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#### REFERÊNCIA

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## Original article

# Update on the 2012 Brazilian Society of Rheumatology Guidelines for the treatment of rheumatoid arthritis: position on the use of tofacitinib



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## ABSTRACT

In 2014, tofacitinib, a target-specific, synthetic disease modifying anti rheumatic drug (DMARD) and a selective inhibitor of Janus kinase (JAK) was approved for use in Brazil. This position paper aims to update the recommendations of the Brazilian Society of Rheumatology (SBR) on the treatment of rheumatoid arthritis (RA) in Brazil, specifically regarding the use of target-specific synthetic DMARDs. The method of this recommendation consisted of a literature review of scientific papers held on the Medline database. After this review, a text was produced, answering questions in Pico structure, considering efficacy and safety issues of tofacitinib use for RA treatment in different scenarios (such as first-line treatment after failure with methotrexate [MTX] or other conventional synthetic DMARDs after failure with biological therapy). Based on existing evidence, and considering the available data on efficacy, safety and cost of medications available to treat the disease in Brazil, the RA Commission of SBR, after a process of discussion and voting on proposals, established the following position on the use of tofacitinib for treatment of RA in Brazil: "Tofacitinib, alone or in combination with MTX, is an alternative for RA patients with moderate or high activity after failure of at least two different synthetic DMARDs and one biological DMARD." The level of agreement with this recommendation was 7.5.

This position may be reviewed in the coming years, in the face of a greater experience with the use of this medication.

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### Posicionamento sobre o uso de tofacitinibe no algoritmo do Consenso 2012 da Sociedade Brasileira de Reumatologia para o tratamento da artrite reumatoide

## RESUMO

Em 2014, o tofacitinibe, um medicamento modificador do curso da doença (MMCD) sintético, alvo-específico, inibidor seletivo das Janus quinases (JAK), foi aprovado para uso no Brasil. Este documento de posicionamento tem o objetivo de atualizar as recomendações da Sociedade Brasileira de Reumatologia (SBR) sobre o tratamento da artrite reumatoide (AR) no Brasil, especificamente com relação ao uso de MMCD sintéticos alvo-específicos. O método dessa recomendação incluiu revisão bibliográfica de artigos científicos, feita na base de dados Medline. Após a revisão, foi produzido um texto, que responde a perguntas na estrutura Pico, e considera questões de eficácia e segurança do uso do tofacitinibe para tratamento de AR em diferentes situações (como primeira linha de tratamento, após falha ao metotrexato [MTX] ou outros MMCD sintéticos convencionais, após falha da terapia biológica). Com base nas evidências existentes, e considerando os dados disponíveis sobre eficácia, segurança e custo das medicações disponíveis para tratamento da doença no Brasil, a Comissão de AR da SBR, após processo de discussão e votação de propostas, estabeleceu o seguinte posicionamento sobre o uso de tofacitinibe para o tratamento da AR no Brasil: "Tofacitinibe, em monoterapia ou em associação ao MTX, é uma opção para os pacientes com AR em atividade moderada ou alta, após falha de pelo menos dois esquemas com diferentes MMCD sintéticos e um esquema de MMCD biológico". O grau de concordância com essa recomendação foi 7,5. Esse posicionamento poderá ser revisto nos próximos anos, com a maior experiência adquirida com o uso do medicamento.

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## Palavras-chave:

Artrite reumatoide

Tratamento

Brasil

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## Introduction

Rheumatoid arthritis (RA) is a systemic, autoimmune inflammatory disease characterized by involvement of the synovial membrane of peripheral joints. It is estimated that the prevalence of RA is 0.5–1% of the population, mainly in women and in people aged from 30 to 50 years.<sup>1</sup>

The treatment of RA has progressed substantially in recent decades, due to a major breakthrough in understanding the pathophysiological mechanisms of the disease, development of new therapeutic classes and implementation of different strategies of treatment and follow-up of patients, for instance, intensive disease control and intervention in the early phase of symptoms.<sup>1</sup>

In 2012 and 2013, the RA Commission of the Sociedade Brasileira de Reumatologia (SBR) published a series of papers aimed at producing recommendations on the diagnosis and treatment of RA in Brazil. The purpose of these documents was to establish consensus guidelines for the treatment of RA in Brazil and to support Brazilian rheumatologists, using evidence from scientific studies and the experience of a committee of experts on the subject in order to standardize the therapeutic approach of RA in the Brazilian socioeconomic context, maintaining the autonomy of the physician in the indication/choice of treatment options available.<sup>2-5</sup>

At that time, the documents predicted that, due to the rapid advances of knowledge in this field of science, it would be necessary to make periodic updates of such recommendations.

Since then, a drug belonging to a different class of previously existing drugs, tofacitinib, a synthetic, target-specific disease-modifying anti-rheumatic drug (DMARD) and selective inhibitor of Janus kinase (JAK) has been approved for use in Brazil.<sup>6</sup> Tofacitinib was submitted for approval to the National Health Surveillance Agency (ANVISA) on April 18, 2012 and approved on December 8, 2014.<sup>7</sup>

Thus, a contingent update of the Treatment Guideline previously reported by SBR was in order to establish the position of the RA Commission on the use of target-specific, synthetic DMARDs in Brazil.

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## Objective

This position paper aims to update SBR recommendations on the treatment of RA in Brazil, specifically regarding the use of target-specific, synthetic DMARDs.

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## Methods

The literature review of scientific articles of this guideline was conducted on MEDLINE database. The search for evidence came from actual clinical settings, using the following keywords (MeSH terms): *Arthritis, Rheumatoid, Therapy, Efficacy, Safety, Prognosis, Remission, Tofacitinib, Herpes zoster vaccine*. Studies published up to May 2015 were evaluated.

After a literature review, a text was produced, answering questions in the PICO structure (Population/patient, Intervention/indicator, Comparator/control, Outcome),<sup>8</sup> taking into account efficacy and safety issues of tofacitinib use for

treatment of RA in different scenarios (such as first-line treatment after failure with methotrexate [MTX] or other conventional synthetic DMARDs, after failure with biological therapy).

