 patients and 12,132 patient-years, has resulted in rare cases of cutaneous psoriasis (OR = 0.60), Sjögren's syndrome (OR = 0, 26) and vasculitis (OR = 0.34).¹⁶²</p>	<p>Regarding vaccination in patients with RA in use of ABAT, a sub-analysis of a study evaluated the efficacy and safety of influenza vaccination in 20 patients.¹⁷¹ A total of 55%, 50% and 35% of the patients developed vaccine response to H1N1, H2N2 and influenza B virus strains, respectively. A study in Brazil investigated the humoral response to vaccination against H1N1 virus in 11 patients with RA treated with MTX in combination with ABAT.¹⁷² Only 9% of the patients treated with a combination of MTX and ABAT achieved seroprotection, compared with 58% of the patients with MTX alone and 70% of healthy individuals. The analysis of the response to pneumococcal vaccine in 21 RA patients treated with ABAT showed that 81% achieved an immune response to at least one serotype.¹⁷³</p>

Table 1 (Continued)

Drugs (mechanism of action)	Infections	Infusion reactions	Hematological reactions	Neurological reactions	Gastrointestinal reactions	Cardiovascular reactions	Solid neoplasms	Hematological neoplasms	Immunogenicity	Other occurrences	Vaccine response
Rituximab (RTX)	<p>With regard to infections, a meta-analysis that included 745 patients treated with RTX in three randomized clinical trials found that there was no increased risk of serious infections compared with placebo.¹⁸⁰ The subgroup of patients with low IgG levels showed a higher risk of serious infections compared to patients who never presented this finding, but the risk of infection was already increased in these patients even before developing decreased levels of IgG. IgG levels must be measured prior to treatment with RTX and monitored over time.¹⁷⁹ With regard to TB, most patients using RTX have been pre-selected for latent tuberculosis in clinical trials and in daily practice. Having emphasized these points, reactivation of tuberculosis was not observed, although the package leaflet for this drug recommend searching for latent tuberculosis infection prior to medication.^{36,181}</p> <p>Regarding hepatitis B and hepatitis C, experts recommend that serology for hepatitis B should be performed before starting treatment with RTX.¹⁷⁹ In both negative and positive patients, reactivation was documented for the surface antigen of hepatitis B.^{182,183}</p>	<p>The most frequent adverse events are infusion reactions, which occur in 30-40% of patients in the first infusion and in about 10% in the second infusion.¹⁹⁰ In most cases, the reactions are mild to moderate. Severe cases that require drug discontinuation occur in less than 1% of the treated patients.¹⁷⁹ Each infusion of RTX should be preceded by the prior use (60min) of methylprednisolone 100 mg IV, 1g of paracetamol and an antihistamine to decrease the severity and frequency of infusion reactions.¹⁹⁰</p>	<p>The effect of B lymphocytes with its depletion is expected and is part of the mechanism of action of this drug. However, a significant reduction in total lymphocyte count is not expected. Patient safety, in the face of B lymphocyte depletion after multiple infusions of RTX (especially related to the cumulative risk of serious infections and malignancies), is not fully established in patients with rheumatoid arthritis.¹⁷⁸ Hematologic adverse events have not been shown relevant in long-term studies.^{178,191}</p>	<p>To date, six cases of MLE have been reported in patients with RA treated with RTX.^{176,179} Most cases had long-term RA and use of multiple immunosuppressive agents. The number of reported cases of MLE in patients with a diagnosis of RA being treated with RTX confers a risk of 0.4/100,000 patient-years, slightly increased versus general population (0.2/100,000) and lower than that observed in patients with systemic lupus erythematosus (4/100,000).¹⁷⁵ Thus, although its occurrence is considered rare (1-20,000) due to the high morbidity and mortality of the condition, clinical surveillance for diagnosis is recommended in this patient population. To date, no reports of peripheral neuropathy associated with the use of RTX were published.</p>	<p>An increase in gastrointestinal adverse events after exposure to RTX has not been observed.^{176,192}</p>	<p>An increased risk of acute myocardial infarction over time in patients treated with RTX has not been observed.¹⁷⁸</p>	<p>An increased risk of solid tumors over time in patients treated with RTX has not been observed.¹⁷⁸</p>	<p>An increased risk of hematology over neoplasia over time in patients treated with RTX has not been observed.¹⁷⁸ RTX is even used in the treatment of certain types of lymphoma.</p>	<p>Safety data from long-term randomized clinical trials in RA indicate that 11% of patients exposed to RTX develop HACA.¹⁹¹ HACA-positive patients did not show a higher number of infusion reactions during the second course of RTX in relation to HACA-negative patients.</p>	<p>Few cases of psoriasisiform condition were reported after infusion of RTX for the treatment of rheumatic diseases, or for other indications.¹⁹² Interstitial lung disease appears to be a rare occurrence with the use of RTX, but with potential for morbidity and mortality.¹⁹³ There are case reports of serum sickness, with the appearance of mild to moderate manifestations after infusion of RTX.¹⁹⁵</p>	<p>The use of RTX is related to a diminished response to vaccines, either those T-cell independent and those T-cell dependent.¹⁵⁸ There is evidence suggesting a compromised response for anti-pneumococcal and influenza vaccines, when administered to patients using RTX.^{179,196,197} The response to anti-influenza vaccine (including also influenza A and H1N1 vaccine) is also particularly compromised when the vaccine is administered prematurely, four to eight weeks after administration of RTX. Thus, influenza and anti-pneumococcal vaccines must be applied before starting RTX, or six months after the first infusion of this agent, and four weeks before the next dose.^{198,179} Patients with high risk of contracting tetanus who were treated with RTX within last 24 weeks must use passive immunization with tetanus immunoglobulin. Other vaccine which should be administered before the use of RTX is that against hepatitis B.¹⁷⁹</p>

Table 1 (Continued)

Drugs (mechanism of action)	Infections	Infusion reactions	Hematological reactions	Neurological reactions	Gastrointestinal reactions	Cardiovascular reactions	Solid neoplasms	Hematological neoplasms	Immunogenicity	Other occurrences	Vaccine response
Tocilizumab (TOCI)	TOCI should not be used in patients with active infection by any pathogen, including bacteria, viruses, fungi and parasites. ^{198,199} The risk of infection is 1.2 times higher for patients treated with TOCI versus those using synthetic DMD. ^{36,200} The risk does not increase with exposure time, with a rate for severe events ranging from 4 to 6/100,000 patient-years. ²⁰² even if combined with other synthetic DMDs. ²⁰³ Apparently, there is no increased risk of reactivation of latent tuberculosis infection (LTBI). ²⁰⁴ However, a LTBI screening before and during the use of immunobiological agents, especially in endemic areas is still recommended. Regarding viral hepatitis B and C,	Infusion reactions are rare events with TOCI and can be minimized by slowing the speed of intravenous infusion and/or administration of premedication with corticosteroids. Severe anaphylactic reaction and a need for permanent discontinuation of TOCI are quite rare.	A mild and transient neutropenia may occur; this does not increase the risk of infection per se. More severe or persistent cases require dose reduction of the medication to 4 mg/kg/infusion, and permanent discontinuation if this problem is not resolved. ²¹⁰	There is a case report of peripheral neuropathy related to the use of TOCI. ²¹⁰	Elevations of hepatic enzymes may occur in 8-10% of the patients, regardless of synthetic DMD. In general, these elevations are mild and transient, and do not increase the risk of irreversible hepatocellular damage. ²¹¹ At the start of treatment, monitoring is recommended every four to eight weeks, and then every three to six months. Persistent elevations deserve wider investigation of other causes, as well as a dose reduction and discontinuation of medication. ²⁰³ Some cases of intestinal perforation, especially in the colon, have been reported in patients using TOCI. An anamnesis for	No consistent clinical studies evaluating cardiovascular events as primary outcomes using TOCI in patients with rheumatic diseases were published. Apparently, the incidences of MI (0.25/100 patient-years) and stroke (0.19/100 patient-years) are low, without increase with a longer exposure time to the drug. ²⁰³	Apparently, there is no higher risk than that observed in the control group. ²¹²	Apparently, there is no higher risk than that observed in the control group. ²¹²	TOCI has antigenic potential, although few immunogenic reports have been described. The ability of formation of neutralizing antibodies HAMA, including intensity, isotype, specificity and kinetics, has been studied, but the frequency is much lower than that reported for TNF blockers. ²¹³	There are some anecdotal cases or case reports of patients who developed other unexpected adverse reactions after TOCI, including skin (ulcers, necrotizing fasciitis) ²¹⁴ and mucosal (persistent aphthous ulcerations in the oral mucosa) disorders, ²¹⁵ as well as eye (bilateral retinopathy with hemorrhage and cotton-wool infiltrates) ²¹⁶ and lung (organizing pneumonia and exacerbation of interstitial picture) ^{217,218} events. Just as observed with TNF antagonists, some cases of psoriasis and uveitis onset ("de novo" cases) were reported after IL-6 blockade, emphasizing paradoxical events that can occur with the use also of this medication. ²¹⁹⁻²²¹	There are few studies on the vaccine response in patients exposed to TOCI. Two studies demonstrated an adequate safety and efficacy profile (seroprotection and seroconversion) for the vaccine against influenza virus in patients with RA, regardless of MTX, ²²² and systemic-onset juvenile idiopathic arthritis. ²²³ In addition, there was no exacerbation of the joint status of these patients. Regarding other vaccines and immunizations, at present there are no data on safety and efficacy profiles.

Table 1 (Continued)

Drugs (mechanism of action)	Infections	Infusion reactions	Hematological reactions	Neurological reactions	Gastrointestinal reactions	Cardiovascular reactions	Solid neoplasms	Hematological neoplasms	Immunogenicity	Other occurrences	Vaccine response
	data from studies are still preliminary. At the moment, TOCI should not be used in this clinical setting. ^{204,208}			personal history of colonic diverticular disease and diverticulitis is recommended. This risk increases with concomitant use of corticosteroids and NSAIDs. Therefore, in this scenario these drugs should be used sparingly. ²⁰³							

ABAT, abatecept; ADA, adalimumab; anti-TNF, tumor necrosis factor blocking drugs; RA, rheumatoid arthritis; apoB/apoA, apolipoprotein B/apolipoprotein A; Str., stroke; CERT, certolizumab; DMD, disease-modifying drug; RPCCT, randomized placebo-controlled clinical trial; ETN, etanercept; GOL, golimumab; HAHAs, human anti-human antibodies; HDL, high-density lipoproteins; IFX, infliximab; MI, myocardial infarction; CHF, congestive heart failure; LTBI, latent tuberculosis infection; LDL, low density lipoproteins; MTX, methotrexate; TOCI, tocilizumab.