Based on the review conducted and on expert opinion, proposals of recommendations on the use of tofacitinib were drawn up, subjected to successive rounds of voting among members of the Committee gathered in person for this purpose, pending approval of positioning (recommendations). The degree of agreement with the text of the approved recommendation on a numerical scale from 0 (strongly disagree) to 10 (completely agree) was also established, with the final degree of agreement calculated by averaging the values assigned individually by each of the members of the Commission. Depending on the approved recommendation, an update of the flowchart for the treatment of RA in Brazil was developed, considering a scenario of tofacitinib insertion.

## Tofacitinib – general aspects

Tofacitinib is a preferential inhibitor of JAK1/JAK3 (members of the tyrosine kinase family, intracellular Janus kinase that transduce cytokine-mediated signals through JAK-STAT signaling pathway). This agent is indicated for patients with active RA who have experienced treatment failure with synthetic DMARDs, or with TNF inhibitors (TNFi). Tofacitinib can be used in combination with synthetic DMARDs or as monotherapy.<sup>6</sup> The approved dosage for tofacitinib is 1 tablet (5 mg) twice daily.<sup>7</sup>

Regarding its main adverse effects, the safety profile is similar to biological immunomodulatory drugs with higher incidence of serious infections, tuberculosis and herpes zoster compared to the control group. The observed incidence of herpes zoster has been higher than that reported for other immunobiological agents, mostly milder cases. Laboratory abnormalities observed include increases in total cholesterol, fractions of low-density lipoprotein – LDL and high-density lipoprotein – HDL, all reversible with specific treatment; neutropenia and lymphopenia, increased liver enzymes, creatine phosphokinase (CPK) and a slight increase in creatinine (not associated with increased incidence of renal failure). The increased incidence of malignancies, nonmelanoma skin cancers and lymphoproliferative diseases has not been observed so far, but one must keep strict surveillance, considering that this is a potent immunosuppressive agent. Briefly, patients with RA who will be treated with tofacitinib should be assessed prior to treatment with respect to potential latent TB (tuberculin skin test, chest X-ray and prior history of contact with people infected with tuberculosis) and periodically monitored with complete blood counts, assessment of renal function, liver enzymes and lipidogram.<sup>9-15</sup>

Tofacitinib is an expensive drug, generally similar to biological DMARDs.

## Is tofacitinib a safe and effective drug for the treatment of RA patients, as first line therapy?

The use of tofacitinib as first line therapy in patients with RA has been evaluated in a study where patients who had received no MTX or who had not been treated with this drug

in therapeutic doses, were randomized to take a dose of tofacitinib 5 mg twice a day, tofacitinib 10 mg twice a day, or MTX.<sup>14</sup>

### Effectiveness

In this study, tofacitinib was superior to MTX in controlling signs and symptoms (ACR70 responses at 6 months: 25.5% in the group receiving tofacitinib 5 mg twice a day, 37.7% in the group of tofacitinib 10 mg twice a day, and 12% of patients receiving MTX,  $p < 0.001$ . ACR70 = an improvement of 70% of the American College of Rheumatology score – ACR). There was also a significantly greater reduction of structural damage in patients receiving tofacitinib compared to patients receiving MTX (progression of Sharp index [modified] in six months = 0.2 points in the group treated with tofacitinib 5 mg and <0.1 points in the 10-mg group, compared to 0.8 in the group receiving MTX,  $p < 0.001$  for both comparisons).<sup>14</sup>

### Safety

Five cases of neoplasm, including 3 cases of lymphoma, have been reported in the group treated with tofacitinib, compared to 1 case in the group receiving MTX. Infections, including herpes zoster, were more common in patients receiving tofacitinib, which also was associated with increases of creatinine, LDL and HDL.<sup>14</sup>

This study suggests that tofacitinib is effective in controlling signs and symptoms and in reducing structural damage as a first-line treatment in patients with RA. The use of tofacitinib in combination with other DMARDs has not been evaluated in this population. The benefit of tofacitinib should be evaluated in the context of the adverse effects described.

### Is tofacitinib a safe and effective drug for the treatment of RA patients after failure with MTX or other synthetic DMARDs?

#### Effectiveness

Six systematic reviews with a meta-analysis evaluated the efficacy of tofacitinib versus placebo in the treatment of patients with RA, following an inadequate response to a DMARD.<sup>16-21</sup> Zhang et al.<sup>16</sup> evaluated 10 randomized studies totaling 4,929 patients. Tofacitinib was superior to placebo in the evaluation by ACR20 response (20% improvement in ACR score), HAQ-DI (Health Assessment Questionnaire – Disability Index) score, and DAS28 (28-joint Disease Activity Score) in week 12 (as monotherapy or in combination with MTX) and in week 24 (combined with MTX; monotherapy data not available). Song et al.<sup>17</sup> included five randomized trials totaling 1590 patients. Tofacitinib at doses of 5 mg and 10 mg (twice daily) was superior to placebo on all evaluated efficacy endpoints: ACR20 response, painful and swollen joint counts, visual scales of pain and of the overall assessment by the physician and patient, HAQ-DI score and C-reactive protein (CRP) levels.

Berhan<sup>18</sup> conducted a meta-analysis of 8 randomized trials totaling 4,283 patients with RA, following an inadequate response to a DMARD or a biological agent. The odds ratio for ACR20 response was 4 times greater with tofacitinib versus placebo (OR = 4.15; 95% CI: 3.23–5.32). The results of tofacitinib combined with MTX or as monotherapy did not differ significantly from each other. There was a decrease in

HAQ-DI score in patients treated with tofacitinib versus controls (mean standardized difference = -0.62, 95% CI = -0.735 to -0.506). He et al.<sup>19</sup> analyzed eight randomized studies, totaling 3,791 patients with RA, following an inadequate response to MTX. Higher ACR20 response rates at week 12 occurred with the use of tofacitinib 5 mg (relative risk [RR] = 2.20; 95% CI = 1.58–3.07) and 10 mg (RR = 2.38; 95% CI: 1.81–3.14) versus placebo. The responses were maintained at week 24.

Kawalec et al.<sup>20</sup> compiled eight randomized studies comparing tofacitinib versus placebo in the treatment of RA, after an inadequate response to a synthetic or biological DMARD. Tofacitinib was superior to placebo in ACR20, ACR50 and ACR70 response rates after 12 weeks of treatment ( $p < 0.0001$  for all comparisons). Tofacitinib also resulted in an improvement in HAQ-DI versus placebo. Kaur et al.<sup>21</sup> conducted a systematic review (without meta-analysis) of 8 phase II and III randomized trials, comparing tofacitinib versus placebo in patients with RA, following an inadequate response to a synthetic or biological DMARD. Tofacitinib was superior to placebo after 12 weeks of treatment in ACR20 and ACR50 responses and in decreases in HAQ-DI score. Together, the six systematic reviews included 12 publications, related to 11 randomized clinical trials.<sup>9-13,22-28</sup> The findings corroborate the effectiveness of tofacitinib combined to MTX or as monotherapy in the treatment of RA.

Two randomized studies evaluated tofacitinib and adalimumab in parallel groups versus placebo.<sup>10,27</sup> No direct comparison between tofacitinib and adalimumab was held. In the first study ( $n = 384$ ), ACR20 response rates at week 12 were 59.2% and 70.5% for tofacitinib at doses of 5 mg and 10 mg, respectively, and 22% in the placebo group ( $p < 0.0001$ ). Differences favoring tofacitinib were also found in ACR50 (50% improvement in ACR score) and ACR70 responses, and in DAS28, HAQ-DI and SF-36 (Medical Outcomes Study 36-Item – Short-Form Health Survey) scores, and also in the evaluation of fatigue by FACIT-F (Functional Assessment of Chronic Illness Therapy – Fatigue). In this study, adalimumab did not differ significantly from placebo with respect to most outcomes.<sup>27</sup> In another study ( $n = 717$ ), ACR20 response rates after 6 months of treatment were 51.5% and 52.6% in groups with tofacitinib 5 mg and 10 mg respectively; 47.2% in groups treated with adalimumab; and 28.3% in the placebo group ( $p < 0.001$  for all comparisons vs. placebo). Also a higher number of subjects in remission ( $DAS28 \leq 2.6$ ) were observed after 6 months in the active treatment groups. The responses were maintained until the 12th month of follow-up.<sup>10</sup>

van der Heijde et al.<sup>11</sup> conducted a randomized, double-blind, placebo-controlled trial to assess the prevention of structural damage by tofacitinib in 797 RA patients. After 6 months of treatment (interim analysis of data), tofacitinib 10 mg (twice daily) significantly reduced the progression of the total modified Sharp/van der Heijde score versus placebo.

The data available from phase II and III studies indicate that tofacitinib is effective in the treatment of RA after failure with a DMARD.

### Safety

The tofacitinib safety outcomes reported here are based on long-term extension studies, which encompassed 4,102

patients from phase I,<sup>29,30</sup> II,<sup>22,23,25,27</sup> and III<sup>9-13,28,31</sup> randomized clinical trials. Overall, discontinuation of treatment was observed in 842 patients (20.8%), and 437 patients (10.7%) were discontinued due to adverse events. The main adverse events associated with discontinuation were infections and laboratory abnormalities (anemia, neutropenia, lymphopenia, changes in liver enzymes, and serum cholesterol, LDL and creatinine increases).<sup>32</sup>

The most common infections were nasopharyngitis, upper respiratory tract infection and urinary tract infection. Infections of particular interest as herpes zoster and tuberculosis were more often observed in Asian patients, for whom the risk of developing herpes zoster was higher (6.7 events per 100 patient-years) compared to Caucasian patients (3.7 events per 100 patient-years).<sup>32</sup> The risk of developing tuberculosis was evaluated in a model by Maiga et al.<sup>33</sup> These authors showed that tofacitinib can induce reactivation of latent tuberculosis infection (LTBI), because the drug induces increases in mycobacteria replication. Long-term extension studies reported the occurrence of 10 cases of tuberculosis in 4,102 patients, reinforcing the recommendation of a LTBI survey before starting treatment with tofacitinib.<sup>32</sup> The most common gastrointestinal manifestations were diarrhea (4.4%), nausea (3.3%) and gastritis (2.5%). Despite reports of gastrointestinal perforation, the occurrence of these adverse events did not differ from those occurring with biological and non-biological DMARD users (0.05–0.17 events per 100 patient-years).<sup>34,35</sup>

Regarding laboratory changes, these effects were characterized as mild to moderate, not being, in most cases, required a permanent discontinuation of treatment with tofacitinib.<sup>32</sup> As to anemia, a hemoglobin drop below 7 g/dL or a decrease greater than 3 g/dL was observed in 1% of patients, with the majority of patients presenting anemia had decreases in hemoglobin values in the order of 1–2 g/dL (12.7%). The incidence of neutropenia was 4.9%, and no patients had neutrophil counts under 500 cells/mm<sup>3</sup>; 3.9% had neutrophil counts of 1500–1999 cells/mm<sup>3</sup>. Liver enzyme elevations occurred in 35% of patients, and the most common finding was a onefold increase of normal value (29.7%). These changes were transient and did not result in treatment discontinuation. A threefold increase of the normal value occurred in 1.2% of patients, whose values returned to normal after discontinuation of tofacitinib. An increase of creatine was observed in 3.3% of patients; this finding was reversible and transient, and does not seem to be related to acute renal failure or progressive worsening of renal function.<sup>32,36</sup> The use of tofacitinib increases serum cholesterol, LDL and HDL, with a mean elevation of cholesterol of 13 mg/dL, a value similar to that observed with HDL elevation. It was not yet properly established the real meaning of these moderate elevations in lipid profile.<sup>37</sup>