^a Most available data on the occurrence of adverse effects concern to the first anti-TNF agents: infliximab, etanercept and adalimumab. There are no definitive comparative studies. Meta-analyses and the assessment of observational studies showed no significant difference in the incidence of complications among different biological agents. Albeit with shorter observation time, the current understanding is that the newer anti-TNF agents, e.g., golimumab and certolizumab pegol, are associated with the same risk of adverse events.

drugs. Choosing the appropriate treatment for pregnant and lactating patients is an extremely challenging task.

The management of pregnancy and lactation in patients with rheumatic diseases in the use of biological DMDs should be multidisciplinary, involving the patient and her partner, the rheumatologist and the obstetrician, being taken into account the risks and benefits of these drugs, other therapeutic options, the intensity of the inflammatory disease and the underlying safety for the mother, fetus and neonate.²²⁵

In general, biological DMDs should be avoided during pregnancy and lactation, since according to the currently available evidence, FDA does not describe any biological therapy as provenly safe during human pregnancy. Anti-TNF drugs are classified as B (animal studies with no fetal risk, with no controlled human studies, or animal studies with risk that has not been proven in humans in the first trimester of gestation, with no evidence of later risk), while RTX, ABAT and TOCI are categorized as C (studies in animals have shown teratogenic effects; and there are no controlled human studies, or no studies available in humans and animals, these being considered substances that should be used only if potential benefits justify potential risks to the fetus).²²⁶

Transplacental transit

Children are protected from infectious diseases in their first months of life by maternal antibodies that cross the placenta in the second half of pregnancy. The antibodies' transfer through the placenta begins in the second trimester, but increases linearly until delivery. At the end of pregnancy, the amount of maternal antibodies of IgG isotype is higher in the fetus than in the mother herself. This same pattern remains, when the IgG is an anti-TNF drug.^{225,227}

There is evidence that a significant amount of anti-TNF cross the placenta, especially during the third trimester. Small amounts of anti-TNF are detected in breast milk.²²⁸

There are no conclusive data on ABAT, TOCI and RTX crossing the human placenta and their possible excretion in breast milk.

As for RTX, by being an IgG antibody, the drug could cross the placenta and interfere with fetal and neonatal B-cell development. Moreover, its pharmacokinetic properties and long-term effects would allow the hypothetical occurrence of adverse effects, even in cases of exposure months before conception.²²⁵ However, as we shall see, in the few cases described of occurrence of pregnancy in women treated with RTX, no fetal or neonatal complications were observed, which, due to the small number of cases, does not allow inferences. Thus, RTX is also contraindicated in pregnancy.

Outcome of pregnancies exposed to biological DMARDs

In a recent SLR, Bogas and Leandro identified all publications in humans with results on the fetus or newborn after exposure to biological therapies during pregnancy. Sixty-five publications and 745 references on the subject were identified and evaluated.²²⁹

Table 2 summarizes the outcome of pregnancies with exposure to biological DMDs, considering each drug in isolation, based on information currently available.

It is important to emphasize the following considerations on pregnancies' outcomes²²⁹:

1. Many women had active disease and were concomitantly exposed to potentially teratogenic drugs such as MTX and leflunomide.
2. The exposure to biological DMDs can be divided into two groups: (a) unplanned pregnancy – the exposure occurred at the time of conception and during the first trimester, and in most cases the drug was discontinued as soon as pregnancy was confirmed; (b) pregnant women who were intentionally treated, due to a refractory active disease.
3. There is great variation in the dose of the biological DMD used, depending on the underlying disease.
4. The outcome of each pregnancy can be dependent on several other factors, including the mother, the underlying disease, disease activity and the presence of comorbidities,²³⁰ and such information was not present in the majority of reports available
5. Overall, congenital abnormalities are described in 3–5% of the live births, and some of them appear to be relatively common, including the involvement of the CNS, heart, limbs, and urinary system (with a prevalence of more than 20 cases per 10,000 births).²³¹ VACTREL is a non-random association of birth defects which occurs in 1.6 per 10,000 live births²³² (V, vertebral defects, a, anal atresia; C, cardiac abnormalities; T, tracheo-esophageal fistula or atresia/tracheal stenosis; E, esophageal atresia; R, renal or radial abnormalities; L, abnormalities in pre-axial members). The possible association between VACTREL and biologicals' use (especially anti-TNF drugs) has been raised, but currently this is being questioned.²²⁵
6. The frequency of premature births varies from 5% to 13% in developed countries.²³³ The risk of congenital anomalies or prematurity appears to be greater in patients with RA, compared to pregnant women without such diagnosis.²³⁰
7. Absence of control groups not treated with biologicals in most series and reports included in Bogas and Leandro's SRL²²⁹ may have occasioned a bias, but, in general, no specific pattern of congenital defect was observed in children exposed to intrauterine biologicals.

In 2011 a review of 231 cases of pregnant women exposed to RTX (the whole range of indications of drug use, including those non-associated to rheumatic diseases) was published.²³⁴ Of the 153 pregnancies with known outcomes, 90 resulted in live births. Twenty-two children were born prematurely, with one neonatal death in six weeks. Eleven neonates exhibited hematologic changes, but not one had corresponding infections. Although only a few congenital malformations or neonatal infections were observed among exposed newborns, women should be advised to avoid pregnancy until 12 months after RTX exposure.

Use of biologicals during lactation

The absorption of maternal antibodies through breast milk is limited in humans, and the predominant Ig isotype in breast

Table 2 (Continued)

Drugs	Publications available	Number of patients exposed during pregnancy	Accidental exposure during the first trimester	Exposure during the second or third trimester	Spontaneous abortions	Elective terminations of pregnancy	Live births without complications	Preterm deliveries	Related malformations	Available information on exposure during lactation
Infliximab (IFX)	24 (4 reports, 3 series, case reports)	156	70%	5-10%					8 neonates with congenital malformations and other complications - 1 intestinal malrotation (concurrent use of leflunomide) - 1 tetralogy of Fallot - 1 child with pulmonary and intracerebral hemorrhage - death at 24 weeks - 1 death on the third day of life (cause unknown) - 2 cases of respiratory failure (1 child with seizures) - 2 cases of delayed development (1 hypothyroidism)	
Abatecept (ABAT)	Case reports	10	No information available	No information available	3	2	1	No information available	No information available	No information available
Rituximab (RTX)	Case reports	16	3	8		1	15	No information available	No information available	No information available
Tocilizumab (TOCI)	No information in literature	No information available	No information available	No information available	No information available	No information available	No information available	No information available	No information available	No information available

Modified from Refs. [226,230].

VACTREL, non-random association of birth defects; V, vertebral defects; A, anal atresia; C, cardiac abnormalities; T, tracheoesophageal fistula or tracheal atresia/stenosis; E, esophageal atresia; R, renal or radial abnormalities; L, abnormalities in pre-axial members.

milk is IgA, which provides immunity to intestinal mucosa in breastfeeding infants.²²⁷

Small amounts of IgG or other major Igs cross breast acini, and thus cannot be found in the blood of breastfeeding infants in significant quantities. For this reason, it is expected that the passage of anti-TNF drugs through breast milk be minimal. There are few data from experimental (animal) or clinical studies producing such information. There are some reported cases of mothers that were treated with anti-TNF, and it does not seem that this class of drug is transferred between the mother and her baby through breast milk.²²⁵

There are no consistent data on the passage of other non-anti-TNF biological drugs through breast milk.

Recommendations for the use of biologicals during pregnancy and lactation

The information in the literature about the use of biologicals during pregnancy and lactation in patients with rheumatic diseases is still scarce, especially with regard to non-anti-TNF drugs; we emphasize that, in general, the use of such drugs should be avoided during pre-conception, pregnancy and lactation periods.

With respect to anti-TNF DMDs, based on information currently available and on the extrapolation of currently existing guidelines on the use of anti-TNF therapy in patients with inflammatory bowel disease,²³⁵ the recommendations listed below are suggested.

Preconception exposure

Considering that anti-TNF drugs hypothetically do not cross the placental barrier in the first trimester, it would be possible to allow the use of anti-TNF until the moment of conception.

Exposure during pregnancy

Anti-TNF drugs should be discontinued during pregnancy. In case of a very intense activity of the underlying disease, we could argue in favor of an eventual prescription or reintroduction of one of these drugs during pregnancy – preferably, if possible, with a dose reduction and a more spaced period between administrations, with its discontinuation eight to 10 weeks before the expected date of confinement.

Exposure during lactation

Anti-TNF drugs should be avoided during lactation. However, in case of intense disease activity, and considering that the limited number of cases reported to date seems to indicate that small amounts of anti-TNF drugs pass into breast milk, the prescription of such drugs during lactation would be possible in those cases where the benefit to the mother outweighs the risk to her child.

In summary, the use of biological DMDs should be avoided during pre-conception, pregnancy and lactation periods. Exceptionally, in the case of an intense activity of the

disease, and when the maternal benefit outweighs the risk to the fetus, and also in common agreement with the obstetrician, the patient and her family, the eventual prescription or reintroduction of an anti-TNF drug during pregnancy may be considered – preferably, if possible, with a dose reduction and a more spaced period between administrations, with its discontinuation eight to 10 weeks before the expected date of confinement. The prescription of anti-TNF during lactation may be possible in cases where the benefit to the mother outweighs the risk to her child.

Final considerations and conclusions

The treatment of rheumatic diseases of immunoinflammatory nature, especially RA and spondyloarthritides, has undergone significant change in recent years. The emphasis on early diagnosis, the immediate introduction of DMDs, and in a rigorous monitoring of therapeutic response, as well as the development of immunobiological agents, have revolutionized the way these diseases are being treated. SBR has been devoted to produce documents that guide the rheumatologist on the diagnostic and therapeutic management of RA^{37,158,224,236–238} and spondyloarthritides,^{12,239} including information on the use of biological DMDs in these conditions.

Due to fears about the safety profile, immunobiological agents were initially reserved for advanced forms of the disease refractory to traditional medicines. Today, some 15 years after the beginning of their commercialization and with the experience gained in patients' monitoring, their use is already indicated in less severe cases and even in selected cases, in earlier stages of these diseases.

The safety of biological agents in the short term has been well established in pivotal studies on each of these products. Although involving difficult to control patients, refractory to several DMDs, the inclusion criteria of these studies excluded patients with systemic manifestations of the diseases and with relevant comorbidities. Register studies, on the other hand, assess the safety also in the medium and long term and include patients more similar to those in our daily practice. So far, these drugs have been shown to be relatively safe. A new challenge arises with the use, in sequence and by the same patient, of different biological agents. Pharmacovigilance studies become even more relevant in the long-term evaluation of these patients.

Experience shows that the most powerful tools may have the most influential adverse consequences. This principle, which is valid also for clinical pharmacology, applies emphatically to immunobiological drugs, due to the wide spectrum of actions exercised in the intimacy of various immunological mechanisms. In fact, this review consistently showed the diversity of adverse events associated with immunobiological therapy. With this warning notice, we would emphasize the importance of dedication and surveillance to the safety aspects of this class of drugs.