Regarding the occurrence of malignancies, Curtis et al. analyzed 5,671 tofacitinib users in 6 phase II studies, 6 phase III studies and two long-term extension studies. They observed the occurrence of 107 malignancies (excluding non-melanoma skin cancer). The most common neoplasm was lung cancer ( $n=24$ ), followed by breast cancer ( $n=19$ ), lymphoma ( $n=10$ ) and gastric cancer ( $n=5$ ). The malignancy rate by six-month intervals of exposure to tofacitinib remained stable during the

period of time analyzed. The incidence rates of these neoplasms were as expected for RA patients with moderate or severe activity.<sup>38</sup>

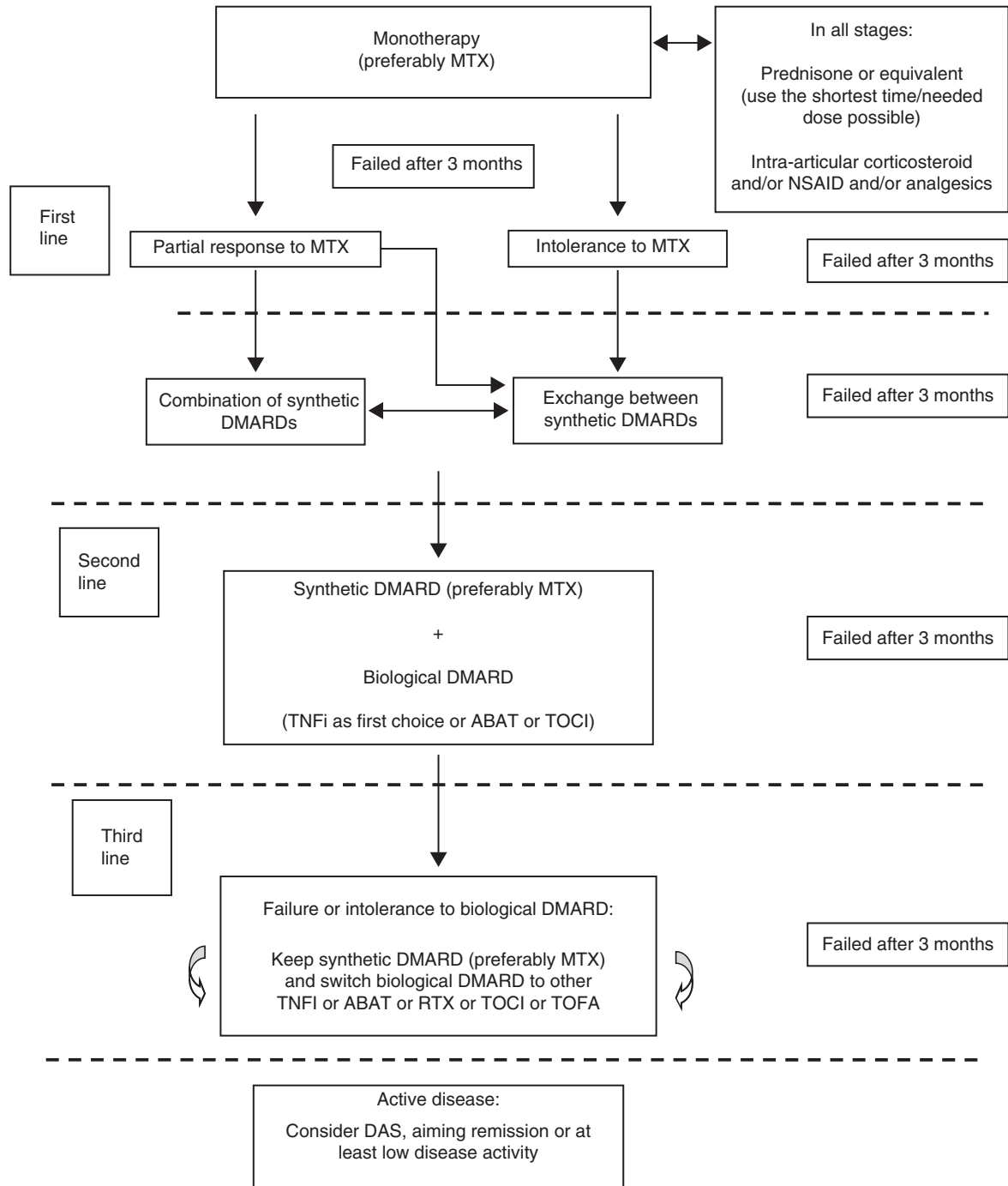
### Is tofacitinib a safe and effective drug for treatment of RA patients after failure with biological drugs?

#### Effectiveness

A phase III, double-blind, placebo-controlled, parallel group trial with six months' duration was conducted in patients with moderate to severe RA who had not responded or were intolerant to one or more TNFi.<sup>12</sup> All patients involved in the study were using, and remained in use, of MTX. 399 patients were included (133 in tofacitinib 5 mg twice daily group, 134 in tofacitinib 10 mg twice daily group, and 132 in the placebo group). After three months, patients in the placebo group were distributed by tofacitinib 5 mg or 10 mg groups. Most patients were female (80.3%), white (84.8%) and with a mean age of 54.4–55.4 years and a mean disease duration of 11.3–13 years. The mean number of prior treatments with TNFi was 1.4–1.5 (64% had been previously treated with a TNFi: 26% with two and 8% with three or more treatments). TNFi had been discontinued for lack of efficacy in 65.2%, for lack of efficacy and intolerance in 19.8%, and for intolerance only in 13.8%. Baseline mean values of HAQ-DI and DAS28-ESR (erythrocyte sedimentation rate) ranged from 1.5–1.6 and 6.4–6.5, respectively. The primary objectives of the study were to evaluate the ACR20 response rate, mean HAQ-DI change from the onset of treatment, and disease activity index (DAS28-VHS) rates <2.6 at the end of three months.<sup>12</sup>