This review sought to provide a broad and balanced update of clinical and experimental data accumulated in the last two decades of use of immunobiological drugs to patients with autoimmune rheumatic diseases, with an emphasis in RA and spondyloarthritides. For chronological reasons, the largest

experience to date refers to immunobiologicals that antagonize TNF. Despite the relative safety of biological agents, we must keep all our attention in the selection and monitoring of patients with indications of these drugs.

Authorship and conflicts of interest

LMHM: Participated in pharmaceutical industry-sponsored clinical and/or experimental studies, related to the consensus in question: Roche, Mantecorp; received personal or institutional aid from industry: Abbott, AstraZeneca, MSD, Roche, Pfizer; has spoken at industry-sponsored events or activities related to the consensus in question: Abbott, Astra-Zeneca, Janssen, MSD, Mantecorp, Roche, Pfizer. Was (is) a member of the advisory or director board of pharmaceutical industry or of regulatory committees on scientific studies sponsored by industry: AstraZeneca, MSD; wrote scientific texts for industry-sponsored Journals: Abbott, Astra-Zeneca and Pfizer.

BAC: Participated in pharmaceutical industry-sponsored clinical and/or experimental studies related to the consensus in question: Roche; received personal or institutional financial support from industry: Abbott, Astra-Zeneca, BMS, Janssen, Merck, Pfizer and Roche; has spoken at industry-sponsored events or activities related to the consensus in question: Abbott, Astra-Zeneca, BMS, Janssen, MSD, Pfizer, Roche; wrote scientific texts for industry-sponsored Journals: Abbott, Astra-Zeneca, Janssen, MSD, Pfizer, Roche.

CVB: Participated in pharmaceutical industry-sponsored clinical and/or experimental studies: Bristol-Myers Squibb, Pfizer, Roche and Wyeth; received personal or institutional financial support from industry: Abbott, Bristol-Myers Squibb, Mantecorp, Roche and Janssen. Speaker at industry-sponsored events or activities: Abbott, Janssen and Roche.

DFP: Main investigator in clinical trials sponsored by Roche; AstraZeneca; Abbott; Pfizer. Participation in councils and boards: AstraZeneca; Bristol-Myers Squibb; Pfizer.

NAS: Participated in pharmaceutical industry-sponsored clinical and/or experimental studies: Roche and Bristol-Myers Squibb; received personal or institutional financial support from industry: Roche, Wyeth/Pfizer and Abbott; speaker at events or activities sponsored by Roche, Janssen and Astra-Zeneca.

IAP: Invited for participation in Conferences, Workshops and Symposia: Abbott, Roche, MSD, Pfizer, Novartis, Lilly, Aventis. Participation as an investigator in research: Roche. Speaker: Abbott, MSD, Pfizer, Roche, Lilly, Novartis, Boehringer, Aventis, Janssen. Consultant (Advisory Board): Pfizer, MSD, Abbott, Roche, Janssen, BMS.

IMML, JFC, LECA, MVCF and NAS declare no conflicts of interest.

MBB: Speaker in industry-sponsored events or activities: Abbott, Pfizer, Sanofi Aventis.

MMP: Participated in pharmaceutical industry-sponsored clinical and/or experimental studies related to the consensus in question: MSD, Abbott; has spoken at industry-sponsored events or activities related to the consensus in question: Abbott, MSD, Roche.

PDSB: Received personal or institutional financial support from industry: Abbott, Astra-Zeneca, Janssen, MSD, Pfizer,

Roche; has spoken at industry-sponsored events or activities related to the consensus in question: Abbott, Janssen, MSD, Pfizer, Roche industry; was (is) a member of the advisory or director board of pharmaceutical industry or of regulatory committees on scientific studies sponsored by industry: (Abbott, Janssen, MSD, Pfizer); wrote scientific texts for industry-sponsored Journals: Abbott, Janssen, MSD, Pfizer.

PLJ: Participated in pharmaceutical industry-sponsored clinical and/or experimental studies related to the consensus in question: Roche, Mantecorp; received personal or institutional financial support from industry: Abbott, Janssen, Roche, Pfizer; has spoken at industry-sponsored events or activities related to the consensus in question: (Bristol, Janssen, MSD, Mantecorp, Roche, Pfizer). Was (is) a member of the advisory or director board of pharmaceutical industry or of regulatory committees on scientific studies sponsored by industry: Bristol.

RACL: Participated in pharmaceutical industry-sponsored clinical and/or experimental studies related to the consensus in question: Roche, Mantecorp; received personal or institutional financial support from industry: Abbott, Astra-Zeneca, MSD, Roche, Pfizer, Actellion; has spoken at industry-sponsored events or activities related to the consensus in question: Roche. Was (is) a member of the advisory or director board of pharmaceutical industry or of regulatory committees on scientific studies sponsored by industry: Astra-Zeneca, MSD.

RDNG: Received fees for consulting and/or lecturing services: Abbott, Astra Zeneca, BMS, Jansen, Pfizer, Roche. Participation in clinical research: Anthera, GSK, HGS, Lilly, Roche, Sanofi Aventis.

REFERENCES

- Upchurch KS, Kay J. Evolution of treatment for rheumatoid arthritis. *Rheumatology (Oxford)*. 2012;5 Suppl. 6:vi28–36.
- Tak PP, Kalden JR. Advances in rheumatology: new targeted therapeutics. *Arthritis Res Ther*. 2011;13 Suppl. 1:S5.
- Rogers JL, Serafin DS, Timoshchenko RG, Tarrant TK. Cellular targeting in autoimmunity. *Curr Allergy Asthma Rep*. 2012;12:495–510.
- Kok MR, Tak PP. Taking advances from bench to bedside during the last decade. *Best Pract Res Clin Rheumatol*. 2012;26:225–36.
- Takeuchi T. Revolutionary change in rheumatoid arthritis management with biological therapy. *Keio J Med*. 2011;60:75–81.
- Soares MR, Reis Neto ET, Luz KR, Ciconelli RM, Pinheiro MM. Switching between anti-TNF-alpha agents does not improve functional capacity in patients with long-term standing and active rheumatoid arthritis. *Rev Bras Reumatol*. 2012;52:9–15.
- Tracey D, Klareskog L, Sasso EH, Salfeld JG, Tak PP. Tumor necrosis factor antagonist mechanisms of action: a comprehensive review. *Pharmacol Ther*. 2008;117:244–79.
- Benucci M, Saviola G, Manfredi M, Sarzi-Puttini P, Atzeni F. Tumor necrosis factors blocking agents: analogies and differences. *Acta Biomed*. 2012;83:72–80.
- Nam JL, Winthrop KL, van Vollenhoven RF, Pavelka K, Valesini G, Hensor EM, et al. Current evidence for the management of rheumatoid arthritis with biological disease-modifying antirheumatic drugs: a systematic literature review informing the EULAR recommendations for the management of RA. *Ann Rheum Dis*. 2010;69:976–86.
- Singh JA, Furst DE, Bharat A, Curtis JR, Kavanaugh AF, Kremer JM, et al. 2012 update of the 2008 American College of Rheumatology recommendations for the use of disease-modifying antirheumatic drugs and biologic agents in the treatment of rheumatoid arthritis. *Arthritis Care Res (Hoboken)*. 2012;64:625–39.
- Gossec L, Smolen JS, Gaujoux-Viala C, Ash Z, Marzo-Ortega H, van der Heijde D, et al. European League Against Rheumatism recommendations for the management of psoriatic arthritis with pharmacological therapies. *Ann Rheum Dis*. 2012;71:4–12.
- Sampaio-Barros PD, Keisermann M, Meirelles ES, Pinheiro MM, Ximenes AC, Azevedo VF, et al. Recomendações sobre o Diagnóstico e Tratamento da Espondilite Anquilosante 2012. *Rev Bras Reumatol*. 2013, <http://dx.doi.org/10.1590/S0482-50042013000300003> [in press].
- van der Heijde D, Sieper J, Maksymowych WP, Dougados M, Burgos-Vargas R, Landewé R, et al. 2010 update of the international ASAS recommendations for the use of anti-TNF agents in patients with axial spondyloarthritis. *Ann Rheum Dis*. 2011;70:905–8.
- Carneiro S, Azevedo VF, Bonfiglioli R, Ranza R, Keisermann M, Gonçalves CR, et al. Recomendações sobre o Diagnóstico e Tratamento da Artrite Psoriásica 2012. *Rev Bras Reumatol*. 2013, <http://dx.doi.org/10.1590/S0482-50042013000300002> [in press].
- Kievit W, Fransen J, Adang EM, den Broeder AA, Bernelot Moens HJ, Visser H, et al. Long-term effectiveness and safety of TNF-blocking agents in daily clinical practice: results from the Dutch Rheumatoid Arthritis Monitoring register. *Rheumatology (Oxford)*. 2011;50:196–203.
- Burmester GR, Panaccione R, Gordon KB, McIlraith MJ, Lacerda AP. Adalimumab: long-term safety in 23 458 patients from global clinical trials in rheumatoid arthritis, juvenile idiopathic arthritis, ankylosing spondylitis, psoriatic arthritis, psoriasis and Crohn's disease. *Ann Rheum Dis*. 2012 [E-pub ahead of print].
- Simard JF, Arkema EV, Sundström A, Geborek P, Saxne T, Baecklund E, et al. Ten years with biologics: to whom do data on effectiveness and safety apply? *Rheumatology (Oxford)*. 2011;50:204–13.
- Baraliakos X, Listing J, Fritz C, Haibel H, Alten R, Burmester GR, et al. Persistent clinical efficacy and safety of infliximab in ankylosing spondylitis after 8 years – early clinical response predicts long-term outcome. *Rheumatology (Oxford)*. 2011;50:1690–9.
- Davis JC Jr, van der Heijde DM, Braun J, Dougados M, Clegg DO, Kivitz AJ, et al. Efficacy and safety of up to 192 weeks of etanercept therapy in patients with ankylosing spondylitis. *Ann Rheum Dis*. 2008;67:346–52.
- Sieper J, van der Heijde D, Dougados M, Brown LS, Lavie S, Pangan AL. Early response to adalimumab predicts long-term remission through 5 years of treatment in patients with ankylosing spondylitis. *Ann Rheum Dis*. 2012;71:700–6.
- Braun J, Deodhar A, Inman RD, van der Heijde D, Mack M, Xu S, et al. Golimumab administered subcutaneously every 4 weeks in ankylosing spondylitis: 104-week results of the GO-RAISE study. *Ann Rheum Dis*. 2012;71:661–7.
- Baraliakos X, Listing J, Brandt J, Zink A, Alten R, Burmester G, et al. Clinical response to discontinuation of anti-TNF therapy in patients with ankylosing spondylitis after 3 years of continuous treatment with infliximab. *Arthritis Res Ther*. 2005;7:R439–44.

23. Carmona L, Gomez-Reino JJ, BIOBADASER Group. Survival of TNF antagonists in spondylarthritis is better than in rheumatoid arthritis. Data from the Spanish registry BIOBADASER. *Arthritis Res Ther.* 2006;8:R72.
24. Antoni C, Krueger GG, de Vlam K, Birbara C, Beutler A, Guzzo C, et al. Infliximab improves signs and symptoms of psoriatic arthritis: results of the IMPACT 2 trial. *Ann Rheum Dis.* 2005;64:1150-7.
25. Mease PJ, Kivitz AJ, Burch FX, Siegel EL, Cohen SB, Ory P, et al. Etanercept treatment of psoriatic arthritis: safety, efficacy, and effect on disease progression. *Arthritis Rheum.* 2004;50:2264-72.
26. Anandarajah AP, Ory P, Salonen D, Feng C, Wong RL, Ritchlin CT. Effect of adalimumab on joint disease: features of patients with psoriatic arthritis detected by magnetic resonance imaging. *Ann Rheum Dis.* 2009;69:206-9.
27. Curtis JR, Patkar N, Xie A, Martin C, Allisson JJ, Saag M. Risk of serious bacterial infections among rheumatoid arthritis patients exposed to tumor necrosis factor alpha antagonists. *Arthritis Rheum.* 2007;56:1125-33.
28. Galloway JB, Hyrich KL, Mercer KL, Dixon WG, Fu B, Ustianovski AP, et al. Anti-TNF therapy is associated with an increased risk of serious infections in patients with rheumatoid arthritis especially in the first 6 months of treatment: updated results from the British Society for Rheumatology Biologics Register with special emphasis on risks in the elderly. *Rheumatology (Oxford).* 2011;50:124-33.
29. Woodrick RS, Ruderman EM. Safety of biologic therapy in rheumatoid arthritis. *Nat Rev Rheumatol.* 2011;7:639-52.
30. Rubbert-Roth A. Assessing the safety of biologic agents in patients with rheumatoid arthritis. *Rheumatology.* 2012;51 Suppl. 5:v38-47.
31. Askling J, Forel CM, Brandt L, Baecklund E, Bertilsson L, Feltelius N, et al. Time-dependent increase in risk of hospitalisation with infection among Swedish RA patients treated with TNF antagonists. *Ann Rheum Dis.* 2007;66:1339-44.
32. García-Doval I, Pérez-Zafrilla B, Descalzo MA, Roselló R, Hernández MV, Gómez-Reino JJ, et al., BIOBADASER 2.0 Study Group. Incidence and risk of hospitalisation due to shingles and chickenpox in patients with rheumatic diseases treated with TNF antagonists. *Ann Rheum Dis.* 2010;69:1751-5.
33. Strangfeld A, Listing J, Herzer P, Liebhaber A, Rockwitz K, Richter C, et al. Risk of herpes zoster in patients with rheumatoid arthritis treated with anti-TNF-alpha agents. *JAMA.* 2009;301:737-44.
34. Carmona L, Gómez-Reino JJ, Rodríguez-Valverde V, Montero D, Pascual-Gómez E, Mola EM, et al. Effectiveness of recommendations to prevent reactivation of latent tuberculosis infection in patients treated with tumor necrosis factor antagonists. *Arthritis Rheum.* 2005;52:1766-72.
35. Dixon WG, Hyrich KL, Watson KD, Lunt M, Galloway J, Ustianowski A. Drug-specific risk of tuberculosis in patients with rheumatoid arthritis treated with anti-TNF therapy: results from the British Society of Rheumatology Biologic Register (BSRBR). *Ann Rheum Dis.* 2010;69:522-8.
36. Singh JA, Wells GA, Christensen R, Tanjong Ghogomu E, Maxwell L, Macdonald JK, et al. Adverse effects of biologics: a network meta-analysis and Cochrane overview. *Cochrane Database Syst Rev.* 2011;16. CD008794.
37. da Mota LM, Cruz BA, Brenol CV, Pereira IA, Rezende-Fronza LS, Bertolo MB, et al. Brazilian Society of Rheumatology Consensus for the treatment of rheumatoid arthritis. *Rev Bras Reumatol.* 2012;52:152-74.
38. Mariette X, Baron G, Tubach F, Lioté F, Combe B, Miceli-Richard C, et al. Influence of replacing tuberculin skin test with ex vivo interferon γ release assays on decision to administer prophylactic antituberculosis antibiotics before anti-TNF therapy. *Ann Rheum Dis.* 2012;71:1783-90.
39. Hernández MV, Sanmartí MMR. Lesiones cutáneas y terapia biológica con antagonistas del factor de necrosis tumoral. *Reumatol Clin.* 2013;9:53-61.
40. Maini RN, Breedveld FC, Kalden JR, Smolen JS, Davis D, Macfarlane JD, et al. Therapeutic efficacy of multiple intravenous infusions of anti-tumor necrosis factor alpha monoclonal antibody combined with low-dose weekly methotrexate in rheumatoid arthritis. *Arthritis Rheum.* 1998;41:1552-63.
41. Weinblatt ME, Kremer JM, Bankhurst AD, Bulpitt KJ, Fleischmann RM, Fox RI, et al. A trial of etanercept, a recombinant tumor necrosis factor receptor:Fc fusion protein, in patients with rheumatoid arthritis receiving methotrexate. *N Engl J Med.* 1999;340:253-9.
42. Weinblatt ME, Keystone EC, Furst DE, Moreland LW, Weisman MH, Birbara CA, et al. Adalimumab, a fully human anti-tumor necrosis factor alpha monoclonal antibody, for the treatment of rheumatoid arthritis in patients taking concomitant methotrexate: the ARMADA trial. *Arthritis Rheum.* 2003;48:35-45.
43. Keystone E, Heijde D, Mason D Jr, Landewe R, Vollenhoven RV, Combe B, et al. Certolizumab pegol plus methotrexate is significantly more effective than placebo plus methotrexate in active rheumatoid arthritis: findings of a fifty-two-week, phase III, multicenter, randomized, double-blind, placebo-controlled, parallel-group study. *Arthritis Rheum.* 2008;58:3319-29.
44. Keystone EC, Genovese MC, Klareskog L, Hsia EC, Hall ST, Miranda PC, et al. Golimumab, a human antibody to tumour necrosis factor alpha given by monthly subcutaneous injections, in active rheumatoid arthritis despite methotrexate therapy: the GO-FORWARD Study. *Ann Rheum Dis.* 2009;68:789-96.
45. Kiely PD, Deighton C, Dixey J, Östör AJ, British Society for Rheumatology Standards, Guidelines and Audit Working Group. Biologic agents for rheumatoid arthritis – negotiating the NICE technology appraisals. *Rheumatology (Oxford).* 2012;51:24-31.
46. Bessisow T, Renard M, Hoffman I, Vermeire S, Rutgeerts P, Van Assche G. Non-malignant haematological complications of anti-tumour necrosis factor alpha therapy. *Aliment Pharmacol Ther.* 2012;36:312-23.
47. Hyrich KL, Silman AJ, Watson KD, Symmons DP. Anti-tumor necrosis factor alpha therapy in rheumatoid arthritis: an update on safety. *Ann Rheum Dis.* 2004;63:1538-43.
48. Vidal F, Fontova R, Richart C. Severe neutropenia and thrombocytopenia associated with infliximab. *Ann Intern Med.* 2003;139. W-W63.
49. Wenham C, Gadsby K, Deighton C. Three significant cases of neutropenia with etanercept. *Rheumatology (Oxford).* 2008;47:376-7.
50. Ramos-Casals M, Brito-Zerón P, Muñoz S, Soria N, Galiana D, Bertolaccini L, et al. Autoimmune diseases induced by TNF-targeted therapies: analysis of 233 cases. *Medicine (Baltimore).* 2007;86:242-51.
51. Ramos-Casals M, Roberto-Perez-Alvarez, Diaz-Lagares C, Cuadrado MJ, Khamashta MA, BIOGEAS Study Group. Autoimmune diseases induced by biological agents: a double-edged sword? *Autoimmun Rev.* 2010;9:188-93.
52. Bosch X, Saiz A, Ramos-Casals M, BIOGEAS Study Group. Monoclonal antibody therapy-associated neurological disorders. *Nat Rev Neurol.* 2011;7:165-72.