After three months, the ACR20 response of tofacitinib 5-mg group was 41.7% (55 of 132; 95% CI: 6.06–28.41;  $p=0.0024$ ) versus placebo 24.4% (32 of 131). Also after three months, the ACR50 response to tofacitinib 5-mg group was 26.5% (35 of 132; [9.21–27.02];  $p<0.0001$ ) versus placebo (8.4%; 11 of 131) and the ACR70 response to tofacitinib 5-mg group was 13.6% (18 of 132; [5.89–18.32];  $p<0.0001$ ) versus placebo, 1.5% (2 of 131). Still, after three months, the mean variation of least mean least squares (LMS) versus baseline for HAQ-DI was  $-0.43$  ([95% CI:  $-0.36$  to  $-0.15$ ];  $p<0.0001$ ) for tofacitinib 5-mg group versus placebo ( $-0.18$ ). Improvement in HAQ-DI  $\geq 0.22$  was observed in 54.2% (71 of 131; [1.76–25.71];  $p=0.0245$ ) for tofacitinib 5-mg group versus placebo, 40.5% (53 of 131). Improvement in HAQ-DI  $\geq 0.5$  was observed in 35.9% (47 of 131; [4.52–26.01];  $p=0.0053$ ) for tofacitinib 5-mg group versus placebo, 20.6% (27 of 131). The proportion of patients with DAS28 <2.6 after three months was 6.7% (8 of 119; [0–10.10];  $p=0.0496$ ) for tofacitinib 5-mg group versus placebo (1.7%, 2 of 120). After six months, this figure increased to 8.2% (10 of 122) with tofacitinib 5 mg versus placebo, 5.0% (6 of 120). In the third and sixth months, remission (defined by Boolean criteria) was reached by 6.1% (8 of 132; [1.99–10.13];  $p=0.0035$ ) for tofacitinib 5-mg group versus 0% in the placebo group.<sup>12</sup>

Regarding the outcomes reported by patients (PRO – Patient Reported Outcomes) after three months, the proportions of patients with greater than or equal answers to minimum clinically important difference (MCDI) were: 1. Overall assessment of disease activity – 41.88% in the placebo group versus 64.91% in tofacitinib 5-mg group ( $p<0.001$ ); 2. Pain – 39.13% in the placebo group versus 69.30% in tofacitinib 5-mg group



ABAT, abatacept; NSAID, nonsteroidal anti-inflammatory agent; DMARD, disease modifying antirheumatic drug; MTX, methotrexate; RTX, rituximab; TNFi, tumor necrosis factor inhibitors; TOFA, tofacitinib; TOCI, tocilizumab.

**Fig. 1 – Updated flowchart of drug treatment for rheumatoid arthritis in Brazil, proposed by the Commission on Rheumatoid Arthritis of the Brazilian Society of Rheumatology.**

( $p < 0.0001$ ); 3. Fatigue (FACIT) – 38.60% in the placebo group versus 61.54% in tofacitinib 5-mg group ( $p < 0.0001$ ); 4. SF-36v2 – physical component – 49.14% in the placebo group versus 67.80% in tofacitinib 5-mg group ( $p < 0.05$ ), and 5. SF-36v2 – mental component – 37.07% in the placebo group versus 54.24% in tofacitinib 5-mg group ( $p < 0.05$ ).<sup>39</sup>

In another phase III, double-blind, placebo-controlled trial, 611 patients with active RA refractory or intolerant to at least one synthetic or biological DMARD were randomized in groups of monotherapy with tofacitinib 5 mg twice daily ( $n = 243$ ), tofacitinib 10 mg twice daily ( $n = 245$ ) and placebo ( $n = 122$ ).<sup>13</sup> A sub-analysis with patients who had already made use of TNFi or other biological agent revealed that 18 of 46 (42.9%) patients in the tofacitinib 5-mg group and 6 of 34 (17.7%) patients in the placebo group achieved ACR 20 response criteria at three months.

### Safety

In the first three months of the phase III trial, 145 adverse events were reported in 71 of 133 patients in tofacitinib 5-mg group (53.4%) versus 167 adverse events in 75 of 132 patients in the placebo group (56.8%). During this period, the most common adverse events were diarrhea (13 of 267; 4.9%), nasopharyngitis (11 of 267; 4.1%), headache (11 of 267; 4.1%) and urinary tract infection (8 of 267; 3.0%) in tofacitinib (5 mg and 10 mg) groups; and nausea (9 of 132; 6.8%) in the placebo group. Serious adverse events occurred in 4 of 267 patients (1.5%) treated with tofacitinib (2 in 5-mg group and 2 in 10-mg group), and 6 in 132 patients (4.5%) in the placebo group. No serious infectious event was reported. Eight patients (6.0%) discontinued the protocol because of adverse events in tofacitinib 5-mg group versus 7 (5.3%) in the placebo group.<sup>12,13</sup>

### Is there evidence for indication of the use of herpes zoster vaccine in tofacitinib users?

The prevention of herpes zoster (HZ) is of great interest to RA patients, since they are in greater risk of infection compared to the general population.<sup>40,41</sup>

In Brazil, the vaccine for HZ prevention (and its complications) contains live attenuated virus, with 14 times more antigens than the varicella vaccine can have from the same manufacturer. HZ vaccine is licensed for use in people over 50 years old. According to the Immunization Guide prepared in 2014 by the Brazilian Society of Immunizations (BSIm) and the Brazilian Society of Rheumatology (SBR), its use should be avoided in patients with severe drug immunosuppression or with immunosuppression caused by disease; however, this vaccine may be indicated in patients with mild immunosuppression. Patients with chronic diseases can be vaccinated, except in case of severe immunosuppression and if in treatment with biological agents.<sup>42</sup>

At the moment, however, there is limited information on the safety and efficacy of this vaccine in RA patients. There are few studies evaluating its value in patients being submitted to different immunosuppressive regimens, including tofacitinib.<sup>40</sup>

Taking into account that vaccination is a preventive measure with the greatest impact on reducing the incidence of

infection in any age group, the SBR Consensus of 2012 on vaccination in RA patients recommends a review and updating of the immunization card before the use of synthetic or biological DMARDs, including the vaccine against herpes zoster in patients over 50 years old.<sup>43</sup>

Likewise, ACR recommends vaccination prior to the onset of treatment with synthetic or biological DMARDs in RA patients over 50 years old. During the use of synthetic DMARDs, the vaccine may also be applied, but this is not recommended during the use of biological DMARDs.<sup>1,3,4</sup> The use of tofacitinib was not addressed in these recommendations.<sup>40,44,45</sup>

Importantly, the vaccine is not available on the public Health Service and is not covered by most health plans and health insurance companies.