53. Molloy ES, Calabrese LH. Progressive multifocal leukoencephalopathy associated with immunosuppressive therapy in rheumatic diseases: evolving role of biologic therapies. *Arthritis Rheum.* 2012;64:3043-51.
54. Lozeron P, Denier C, Lacroix C, Adams D. Long term course of demyelinating neuropathies occurring during tumor necrosis factor alpha blocker therapy. *Arch Neurol.* 2009;66:490-7.
55. The Lenercept Multiple Sclerosis Study Group and the University of British Columbia MS/MRI Analysis Group. TNF neutralization in MS: results of placebo-controlled multicenter study. *Neurology.* 1999;53:457-65.
56. van Oosten BW, Barkhof F, Truyen L, Boringa JB, Bertelsmann FW, von Blomberg BM, et al. Increased MRI activity and immune activation in two multiple sclerosis patients treated with the monoclonal anti-tumor necrosis factor antibody cA2. *Neurology.* 1996;47:1531-4.
57. Fernández-Espartaco CM, Pérez-Zafrilla B, Naranjo A, Esteban C, Ortiz AM, Gomez-Reino JJ, BIOBADASER Study Group. Demyelinating disease in patients treated with TNF antagonists in rheumatology: data from BIOBADASER, a pharmacovigilance database, and a systematic review. *Semin Arthritis Rheum.* 2011;40:330-7.
58. Bernatsky S, Renoux C, Suissa S. Demyelinating events in rheumatoid arthritis after drug exposures. *Ann Rheum Dis.* 2010;69:1691-3.
59. Nicola PJ, Crowson CS, Maradit-Kremers H, Ballman KV, Roger VL, Jacobsen SJ, et al. Contribution of congestive heart failure and ischemic heart disease to excess mortality in rheumatoid arthritis. *Arthritis Rheum.* 2006;54:60-7.
60. Heeneman S, Daemen JAP. Cardiovascular risks in spondyloarthritides. *Curr Opin Rheumatol.* 2007;19:358-62.
61. Gonzalez-Gay MA, Gonzalez-Juanatey C, Miranda-Filloo JA, Garcia-Porrúa C, Llorca J, Martin J. Cardiovascular disease in rheumatoid arthritis. *Biomed Pharmacother.* 2006;60:673-7.
62. Levine B, Kalman J, Mayer L, Fillit HM, Packer M. Elevated circulating levels of tumor necrosis factor in severe chronic heart failure. *N Engl J Med.* 1990;323:236-41.
63. Mann DL, McMurray JJV, Packer M, Swedberg K, Borer JS, Colucci WS, et al. Targeted anticytokine therapy in patients with chronic heart failure. Results of the Randomized Etanercept Worldwide Evaluation (RENEWAL). *Circulation.* 2004;109:1594-602.
64. Chung ES, Packer M, Lo KH, Fasanmade AA, Willerson JT. Randomized, double-blind, placebo-controlled, pilot trial of infliximab, a chimeric monoclonal antibody to tumor necrosis factor-alpha, in patients with moderate-to-severe heart failure. Results of the Anti-TNF Therapy Against Congestive Heart Failure (ATTACH) Trial. *Circulation.* 2003;107:3133-40.
65. Kwon HJ, Cote TR, Cuffe MS, Kramer JM, Braun MM. Case reports of heart failure after therapy with a tumor necrosis factor antagonist. *Ann Intern Med.* 2003;138:807-11.
66. Mann DL. Inflammatory mediators and the failing heart: past, present, and the foreseeable future. *Circ Res.* 2002;91:988-98.
67. Weisman MH, Paulus HE, Burch FX, Kivitz AJ, Fierer J, Dunn M, et al. A placebo-controlled, randomized, double-blinded study evaluating the safety of etanercept in patients with rheumatoid arthritis and concomitant comorbid diseases. *Rheumatology (Oxford).* 2007;46:1122-5.
68. Jacobsson LT, Turesson C, Gülfe A, Kapetanovic MC, Petersson IF, Saxne T, et al. Treatment with tumor necrosis factor blockers is associated with a lower incidence of first cardiovascular events in patients with rheumatoid arthritis. *J Rheumatol.* 2005;32:1213-8.
69. Carmona L, Descalzo MA, Perez-Pampin E, Ruiz-Montesinos D, Erra A, Cobo T, et al. All-cause and cause-specific mortality in rheumatoid arthritis are not greater than expected when treated with tumor necrosis factor antagonists. *Ann Rheum Dis.* 2007;66:880-5.
70. Kremer JM. Analysis of risk factors and effect of treatment on the development of cardiovascular disease in patients with rheumatoid arthritis. *Ann Rheum Dis.* 2006;65 Suppl. II:307.
71. Hochberg MC, Johnston SS, John AK. The incidence and prevalence of extra-articular and systemic manifestations in a cohort of newly-diagnosed patients with rheumatoid arthritis between 1999 and 2006. *Curr Med Res Opin.* 2008;24:469-80.
72. Solomon DH, Avorn J, Katz JN, Weinblatt ME, Setoguchi S, Levin R, et al. Immunosuppressive medications and hospitalization for cardiovascular events in patients with rheumatoid arthritis. *Arthritis Rheum.* 2006;54:3790-8.
73. Naranjo A, Sokka T, Descalzo MA, Calvo-Alén J, Hørslev-Petersen K, Luukkainen RK, et al. Cardiovascular disease in patients with rheumatoid arthritis: results from the QUEST-RA study. *Arthritis Res Ther.* 2008;10:R30.
74. Dixon WG, Watson KD, Lunt M, Hyrich KL, Silman AJ, Symmons DP. Reduction in the incidence of myocardial infarction in patients with rheumatoid arthritis who respond to anti-tumor necrosis factor alpha therapy: results from the British Society for Rheumatology Biologics Register. *Arthritis Rheum.* 2007;56:2905-12.
75. Suissa S, Bernatsky S, Hudson M. Antirheumatic drug use and the risk of acute myocardial infarction. *Arthritis Rheum.* 2006;55:531-6.
76. Radovits BJ, Popa-Diaconu DA, Popa C, Eijsbouts A, Laan RF, van Riel PL, et al. Disease activity as a risk factor for myocardial infarction in rheumatoid arthritis. *Ann Rheum Dis.* 2009;68:1271-6.
77. Singh G. Combination TNF-inhibitor-methotrexate therapy is superior to methotrexate monotherapy in reducing the risk of acute myocardial infarction in patients with rheumatoid arthritis. *Arthritis Rheum.* 2007;56 Suppl.:S535.
78. Wolfe F, Michaud K. The risk of myocardial infarction and pharmacologic and nonpharmacologic myocardial infarction predictors in rheumatoid arthritis: a cohort and nested case-control analysis. *Arthritis Rheum.* 2008;58:2612-21.
79. Dixon WG, Watson KD, Lunt M, Hyrich KL, BSRBR Control Centre Consortium, Silman AJ, et al., on behalf of the BSR Biologics Register. Rates of myocardial infarction (MI) and cerebrovascular accident (CVA) in patients with rheumatoid arthritis (RA) treated with anti-TNF therapy: results from the British Society of Rheumatology Biologics Register (BSRBR). *Arthritis Rheum.* 2006;54 Suppl.:S311.
80. Listing J, Strangfeld A, Kekow J, Schneider M, Kapelle A, Wassenberg S, et al. Does tumor necrosis factor alpha inhibition promote or prevent heart failure in patients with rheumatoid arthritis? *Arthritis Rheum.* 2008;58:667-77.
81. Curtis JR, Kramer JM, Martin C, Saag KG, Patkar N, Shatin D, et al. Heart failure among younger rheumatoid arthritis and Crohn's patients exposed to TNF-alpha antagonists. *Rheumatology (Oxford).* 2007;46:1688-93.
82. Cole J, Busti A, Kazi S. The incidence of new onset congestive heart failure and heart failure exacerbation in Veteran's Affairs patients receiving tumor necrosis factor alpha antagonists. *Rheumatol Int.* 2007;27:369-73.
83. Wolfe F, Michaud K. Heart failure in rheumatoid arthritis: rates, predictors, and the effect of anti-tumor necrosis factor therapy. *Am J Med.* 2004;116:305-11.

84. Setoguchi S, Schneeweiss S, Avorn J, Katz JN, Weinblatt ME, Levin R, et al. Tumor necrosis factor-alpha antagonist use and heart failure in elderly patients with rheumatoid arthritis. *Am Heart J*. 2008;156:336-41.
85. Bernatsky S, Hudson M, Suissa S. Anti-rheumatic drug use and risk of hospitalization for congestive heart failure in rheumatoid arthritis. *Rheumatology*. 2005;44:677-80.
86. Cush JJ, Dao KH. Malignancy risks with biologic therapies. *Rheum Dis Clin N Am*. 2012;38:761-70.
87. Solomon DH, Mercer E, Kavanaugh A. Observational studies on the risk of cancer associated with tumor factor inhibitors in rheumatoid arthritis: a review of their methodologies and results. *Arthritis Rheum*. 2012;64:21-32 [review].
88. Wolfe F, Michaud K. Biologic treatment of rheumatic arthritis and the risk of malignancy: analyses from a large US observational study. *Arthritis Rheum*. 2007;56:2886-95.
89. 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;70:1895-904.
90. Amari W, Zeringue AL, McDonald JR, Caplan L, Eisen SA, Ranganathan P. Risk of non-melanoma skin cancer in a national cohort of veterans with rheumatoid arthritis. *Rheumatology (Oxford)*. 2011;50:1431.
91. Askling J, Fahrback K, Nordstrom B, Ross S, Schmid CH, Symmons D. Cancer risk with tumor necrosis factor alpha (TNF) inhibitors: meta-analysis of randomized controlled trials of adalimumab, etanercept, and infliximab using patient level data. *Pharmacoepidemiol Drug Saf*. 2011;20:119.
92. Carmona L, Abasolo L, Descalzo MA, Perez-Zafrilla B, Sellas A, De Abajo F, et al. Cancer in patients with rheumatic diseases exposed to TNF antagonists. *Semin Arthritis Rheum*. 2011;41:71-80.
93. Chakravarty EF, Michaud K, Wolfe F. Skin cancer, rheumatoid arthritis, and tumor necrosis factor inhibitors. *J Rheumatol*. 2005;32:2130-5.
94. Katoulis AC, Kanelleas A, Zambacos G, Panayiotides I, Stavrianeas NG. Development of two primary malignant melanomas after treatment with adalimumab: a case report and review of the possible link between biological therapy with TNF-alpha antagonists and melanocytic proliferation. *Dermatology*. 2010;221:9-12.
95. Kowalzik L, Eickenscheidt L, Komar M, Schaarschmidt E. Long term treatment of psoriasis with TNF-alpha antagonists Occurrence of malignant melanoma. *Hautarzt*. 2009;60:655-7.
96. Khan I, Rahman L, McKenna DB. Primary cutaneous melanoma: a complication of infliximab treatment. *Clin Exp Dermatol*. 2009;34:524-6.
97. Basavaraj KH, Ashok NM, Rashmi R, Praveen TK. The role of drugs in the induction and/or exacerbation of psoriasis. *Int J Dermatol*. 2010;49:1351-61.
98. Scheinberg M, Gonçalves DP, Laurindo IM. Anti-TNF agents inducing psoriasis: a recognized adverse effect. *J Clin Rheumatol*. 2008;14:130.
99. Lee HH, Song IH, Friedrich M, Gauliard A, Detert J, Rowert J, et al. Cutaneous side-effects in patients with rheumatic diseases during application of tumour necrosis factor-alpha antagonists. *Br J Dermatol*. 2007;156:486-91.
100. Harrison MJ, Dixon WG, Watson KD, King Y, Groves R, Hyrich KL, et al. Rates of new-onset psoriasis in patients with rheumatoid arthritis receiving anti-tumour necrosis factor alpha therapy: results from the British Society for Rheumatology Biologics Register. *Ann Rheum Dis*. 2009;68:209-15.
101. Ko JM, Gottlieb AB, Kerbleski JF. Induction and exacerbation of psoriasis with TNF-blockade therapy: a review and analysis of 127 cases. *J Dermatol Treat*. 2009;20:100-8.
102. De Gannes GC, Ghoreishi M, Pope J, Russell A, Bell D, Adams S, et al. Psoriasis and pustular dermatitis triggered by TNF- α inhibitors in patients with rheumatologic conditions. *Arch Dermatol*. 2007;143:223-31.
103. Michaelsson G, Kajermo U, Michaelsson A, Hagforsen E. Infliximab can precipitate as well as worsen palmo plantar pustulosis: possible linkage to the expression of tumour necrosis factor-alpha in the normal palmar eccrine sweat duct. *Br J Dermatol*. 2005;153:1243-4.
104. Collamer AN, Battafarano DF. Psoriatic skin lesions induced by tumor necrosis factor antagonist therapy: clinical features and possible immunopathogenesis. *Semin Arthritis Rheum*. 2010;40:233-40.
105. Isomaki HA, Hakulinen T, Joutsenlahti U. Excess risk of lymphomas, leukemia and myeloma in patients with rheumatoid arthritis. *J Chronic Dis*. 1978;31:691-6.
106. 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;62:1252-8.
107. Mercer LK, Davies R, Galloway JB, Low A, Lunt M, Dixon WG, et al. Risk of cancer in patients receiving non-biologic disease-modifying therapy for rheumatoid arthritis compared with the UK general population. *Rheumatology (Oxford)*. 2013;52:91-8.
108. Baecklund E, Ekblom A, Sparén P, Feltelius N, Klareskog L. Disease activity and risk of lymphoma in patients with rheumatoid arthritis: nested case-control study. *BMJ*. 1998;18:180-1.
109. Baecklund E, Iliadou A, Askling J, Ekblom A, Backlin C, Granath F, et al. Association of chronic inflammation, not its treatment, with increased lymphoma risk in rheumatoid arthritis. *Arthritis Rheum*. 2006;54:692-701.
110. Lopez-Olivo MA, Tayar JH, Martinez-Lopez JA, Pollono EN, Cueto JP, Gonzales-Crespo MR, et al. Risk of malignancies in patients with rheumatoid arthritis treated with biologic therapy: a meta-analysis. *JAMA*. 2012;308:898-908.
111. Brown SL, Greene MH, Gershon SK, Edwards ET, Braun MM. Tumor necrosis factor antagonist therapy and lymphoma development: twenty-six cases reported to the Food and Drug Administration. *Arthritis Rheum*. 2002;46:3151-8.
112. Askling J, van Vollenhoven RF, Granath F, Raaschou P, Forede 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;60:3180-9.
113. Pallavicini FB, Caporali R, Sarzi-Puttini P, Atzeni F, Bazzani C, Gorla R, et al. Tumour necrosis factor antagonist therapy and cancer development: analysis of the LORHEN registry. *Autoimmun Rev*. 2010;9:175-80.
114. Mariette X, Tubach F, Bagheri H, Bardet M, Berthelot JM, Gaudin P, et al. Lymphoma in patients treated with anti-TNF: results of the 3-year prospective French RATIO registry. *Ann Rheum Dis*. 2010;69:400-8.
115. Wolfe F, Michaud K. Lymphoma in rheumatoid arthritis: the effect of methotrexate and anti-tumor necrosis factor therapy in 18,572 patients. *Arthritis Rheum*. 2004;50:1740-51.
116. Greenberg J, Strand V, Keystone E, Curtis J, Maury E, Reed G, et al. TNF inhibitors (TNF-I) and risk of malignancy in 8,072 RA patients followed over 15,495 patient years. In: American College of Rheumatology Annual Meeting. 2007 [abstract 282].