### RA Commission of SBR position on the use of tofacitinib for the treatment of RA in Brazil

Based on previous evidence and considering the available data on efficacy, safety and cost of medications available to treat the disease in Brazil, the RA Commission of SBR, after a process of discussion and voting on proposals, established the following position on the use of tofacitinib for treatment of RA in Brazil: "Tofacitinib, alone or in combination with MTX, is an alternative for RA patients with moderate or high activity after failure of at least two different synthetic DMARDs and one biological DMARD." The level of agreement with this recommendation was 7.5.

The RA Commission considers it necessary to establish a timely and objective recommendation, which would help the rheumatologist in his/her decision making about the use of this new medication in RA treatment flowchart. But we also considered – and this was quite clear on the basis of a fairly debated voting and discussion process – that, under certain conditions and in very specific clinical scenarios, the earlier use of tofacitinib could be indicated, at the physician's discretion, since, as shown, there is evidence of efficacy of this drug at different times in the treatment of RA.

The decision of this Commission of experts, to indicate the use of tofacitinib after failure of at least two different synthetic DMARDs and one biological DMARD, took into account mainly the still restricted period of post-marketing experience. We believe that this aspect limits the information relevant on safety, compared to other medications already in use for RA treatment. This position may be reviewed in coming years, in the face of the acquisition of a greater experience with the use of this drug.

### RA treatment flow chart update in Brazil

Fig. 1 summarizes the updated flowchart of drug treatment for RA in Brazil, as proposed by the RA Committee of SBR.

## Conclusion

The current position of the RA Commission of SBR is that, despite the proven clinical efficacy of tofacitinib in patients with RA who have failed synthetic or biological DMARDs, it



is suggested that its use is considered in a scenario of failure in at least two synthetic DMARD and at least one biological DMARD, thanks to a lesser long-term clinical experience with this drug in clinical practice.

This positioning may be revised over time, in the face of the acquisition of a greater experience with the use of this drug.

### Conflicts of interest

Licia Maria Henrique da Mota is a consultant/speaker for Abbvie, Bristol-Myers Squibb, Janssen, Hospira, Lilly, Pfizer, Roche and UCB. Cleandro Pires de Albuquerque reports grants, personal fees and non-financial support from Pfizer, grants, personal fees and non-financial support from Abbvie, grants, personal fees and non-financial support from AstraZeneca, grants and non-financial support from Janssen, non-financial support from Bristol-Myers-Squibb, outside the submitted work. Rodrigo Aires Corrêa Lima works as speaker for Abbvie, Pfizer Janssen and UCB. Geraldo da Rocha Castelar Pinheiro works as consultant for Astra-Zeneca, Bristol Myers Squibb, Janssen, Novartis, Pfizer, Roche, RuiYi and Sanofi. Ieda Maria Magalhães Laurindo works as a speaker and/or consultant for Abbvie, Astra-Zeneca, Bristol, GSK, Lilly, Janssen, Pfizer, Roche and UCB. Manoel Barros Bertolo lectures for Pfizer, Abbvie, Roche, Janssen and Aventis. The author conducts clinical research for MSD, Bristol, Aventis and Roche. Paulo Louzada Júnior held services for UCB and Roche. Rina Dalva Neubarth Giorgi is a honorary member in clinical research for UCB, HGS (GSK), Sanofi-Aventis and Roche; and works as consultant and lectures for BMS, Pfizer, Janssen and Lilly. Ricardo Machado Xavier works as a speaker and consultant; and reports research grants or non-financial support for participation in scientific events for Abbvie, Hospira, Janssen, Lilly, Pfizer, Roche. The other authors declare no conflicts of interest.