117. 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;68:648-53.
118. Lovell DJ, Giannini EH, Reiff A, Cawkwell GD, Silverman ED, Nocton JJ, et al., Pediatric Rheumatology Collaborative Study Group. Etanercept in children with polyarticular juvenile rheumatoid arthritis. *N Engl J Med*. 2000;342:763-9.
119. Aikawa NE, de Carvalho JF, Silva CAA, Bonfá E. Immunogenicity of anti-TNF-alpha agents in autoimmune diseases. *Clin Rev Allergy Immunol*. 2010;38:82-9.
120. Flendrie M, Vissers WH, Creemers MC, De Jong EM, Van de Kerkhof PC, Van Riel PL. Dermatological conditions during TNF-alpha-blocking therapy in patients with rheumatoid arthritis: a prospective study. *Arthritis Res Ther*. 2005;7:R666-76.
121. Wetter DA, Davis MD. Lupus-like syndrome attributable to anti-tumor necrosis factor alpha therapy in 14 patients during an 8-year period at Mayo Clinic. *Mayo Clin Proc*. 2009;84:979-84.
122. Stratigos AJ, Antoniou C, Stamatouli S, Avgerinou G, Tsega A, Katsambas AD. Discoid lupus erythematosus-like eruption induced by infliximab. *Clin Exp Dermatol*. 2004;29:150-3.
123. Costa MF, Said NR, Zimmermann B. Drug-induced lupus due to anti-tumor necrosis factor alpha agents. *Semin Arthritis Rheum*. 2008;37:381-7.
124. Vezzoli P, Violetti SA, Serini SM, Muratori S, Berti E, Crosti C. Cutaneous lupus erythematosus induced by adalimumab. *J Dermatol*. 2011;38:283-4.
125. Etefagh L, Nedorost S, Mirmirani P. Alopecia areata in a patient using infliximab: new insights into the role of tumor necrosis factor on human hair follicles. *Arch Dermatol*. 2004;140:1012.
126. Posten W, Swan J. Recurrence of alopecia areata in a patient receiving etanercept injections. *Arch Dermatol*. 2005;141:759-60.
127. Garcia Bartels N, Lee HH, Worm M, Burmester GR, Sterry W, Blume-Peytavi U. Development of alopecia areata universalis in a patient receiving adalimumab. *Arch Dermatol*. 2006;142:1654-5.
128. Hernandez MV, Nogue S, Ruiz-Esqueda V, Alsina M, Canete JD, Sanmarti R. Development of alopecia areata after biological therapy with TNF-alpha blockers: description of a case and review of the literature. *Clin Exp Rheumatol*. 2009;27:892-3.
129. Pelivani N, Hassan AS, Braathen LR, Hunger RE, Yawalkar N. Alopecia areata universalis elicited during treatment with adalimumab. *Dermatology*. 2008;216:320-3.
130. Chaves Y, Duarte G, Ben-Said B, Tebib J, Berard F, Nicolas JF. Alopecia areata universalis during treatment of rheumatoid arthritis with anti-TNF-alpha antibody (adalimumab). *Dermatology*. 2008;217:380.
131. Fabre C, Dereure O. Worsening alopecia areata and de novo occurrence of multiple halo nevi in a patient receiving infliximab. *Dermatology*. 2008;216:185-6.
132. Ferran M, Calvet J, Almirall M, Pujol RM, Maymo J. Alopecia areata as another immune-mediated disease developed in patients treated with tumour necrosis factor-alpha blocker agents: report of five cases and review of the literature. *J Eur Acad Dermatol Venereol*. 2011;25:479-84.
133. Tosti A, Pazzaglia M, Starace M, Bellavista S, Vincenzi C, Tonelli G. Alopecia areata during treatment with biologic agents. *Arch Dermatol*. 2006;142:1653-4.
134. Ramos-Casals M, Brito-Zeron P, Munoz S, Soria N, Galiana D, Bertolaccini L, et al. Autoimmune diseases induced by TNF-targeted therapies: analysis of 233 cases. *Medicine (Baltimore)*. 2007;86:242-51.
135. Exarchou SA, Voulgari PV, Markatseli TE, Zioga A, Drosos AA. Immune-mediated skin lesions in patients treated with anti-tumour necrosis factor alpha inhibitors. *Scand J Rheumatol*. 2009;38:328-31.
136. Pontikaki I, Shahi E, Frasin LA, Gianotti R, Gelmetti C, Gerloni V, et al. Skin manifestations induced by TNF-alpha inhibitors in juvenile idiopathic arthritis. *Clin Rev Allergy Immunol*. 2012;42:131-4.
137. Mohan N, Edwards ET, Cupps TR, Slifman N, Lee JH, Siegel JN, et al. Leukocytoclastic vasculitis associated with tumor necrosis factor-alpha blocking agents. *J Rheumatol*. 2004;31:1955-8.
138. Fujikawa K, Kawakami A, Hayashi T, Iwamoto N, Kawashiri SY, Aramaki T, et al. Cutaneous vasculitis induced by TNF inhibitors: a report of three cases. *Mod Rheumatol*. 2010;20:86-9.
139. Ramirez-Hernandez M, Marras C, Martinez-Escribano JA. Infliximab-induced vitiligo. *Dermatology*. 2005;210:79-80.
140. Lahita RG, Vernace MA. Vasculitis, vitiligo, thyroiditis, and altered hormone levels after anti-tumor necrosis factor therapy. *J Rheumatol*. 2011;38:579-80.
141. Hernandez MV, Ruiz-Esqueda V, Gomez-Caballero ME, Gomez-Puerta JA, Canete JD, Sanmarti R. Relapsing polychondritis: a new adverse event secondary to the use of tumour necrosis factor antagonists. *Rheumatology (Oxford)*. 2011;50:1523-5.
142. Hall HA, Zimmermann B. Evolution of dermatomyositis during therapy with a tumor necrosis factor alpha inhibitor. *Arthritis Rheum*. 2006;55:982-4.
143. Ishikawa Y, Yukawa N, Ohmura K, Hosono Y, Imura Y, Kawabata D, et al. Etanercept-induced anti-Jo-1-antibody-positive polymyositis in a patient with rheumatoid arthritis: a case report and review of the literature. *Clin Rheumatol*. 2010;29:563-6.
144. Ramirez J, Hernandez MV, Galve J, Canete JD, Sanmarti R. Morphea associated with the use of adalimumab: a case report and review of the literature. *Mod Rheumatol*. 2011 [Epub ahead of print].
145. Ranganathan P. Infliximab-induced scleredema in a patient with rheumatoid arthritis. *J Clin Rheumatol*. 2005;11:319-22.
146. Mattozzi C, Richetta AG, Cantisani C, Giancristoforo S, D'Epiro S, Gonzalez Serva A, et al. Morphea, an unusual side effect of anti-TNF-alpha treatment. *Eur J Dermatol*. 2010;20:400-1.
147. Voulgari PV, Markatseli TE, Exarchou SA, Zioga A, Drosos AA. Granuloma annulare induced by anti-tumour necrosis factor therapy. *Ann Rheum Dis*. 2008;67:567-70.
148. Bonnet N, Guis S, Koeppel MC, Roudier J, Grimaud JC, Jean-Pastor MJ, et al. Cutaneous events during anti-TNF alpha therapy: a prospective observational study of 41 cases. *Ann Dermatol Venereol*. 2010;137:12-20.
149. Boussemart L, Jacobelli S, Batteux F, Goulvestre C, Grange P, Carlotti A, et al. Autoimmune bullous skin diseases occurring under anti-tumor necrosis factor therapy: two case reports. *Dermatology*. 2010;221:201-5.
150. Kluk J, Goulding JM, Bhat J, Finch TM. Drug-induced bullous pemphigoid: cases triggered by intravenous iodine and etanercept. *Clin Exp Dermatol*. 2011;36:871-3.
151. Bordignon M, Belloni-Fortina A, Pigozzi B, Tarantello M, Alaibac M. Bullous pemphigoid during long-term TNF-alpha blocker therapy. *Dermatology*. 2009;219:357-8.
152. Fomin I, Caspi D, Levy V, Varsano N, Shalev Y, Paran D, et al. Vaccination against influenza in rheumatoid arthritis: the

- effect of disease modifying drugs, including TNF alpha blockers. *Ann Rheum Dis.* 2006;65:191-4.
153. Kaine JL, Kivitz AJ, Birbara C, Luo AY. Immune responses following administration of influenza and pneumococcal vaccines to patients with rheumatoid arthritis receiving adalimumab. *J Rheumatol.* 2007;34:272-9.
 154. Kubota T, Nii T, Nanki T, Kohsaka H, Harigai M, Komano Y, et al. Anti-tumor necrosis factor therapy does not diminish the immune response to influenza vaccine in Japanese patients with rheumatoid arthritis. *Mod Rheumatol.* 2007;17:531-3.
 155. Kapetanovic MC, Saxne T, Nilsson JA, Geborek P. Influenza vaccination as model for testing immune modulation induced by anti-TNF and methotrexate therapy in rheumatoid arthritis patients. *Rheumatology (Oxford).* 2007;46:608-11.
 156. Ribeiro AC, Guedes LK, Moraes JC, Saad CG, Aikawa NE, Calich AL, et al. Reduced seroprotection after pandemic H1N1 influenza adjuvant-free vaccination in patients with rheumatoid arthritis: implications for clinical practice. *Ann Rheum Dis.* 2014;70:2144-7.
 157. Garrido Lopez BC, Navarro Compain MV, Navarro Sarabia F. Vaccines and chemo-prophylaxis in rheumatoid arthritis: is a vaccine calendar necessary? *Reumatol Clin.* 2011;7:412-6.
 158. Brenol CV, da Mota LM, Cruz BA, Pileggi GS, Pereira IA, Rezende LS, et al. 2012 Brazilian Society of Rheumatology Consensus on vaccination of patients with rheumatoid arthritis. *Rev Bras Reumatol.* 2013;53:4-23.
 159. Kremer JM. Selective costimulation modulators: a novel approach for the treatment of rheumatoid arthritis. *J Clin Rheumatol.* 2005;11:S55-62.
 160. Maxwell LJ, Singh JA. Abatacept for rheumatoid arthritis: a Cochrane systematic review. *J Rheumatol.* 2010;37:234-45.
 161. Pham T, Bachelez H, Berthelot JM, Blacher J, Claudepierre P, Constantin A, et al. Abatacept therapy and safety management. *Joint Bone Spine.* 2012;79 Suppl. 1:3-84.
 162. Weinblatt ME, Moreland LW, Westhovens R, Cohen RB, Kelly SM, Khan N, et al. Safety of abatacept administered intravenously in treatment of rheumatoid arthritis: integrated analyses of up to 8 years of treatment from the abatacept clinical trial program. *J Rheumatol.* 2013 [Epub ahead of print].
 163. Kremer JM, Genant HK, Moreland LW, Russell AS, Emery P, Abud-Mendoza C, et al. Results of a two-year followup study of patients with rheumatoid arthritis who received a combination of abatacept and methotrexate. *Arthritis Rheum.* 2008;58:953-63.
 164. Weinblatt M, Combe B, Covucci A, Aranda R, Becker JC, Keystone E. Safety of the selective costimulation modulator abatacept in rheumatoid arthritis patients receiving background biologic and nonbiologic disease-modifying antirheumatic drugs: a one-year randomized, placebo-controlled study. *Arthritis Rheum.* 2006;54:2807-16.
 165. von Kempis J, Dudler J, Hasler P, Kyburz D, Tyndall A, Zufferey P, et al. Use of abatacept in rheumatoid arthritis. *Swiss Med Wkly.* 2012;142:w13581.
 166. Bigbee CL, Gonchoroff DG, Vratsanos G, Nadler SG, Haggerty HG, Flynn JL. Abatacept treatment does not exacerbate chronic *Mycobacterium tuberculosis* infection in mice. *Arthritis Rheum.* 2007;56:2557-65.
 167. Kremer JM, Genant HK, Moreland LW, Russell AS, Emery P, Abud-Mendoza C, et al. Effects of abatacept in patients with methotrexate-resistant active rheumatoid arthritis: a randomized trial. *Ann Intern Med.* 2006;144:865-76.
 168. Simon TA, Smitten AL, Franklin J, Lacaille D, Wolfe F, et al. Malignancies in the rheumatoid arthritis abatacept clinical development programme: an epidemiological assessment. *Ann Rheum Dis.* 2009;68:1819-26.
 169. Sibilila T, Westhovens R. Safety of T-cell co-stimulation modulation with abatacept in patients with rheumatoid arthritis. *Clin Exp Rheumatol.* 2007;25 Suppl. 46:546-56.
 170. Smitten AL, Qi K, Simon TA, Becken JC. Autoimmune adverse events in the abatacept RA clinical development program: a safety analysis with >10000 person - years of exposure. *Arthritis Rheum.* 2008;58 Suppl.:5786 [abstract 1673].
 171. Schiff M, Saewert M, Bahrt K, Genovese MC. Response to influenza vaccine in rheumatoid arthritis patients with an inadequate response to anti-TNF therapy treated with abatacept in the ARRIVE trial. Poster FRI 943/175. In: American College of Rheumatology Congress. 2007.
 172. Ribeiro A, Guedes L, Moraes J, Saad C, Calich A, Aikawa N, et al. Abatacept in association with traditional DMARDs severely impairs humoral response to pandemic A H1N1 influenza vaccination in rheumatoid arthritis patients. *Ann Rheum Dis.* 2011;70 Suppl. 3:458 [abstract FRI0342].
 173. Schiff M, Kaell A, Tay L, Vratsanos G, Bahrt K. Response to pneumococcal vaccine in rheumatoid arthritis patients with an inadequate response to anti-TNF therapy treated with abatacept in the ARRIVE trial. In: Poster SAT0029, EULAR. 2007.
 174. Cohen SB, Emery P, Greenwald MW, Dougados M, Furie RA, Genovese MC, et al. Rituximab for rheumatoid arthritis refractory to anti-tumor necrosis factor therapy: results of a multicenter, randomized, double-blind, placebo-controlled, phase III trial evaluating primary efficacy and safety at twenty-four weeks. *Arthritis Rheum.* 2006;54:2793-806.
 175. Chatzidionysiou K, Lie E, Nasonov E, Lukina G, Hetland ML, Tarp U, et al. Highest clinical effectiveness of rituximab in autoantibody-positive patients with rheumatoid arthritis and in those for whom no more than one previous TNF antagonist has failed: pooled data from 10 European registries. *Ann Rheum Dis.* 2011;70:1575-80.
 176. Keystone EC, Cohen SB, Emery P, Kremer JM, Dougados M, Lovelless JE, et al. Multiple courses of rituximab produce sustained clinical and radiographic efficacy and safety in patients with rheumatoid arthritis and an inadequate response to 1 or more tumor necrosis factor inhibitors: 5-year data from the reflex study. *J Rheumatol.* 2012.
 177. Lee YH, Bae SC, Song GG. The efficacy and safety of rituximab for the treatment of active rheumatoid arthritis: a systematic review and meta-analysis of randomized controlled trials. *Rheumatol Int.* 2011;31:1493-9.
 178. van Vollenhoven RF, Emery P, Bingham CO 3rd, Keystone EC, Fleischmann RM, Furst DE, et al. Long-term safety of rituximab in rheumatoid arthritis: 9.5-year follow-up of the global clinical trial programme with a focus on adverse events of interest in RA patients. *Ann Rheum Dis.* 2012.
 179. Buch MH, Smolen JS, Betteridge N, Breedveld FC, Burmester G, Dorner T, et al. Updated consensus statement on the use of rituximab in patients with rheumatoid arthritis. *Ann Rheum Dis.* 2011;70:909-20.
 180. Salliot C, Dougados M, Gossec L. Risk of serious infections during rituximab, abatacept and anakinra treatments for rheumatoid arthritis: meta-analyses of randomised placebo-controlled trials. *Ann Rheum Dis.* 2009;68:25-32.
 181. Ruderman EM. Overview of safety of non-biologic and biologic DMARDs. *Rheumatology (Oxford).* 2012;51 Suppl. 6:vi37-43.
 182. Pei SN, Chen CH, Lee CM, Wang MC, Ma MC, Hu TH, et al. Reactivation of hepatitis B virus following rituximab-based regimens: a serious complication in both HBsAg-positive and HBsAg-negative patients. *Ann Hematol.* 2010;89: 255-62.
 183. Koo YX, Tan DS, Tan BH, Quek R, Tao M, Lim ST. Risk of hepatitis B virus reactivation in patients who are hepatitis B surface antigen negative/antibody to hepatitis B core