### REFERENCES

- Smolen JS, Landewé R, Breedveld FC, Buch M, Burmester G, Dougados M, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2013 update. *Ann Rheum Dis.* 2014;73:492-509.
- da Mota LM, Cruz BA, Brenol CV, Pereira IA, Fronza LS, Bertolo MB, et al. 2011 Consensus of the Brazilian Society of Rheumatology for diagnosis and early assessment of rheumatoid arthritis. *Rev Bras Reumatol.* 2011;51:199-219.
- da Mota LM, Cruz BA, Brenol CV, Pereira IA, Rezende-Fronza LS, Bertolo MB, et al. 2012 Brazilian Society of Rheumatology Consensus for the treatment of rheumatoid arthritis. *Rev Bras Reumatol.* 2012;52:152-74.
- 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.
- Mota LM, Cruz BA, Brenol CV, Pereira IA, Rezende-Fronza LS, Bertolo MB, et al. Guidelines for the drug treatment of rheumatoid arthritis. *Rev Bras Reumatol.* 2013;53:158-83.
- O'Shea JJ, Kontzias A, Yamaoka K, Tanaka Y, Laurence A. Janus kinase inhibitors in autoimmune diseases. *Ann Rheum Dis.* 2013;72 Suppl. 2:ii111-5.
- Diário Oficial da União -Suplemento Anvisa - DOU1 - Edição nr 237 de 08/12/2014 Pag. 13. Available at: <http://pesquisa.in.gov.br/imprensa/jsp/visualiza/index.jsp?journal=1010&pagina=13&data=08/12/2014> [accessed 19.06.15].
- Schardt C, Adams MB, Owens T, Keitz S, Fontelo P. Utilization of the PICO framework to improve searching PubMed for clinical questions. *BMC Med Inform Decis Mak.* 2007;7:16.
- Kremer J, Li ZG, Hall S, Fleischmann R, Genovese M, Martin-Mola E, et al. Tofacitinib in combination with nonbiologic disease-modifying antirheumatic drugs in patients with active rheumatoid arthritis: a randomized trial. *Ann Intern Med.* 2013;159:253-61.
- van Vollenhoven RF, Fleischmann R, Cohen S, Lee EB, Garcia Meijide JA, Wagner S, et al. Tofacitinib or adalimumab versus placebo in rheumatoid arthritis. *N Engl J Med.* 2012;367:508-19.
- van der Heijde D, Tanaka Y, Fleischmann R, Keystone E, Kremer J, Zerbini C, et al. Tofacitinib (CP-690,550) in patients with rheumatoid arthritis receiving methotrexate: twelve-month data from a twenty-four-month phase III randomized radiographic study. *Arthritis Rheum.* 2013;65:559-70.
- Burmester GR, Blanco R, Charles-Schoeman C, Wollenhaupt J, Zerbini C, Benda B, et al. Tofacitinib (CP-690,550) in combination with methotrexate in patients with active rheumatoid arthritis with an inadequate response to tumour necrosis factor inhibitors: a randomised phase 3 trial. *Lancet.* 2013;381:451-60.
- Fleischmann R, Kremer J, Cush J, Schulze-Koops H, Connell CA, Bradley JD, et al. Placebo-controlled trial of tofacitinib monotherapy in rheumatoid arthritis. *N Engl J Med.* 2012;367:495-507.
- Lee EB, Fleischmann R, Hall S, Wilkinson B, Bradley JD, Gruben D, et al. Tofacitinib versus methotrexate in rheumatoid arthritis. *N Engl J Med.* 2014;370:2377-86.
- Bula XELJANZ, Citrato de Tofacitinibe; 2014.
- Zhang X, Liang F, Yin X, Xiao X, Shi P, Wei D, et al. Tofacitinib for acute rheumatoid arthritis patients who have had an inadequate response to disease-modifying antirheumatic drug (MMCD): a systematic review and meta-analysis. *Clin Rheumatol.* 2014;33:165-73. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/24389749> [accessed 10.06.15; cited 25.04.15].
- Song GG, Bae S-C, Lee YH. Efficacy and safety of tofacitinib for active rheumatoid arthritis with an inadequate response to methotrexate or disease-modifying antirheumatic drugs: a meta-analysis of randomized controlled trials. *Korean J Intern Med.* 2014;29:656-63. Available from: <http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=4164730&tool=pmcentrez&rendertype=abstract> [accessed 08.06.15; cited 31.03.15].
- Berhan A. Efficacy, safety and tolerability of tofacitinib in patients with an inadequate response to disease modifying anti-rheumatic drugs: a meta-analysis of randomized double-blind controlled studies. *BMC Musculoskelet Disord.* 2013;14:332. Available from: <http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=4222887&tool=pmcentrez&rendertype=abstract> [accessed 12.06.2015; cited 29.03.15].
- He Y, Wong AYS, Chan EW, Lau WCY, Man KKC, Chui CSL, et al. Efficacy and safety of tofacitinib in the treatment of rheumatoid arthritis: a systematic review and meta-analysis. *BMC Musculoskelet Disord.* 2013;14:298. Available from: <http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=3819708&tool=pmcentrez&rendertype=abstract> [accessed 28.05.15; cited 29.03.15].

20. Kawalec P, Mikrut A, Wiśniewska N, Pilc A. The effectiveness of tofacitinib, a novel Janus kinase inhibitor, in the treatment of rheumatoid arthritis: a systematic review and meta-analysis. *Clin Rheumatol*. 2013;32:1415–24. Available from: <http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=3778229&tool=pmcentrez&rendertype=abstract> [accessed 10.06.15; cited 03.03.15].
21. Kaur K, Kalra S, Kaushal S. Systematic review of tofacitinib: a new drug for the management of rheumatoid arthritis. *Clin Ther*. 2014;36:1074–86. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/25047498> [accessed 16.06.15; cited 23.04.15].
22. Kremer JM, Bloom BJ, Breedveld FC, Coombs JH, Fletcher MP, Gruben D, et al. The safety and efficacy of a JAK inhibitor in patients with active rheumatoid arthritis: results of a double-blind, placebo-controlled phase IIa trial of three dosage levels of CP-690,550 versus placebo. *Arthritis Rheum*. 2009;60:1895–905. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/19565475> [accessed 30.05.15; cited 28.02.15].
23. Kremer JM, Cohen S, Wilkinson BE, Connell CA, French JL, Gomez-Reino J, et al. A phase IIb dose-ranging study of the oral JAK inhibitor tofacitinib (CP-690,550) versus placebo in combination with background methotrexate in patients with active rheumatoid arthritis and an inadequate response to methotrexate alone. *Arthritis Rheum*. 2012;64:970–81. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/22006202> [accessed 11.06.15; cited 19.04.15].
24. Tanaka Y, Takeuchi T, Yamanaka H. Tofacitinib (CP-690,550), an oral Janus kinase inhibitor, as monotherapy in Japanese patients with active rheumatoid arthritis: a 12-week phase 2b study [abstract]. *Arthritis Rheum*. 2011;63 Suppl. 10:2192 [accessed 09.06.15].
25. Tanaka Y, Suzuki M, Nakamura H, Toyozumi S, Zwillich SH. Phase II study of tofacitinib (CP-690,550) combined with methotrexate in patients with rheumatoid arthritis and an inadequate response to methotrexate. *Arthritis Care Res (Hoboken)*. 2011;63:1150–8. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/21584942> [accessed 02.06.15; cited 01.04.15].
26. Tanaka Y, Takeuchi T, Yamanaka H, Nakamura H, Toyozumi S, Zwillich S. Efficacy and safety of tofacitinib as monotherapy in Japanese patients with active rheumatoid arthritis: a 12-week, randomized, phase 2 study. *Mod Rheumatol*. 2014;1–25. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/25496464> [accessed 05.06.15; cited 03.05.15].
27. Fleischmann R, Cutolo M, Genovese MC, Lee EB, Kanik KS, Sadis S, et al. Phase IIb dose-ranging study of the oral JAK inhibitor tofacitinib (CP-690,550) or adalimumab monotherapy versus placebo in patients with active rheumatoid arthritis with an inadequate response to disease-modifying antirheumatic drugs. *Arthritis Rheum*. 2012;64:617–29. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/21952978> [accessed 05.06.15; cited 19.04.15].
28. Coombs JH, Bloom BJ, Breedveld FC, Fletcher MP, Gruben D, Kremer JM, et al. Improved pain, physical functioning and health status in patients with rheumatoid arthritis treated with CP-690,550, an orally active Janus kinase (JAK) inhibitor: results from a randomised, double-blind, placebo-controlled trial. *Ann Rheum Dis*. 2010;69:413–6. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/19587388> [accessed 12.06.15; cited 19.04.15].
29. Krishnaswami S, Kudlacz E, Wang R, Chan G. A supratherapeutic dose of the Janus kinase inhibitor tasocitinib (CP-690,550) does not prolong QTc interval in healthy participants. *J Clin Pharmacol*. 2011;51:1256–63. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/21148043> [accessed 04.06.15; cited 05.05.15].
30. Cohen S, Zwillich SH, Chow V, Labadie RR, Wilkinson B. Co-administration of the JAK inhibitor CP-690,550 and methotrexate is well tolerated in patients with rheumatoid arthritis without need for dose adjustment. *Br J Clin Pharmacol*. 2010;69:143–51. Available from: <http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=2824475&tool=pmcentrez&rendertype=abstract> [accessed 25.05.15; cited 03.05.15].
31. Lee EB, Fleishmann RM, Hall S, van Vollenhoven RF, Bradley J, Gruben D, et al. Radiographic, clinical and functional comparison of tofacitinib monotherapy versus methotrexate in methotrexate-naïve patients with rheumatoid arthritis [abstract]. *Arthritis Rheum*. 2012;64 Suppl.:S1049 [accessed 05.06.15].
32. Wollenhaupt J, Silverfield J, Lee EB, Curtis JR, Wood SP, Soma K, et al. Safety and efficacy of tofacitinib, an oral Janus kinase inhibitor, for the treatment of rheumatoid arthritis in open-label, longterm extension studies. *J Rheumatol*. 2014;41:837–52. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/24692527> [accessed 17.06.15; cited 03.05.15].
33. Maiga M, Lun S, Guo H, Winglee K, Ammerman NC, Bishai WR. Risk of tuberculosis reactivation with tofacitinib (CP-690550). *J Infect Dis*. 2012;205:1705–8. Available from: <http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=3415851&tool=pmcentrez&rendertype=abstract> [accessed 02.06.15; cited 05.05.15].
34. Curtis JR, Xie F, Chen L, Spettell C, McMahan RM, Fernandes J, et al. The incidence of gastrointestinal perforations among rheumatoid arthritis patients. *Arthritis Rheum*. 2011;63:346–51. Available from: <http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=3031757&tool=pmcentrez&rendertype=abstract> [accessed 03.06.15; cited 03.05.15].
35. Curtis JR, Lanas A, John A, Johnson DA, Schulman KL. Factors associated with gastrointestinal perforation in a cohort of patients with rheumatoid arthritis. *Arthritis Care Res (Hoboken)*. 2012;64:1819–28. Available from: <http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=3508293&tool=pmcentrez&rendertype=abstract> [accessed 06.06.15; cited 05.05.15].
36. Lundquist LM, Cole SW, Sikes ML. Efficacy and safety of tofacitinib for treatment of rheumatoid arthritis. *World J Orthop*. 2014;5:504–11. Available from: <http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=4133456&tool=pmcentrez&rendertype=abstract> [accessed 28.05.15; cited 29.03.15].
37. Souto A, Salgado E, Maneiro JR, Mera A, Carmona L, Gómez-Reino JJ. Lipid profile changes in patients with chronic inflammatory arthritis treated with biologic agents and tofacitinib in randomized clinical trials: a systematic review and meta-analysis. *Arthritis Rheumatol (Hoboken NJ)*. 2015;67:117–27. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/25303044> [accessed 29.05.15; cited 25.04.15].
38. Curtis JR, Lee EB, Kaplan IV, Kwok K, Geier J, Benda B, et al. Tofacitinib, an oral Janus kinase inhibitor: analysis of malignancies across the rheumatoid arthritis clinical development programme. *Ann Rheum Dis*. 2015, <http://dx.doi.org/10.1136/annrheumdis-2014-205847>, pii:annrheumdis-2014-205847 [accessed 05.06.15].
39. Strand V, Burmester GR, Zerbini CAF, Mebus CA, Zwillich SH, Gruben D. Tofacitinib with methotrexate in third-line treatment of patients with active rheumatoid arthritis: patient-reported outcomes from a phase III trial. *Arthritis Care Res*. 2015;67:475–83.

40. Winthrop KL, Yamanaka H, Valdez H, Mortensen E, Chew R, Krishnaswami S, et al. Herpes zoster and tofacitinib therapy in patients with rheumatoid arthritis. *Arthritis Rheumatol*. 2014;66:2675-84.
41. Smitten AL, Choi HK, Hochberg MC, Suissa S, Simon TA, Testa MA, et al. The risk of herpes zoster in patients with rheumatoid arthritis in the United States and the United Kingdom. *Arthritis Rheum*. 2007;57:1431-8.
42. Pileggi GS, Ballalai I, Brenol C, Saad CGS, Titton D, Klumb EM, et al. Guia de Imunização SBIIm/SBR. *Reumatologia*. 2014/15.
43. 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.
44. 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.
45. Harpaz R, Ortega-Sanchez IR, Seward JF. Prevention of herpes zoster: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm Rep*. 2008;57:1-30 [quiz CE32-34].