- antigen positive and the role of routine antiviral prophylaxis. *J Clin Oncol.* 2009;20:2570-1.
184. Liaw YF, Leung N, Kao JH, Piratvisuth T, Gane E, Han KH, et al. Chronic hepatitis B guideline working party of the Asian-Pacific association for the study of the liver. Asian-Pacific consensus statement on the management of chronic hepatitis B: a 2008 update. *Hepatol Int.* 2008;2:263-83.
 185. Lok AS, McMahon BJ. Chronic hepatitis B. *Hepatology.* 2007;45:507-39.
 186. Weinbaum CM, Mast EE, Ward JW. Recommendations for identification and public health management of persons with chronic hepatitis b virus infection. *Hepatology.* 2009;49 Suppl. 5:S35-44.
 187. Ferri C, Govoni M, Calabrese L. The A, B, Cs of viral hepatitis in the biologic era. *Curr Opin Rheumatol.* 2010;22:443-50.
 188. Yazdany J, Calabrese L. Preventing hepatitis B reactivation in immunosuppressed patients: is it time to revisit the guidelines? *Arthritis Care Res (Hoboken).* 2010;62:585-9.
 189. Artz AS, Somerfield MR, Feld JJ, Giusti AF, Kramer BS, Sabichi AL, et al. American Society of Clinical Oncology provisional clinical opinion: chronic hepatitis B virus infection screening in patients receiving cytotoxic chemotherapy for treatment of malignant diseases. *J Clin Oncol.* 2010;28:3199-202.
 190. Emery P, Deodhar A, Rigby WF, Isaacs JD, Combe B, Racewicz AJ, et al. Efficacy and safety of different doses and retreatment of rituximab: a randomised, placebo-controlled trial in patients who are biological naive with active rheumatoid arthritis and an inadequate response to methotrexate (Study Evaluating Rituximab's Efficacy in MTX iNadequate rEsponders (SERENE)). *Ann Rheum Dis.* 2010;69:1629-35.
 191. van Vollenhoven RF, Emery P, Bingham CO 3rd, Keystone EC, Fleischmann R, Furst DE, et al. Longterm safety of patients receiving rituximab in rheumatoid arthritis clinical trials. *J Rheumatol.* 2010;37:558-67.
 192. Dass S, Vital EM, Emery P. Development of psoriasis after B cell depletion with rituximab. *Arthritis Rheum.* 2007;56:2715-8.
 193. Hadjinicolaou AV, Nisar MK, Parfrey H, Chilvers ER, Ostör AJ. Non-infectious pulmonary toxicity of rituximab: a systematic review. *Rheumatology (Oxford).* 2012;51:653-62.
 194. Gottenberg JE, Guillevin L, Lambotte O, Combe B, Allanore Y, Cantagrel A, et al. Tolerance and short term efficacy of rituximab in 43 patients with systemic autoimmune diseases. *Ann Rheum Dis.* 2005;64:913-20.
 195. Todd DJ, Helfgott SM. Serum sickness following treatment with rituximab. *J Rheumatol.* 2007;34:430-3.
 196. van Assen S, Agmon-Levin N, Elkayam O, Gervera R, Doran MF, Dougados M, et al. EULAR recommendations for vaccination in adult patients with autoimmune inflammatory rheumatic diseases. *Ann Rheum Dis.* 2011;70:414-22.
 197. Bingham CO 3rd, Looney RJ, Deodhar A, Halsey N, Greenwald M, Coddling C, et al. Immunization responses in rheumatoid arthritis patients treated with rituximab: results from a controlled clinical trial. *Arthritis Rheum.* 2010;62: 64-74.
 198. Keyser FD. Choice of biological therapy for patients with rheumatoid arthritis: the infection perspective. *Curr Rheumatol Rev.* 2011;7:77-87.
 199. Lang VR, Englbrecht M, Rech J, Nüsslein H, Manger K, Schuch F, et al. Risk of infections in rheumatoid arthritis patients treated with tocilizumab. *Rheumatology (Oxford).* 2012;51:852-7.
 200. Singh JA, Beg S, Lopez-Olivo MA. Tocilizumab for rheumatoid arthritis: a Cochrane systematic review. *J Rheumatol.* 2011;38:10-20.
 201. Nishimoto N, Ito K, Takagi N. Safety and efficacy profiles of tocilizumab monotherapy in Japanese patients with RA: meta-analysis of six initial trials and five long-term extensions. *Mod Rheumatol.* 2010;20:222-32.
 202. Ogata A, Hirano T, Hishitani Y, Tanaka T. Safety and efficacy of tocilizumab for the treatment of rheumatoid arthritis. *Clin Med Insights Arthritis Musculoskelet Disord.* 2012;5:27-42.
 203. Schiff MH, van Vollenhoven RF, Jahreis A, Vernon E, Isaacs JD, van Vollenhoven RF. Integrated safety in tocilizumab randomized clinical trials. *Arthritis Res Ther.* 2011;13: R141.
 204. Campbell L, Chen C, Bhagat SS, Parker RA, Östör AJ. Risk of adverse events including serious infections in rheumatoid arthritis patients treated with tocilizumab: a systematic literature review and meta-analysis of randomized controlled trials. *Rheumatology (Oxford).* 2011;50: 552-62.
 205. Mori S, Tokuda H, Sakai F, Johkoh T, Mimori A, Nishimoto N, et al. Radiological features and therapeutic responses of pulmonary nontuberculosis mycobacterial disease in rheumatoid arthritis patients receiving biological agents: a retrospective multicenter study in Japan. *Mod Rheumatol.* 2012;22:727-37.
 206. Hirao M, Hashimoto J, Tsuboi H, Nampei A, Nakahara H, Yoshio N, et al. Laboratory and febrile features after joint surgery in patients with RA treated with tocilizumab. *Ann Rheum Dis.* 2009;68:654-7.
 207. Momohara S, Hashimoto J, Tsuboi H, Miyahara H, Nakagawa N, Kaneko A, et al. Analysis of perioperative clinical features and complications after orthopaedic surgery in rheumatoid arthritis patients treated with tocilizumab in a real-world setting: results from the multicentre TOcilizumab in Perioperative Period (TOPP) study. *Mod Rheumatol.* 2012 [Epub ahead of print].
 208. Koike T, Harigai M, Inokuma S, Ishiguro N, Ryu J, Takeuchi T, et al. Postmarketing surveillance of tocilizumab for rheumatoid arthritis in Japan: interim analysis of 3881 patients. *Ann Rheum Dis.* 2011;70:2148-51.
 209. Nagamine R, Chen W, Hara T, Kondo K, Sugioka Y. Immediate reduction of white blood cell count after tocilizumab administration was observed in some cases. *Mod Rheumatol.* 2009;19:348-50.
 210. Nakamura I, Omata Y, Naito M, Ito K. Blockade of interleukin 6 signaling induces marked neutropenia in patients with rheumatoid arthritis. *J Rheumatol.* 2009;36:459-60.
 211. Sugiura F, Kojima T, Oguchi T, Urata S, Yuzawa Y, Sakakibara A, et al. A case of peripheral neuropathy and skin ulcer in a patient with rheumatoid arthritis after a single infusion of tocilizumab. *Mod Rheumatol.* 2009;19:199-203.
 212. Jones G, Sebba A, Gu J, Lowenstein MB, Calvo A, Gomez-Reino JJ, et al. Comparison of tocilizumab monotherapy versus methotrexate monotherapy in patients with moderate to severe rheumatoid arthritis: the AMBITION study. *Ann Rheum Dis.* 2010;69: 88-96.
 213. Mariette X, Gottenberg JE, Ravaud P, Combe B. Registries in rheumatoid arthritis and autoimmune diseases: data from the French registries. *Rheumatology (Oxford).* 2011;50:222-9.
 214. Stubenrauch K, Wessels U, Vogel R, Schleypen J. Evaluation of a biosensor immunoassay for simultaneous characterization of isotype and binding region of human anti-tocilizumab antibodies with control by surrogate standards. *Anal Biochem.* 2009;390:189-96.
 215. van de Sande MG, van Slobbe-Bijlsma ER. Necrotizing fasciitis in a rheumatoid arthritis patient treated with tocilizumab. *Rheumatology (Oxford).* 2012;51: 577-8.

216. Samimi M, Lauferon F, Hüttenberger B, Vaillant L, Goupille P, Machet L. *Ann Dermatol Venereol*. 2013;140:120-4.
217. Tada A, Hashida N, Tanaka T, Nishida K. Anti-interleukin-6 receptor antibody therapy-induced retinopathy in a patient with rheumatoid arthritis. *Case Rep Rheumatol*. 2012;2012:270315.
218. Ikegawa K, Hanaoka M, Ushiki A, Yamamoto H, Kubo K. A case of organizing pneumonia induced by tocilizumab. *Intern Med*. 2011;50:2191-3.
219. Kawashiri SY, Kawakami A, Sakamoto N, Ishimatsu Y, Eguchi K. A fatal case of acute exacerbation of interstitial lung disease in a patient with rheumatoid arthritis during treatment with tocilizumab. *Rheumatol Int*. 2012;32:4023-6.
220. Wendling D, Letho-Gyselinck H, Guillot X, Prati C. Psoriasis onset with tocilizumab treatment for rheumatoid arthritis. *J Rheumatol*. 2012;39:657.
221. Wendling D, Dernis E, Prati C, Frisch E, Delbosc B. Onset of inflammatory eye disease under tocilizumab treatment for rheumatologic conditions: a paradoxical effect? *J Rheumatol*. 2011;38:2284.
222. Laurent S, Le Parc JM, Clérici T, Bréban M, Mahé E. Onset of psoriasis following treatment with tocilizumab. *Br J Dermatol*. 2010;163:1364-5.
223. Mori S, Ueki Y, Hirakata N, Oribe M, Hidaka T, Oishi K. Impact of tocilizumab therapy on antibody response to influenza vaccine in patients with rheumatoid arthritis. *Ann Rheum Dis*. 2012;71:2006-10.
224. Shinoki T, Hara R, Kaneko U, Miyamae T, Imagawa T, Mori M, et al. Safety and response to influenza vaccine in patients with systemic-onset juvenile idiopathic arthritis receiving tocilizumab. *Mod Rheumatol*. 2012;22:871-6.
225. da Mota LM, Cruz BA, Brenol CV, Pereira IA, Fronza LS, Bertolo MB, et al. Consensus of the Brazilian Society of Rheumatology for diagnosis and early assessment of rheumatoid arthritis. *Rev Bras Reumatol*. 2011;51:199-219.
226. Clowse MEB. The use of anti-TNF medications for rheumatologic disease in pregnancy. *Int J Womens Health*. 2010;2:199-209.
227. US Food and Drug Administration. United States FDA pharmaceutical pregnancy categories. *Fed Reg*. 1980;44:37434-67. Ref: US Food and Drug Administration <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/Labeling/ucm093307.htm> [accessed 20.10.12].
228. Kane SV, Acquah LA. Placental transport of immunoglobulins: a clinical review for gastroenterologists who prescribe therapeutic monoclonal antibodies to women during conception and pregnancy. *Am J Gastroenterol*. 2009;104:228-33.
229. Østensen M, Lockshin M, Doria A, Valesini G, Meroni P, Gordon C, et al. Update on safety during pregnancy of biological agents and some immunosuppressive anti-rheumatic drugs. *Rheumatology (Oxford)*. 2008;47 Suppl. 3:iii28-31.
230. Bogas M, Leandro MJ. Biologic therapy and pregnancy. A systematic literature review. *Acta Reumatol Port*. 2011;36:219-32.
231. Nørgaard M, Larsson H, Pedersen L, Granath F, Askling J, Kieler H, et al. Rheumatoid arthritis and birth outcomes: a Danish and Swedish nationwide prevalence study. *J Intern Med*. 2010;268:329-37.
232. European Surveillance of Congenital Anomalies Home Page. <http://www.eurocat-network.eu> [accessed 20.10.12].
233. Barnes JC, Smith WL, The VATER Association. *Radiology*. 1978;126:445-9.
234. Goldenberg RL, Culhane JF, Iams JD, Romero R. Epidemiology and causes of preterm birth. *Lancet*. 2008;371:75-84.
235. Chakravarty EF, Murray ER, Kelman A, Farmer P. Pregnancy outcomes after maternal exposure to rituximab. *Blood*. 2011;117:1499-506.
236. Habal FM, Huang VW. Review article: a decision-making algorithm for the management of pregnancy in the inflammatory bowel disease patient. *Aliment Pharmacol Ther*. 2012;35:501-15.
237. Mota LM, Cruz BA, Brenola CV, Pereira IA, Rezende-Fronza LS, Bertolo MB, et al. Diretriz de artrite reumatoide - Diagnóstico. *Rev Bras Reumatol*. 2013;53:141-57.
238. Mota LM, Cruz BA, Brenol CV, Pereira IA, Rezende-Fronza LS, Bertolo MB, et al. Diretriz de artrite reumatoide - Tratamento medicamentoso. *Rev Bras Reumatol*. 2013;53:158-83.
239. Pereira IA, Mota LM, Cruz BA, Brenol CV, Fronza LS, Bertolo MB, et al. 2012 Brazilian Society of Rheumatology Consensus on the management of comorbidities in patients with rheumatoid arthritis. *Rev Bras Reumatol*. 2012;52:474-95.