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## Review article

# Severe infection in patients with rheumatoid arthritis taking anakinra, rituximab, or abatacept: a systematic review of observational studies



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## ABSTRACT

A question is raised about an increased risk of severe infection from the use of biological drugs in patients with rheumatoid arthritis. This systematic review of observational studies aimed at assessing the risk of severe infection associated with the use of anakinra, rituximab, and abatacept in patients with rheumatoid arthritis. The following databases were searched: PubMed, Science Direct, Scopus, Web of Knowledge, Scirus, Cochrane, Exerpta Medica Database, Scielo, and Lilacs up to July 2010. Severe infections were defined as those life-threatening ones in need of the use of parenteral antibiotics or of hospitalization. Longitudinal observational studies were selected without language restriction, involving adult patients diagnosed with rheumatoid arthritis and who used anakinra, rituximab, or abatacept. In four studies related to anakinra, 129 (5.1%) severe infections were related in 2896 patients, of which three died. With respect to rituximab, two studies reported 72 (5.9%) severe infections in 1224 patients, of which two died. Abatacept was evaluated in only one study in which 25 (2.4%) severe infections were reported in 1046 patients. The main site of infection for these three drugs was the respiratory tract. One possible explanation for the high frequency of severe infections associated with anakinra may be the longer follow-up time in the selected studies. The high frequency of severe infections associated with rituximab could be credited to the less strict inclusion criteria for the patients studied. Therefore, infection monitoring should be cautious in patients with rheumatoid arthritis in use of these three drugs.

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## Infecções graves em pacientes com artrite reumatoide em uso de anakinra, rituximab ou abatacept: revisão sistemática de estudos observacionais

### R E S U M O

#### Palavras-chave:

Artrite reumatoide/terapia  
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Infecção  
Terapia biológica/efeitos adversos  
Revisão de literatura como assunto

Existe um questionamento sobre aumento do risco de infecções graves pelo uso de medicamentos biológicos por pacientes com artrite reumatoide. Esta revisão sistemática de estudos observacionais objetivou avaliar o risco de infecções graves associadas ao uso de anakinra, rituximab e abatacept em pacientes com artrite reumatoide. Foram pesquisadas as bases PubMed, Science Direct, Scopus, Web of Knowledge, Scirus, Cochrane, Exerpta Medica Database, Scielo e Lilacs até julho/2010. Infecções graves foram definidas como aquelas com de risco de vida, necessidade de antibióticos parenterais ou de hospitalização. Foram selecionados estudos observacionais longitudinais, sem restrição de idioma, que envolviam pacientes adultos com diagnóstico de artrite reumatoide que usaram anakinra, rituximab, abatacept. Em quatro estudos relacionados ao anakinra, foram relatadas 129 (5,1%) infecções graves em 2.896 pacientes, dos quais três evoluíram para óbito. Sobre o rituximab, dois estudos relataram 72 (5,9%) infecções graves em 1.224 pacientes, dos quais dois evoluíram para óbito. O abatacept foi avaliado em apenas um estudo, no qual foram relatadas 25 (2,4%) infecções graves em 1.046 pacientes. O principal sítio de infecção para os três medicamentos foi o trato respiratório. Uma possível explicação para a frequência elevada de infecções graves associadas ao anakinra pode ser o maior tempo de acompanhamento nos estudos selecionados. A frequência elevada de infecções graves associadas ao rituximab poderia ser creditada ao critério menos restrito de inclusão de pacientes. Portanto, deve ser cautelosa a monitoração de infecções nos pacientes com artrite reumatoide que usam esses três medicamentos.

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## Introduction

Rheumatoid arthritis (RA) is a chronic inflammatory disease of unknown etiology that affects 0.5–1% of the world adult population, predominantly in women, and with the highest incidence in the age range of 30–50 years.<sup>1</sup> The symmetric polyarthritis characteristic of RA can cause pain and joint destruction and deformity, especially in the joints of the hands and wrists, as well as pain and systemic manifestations such as fatigue, morning stiffness, and weight loss.<sup>2</sup>

RA patients may remain with active disease despite the use of synthetic (or “non-biological”) Disease Modifying Antirheumatic Drugs (DMARDs) such as methotrexate, leflunomide, azathioprine, and cyclosporine. Thus, since 1997 new therapies, such as “biological DMARDs”, have been employed, demonstrating greater efficacy in the treatment of RA,<sup>3</sup> among which one can mention tumor- $\alpha$  necrosis factor (TNF- $\alpha$ )-antagonists (infliximab, etanercept, adalimumab, and golimumab) and non-TNF- $\alpha$  antagonists (abatacept, rituximab, anakinra, and tocilizumab) DMARDs.<sup>4</sup>

Some randomized controlled trials have shown an increase in infection with the use of non-TNF- $\alpha$  antagonist DMARDs in patients with RA, both with rituximab (5.2/100 patient-years for methotrexate/rituximab association vs. 3.7/100 patient-years for methotrexate only),<sup>5</sup> as well as with abatacept (2.9% for the association vs. 1.9% for methotrexate only).<sup>6</sup> However, other authors have not found this increase for rituximab,<sup>7</sup> abatacept,<sup>8</sup> or anakinra.<sup>9</sup>

Three systematic reviews (SRs) that evaluated non-TNF- $\alpha$  antagonist DMARDs were published.<sup>4,10,11</sup>

Gartlehner et al.<sup>10</sup> have examined the comparative efficacy and safety of three TNF- $\alpha$  antagonists and of a non-TNF- $\alpha$  antagonist (anakinra) for the treatment of rheumatoid arthritis in 18 observational and experimental studies, but the authors did not present results on infections.

Based on 12 clinical trials, Salliot et al.<sup>11</sup> have suggested a trend (not statistically significant) for increased risk of severe infection during the treatment with rituximab (odds ratio [OR]=1.45, confidence interval [CI] 95%: 0.56–3.73), abatacept (OR=1.35; 95% CI: 0.78–2.32), and anakinra (OR=2.75; 95% CI: 0.91–8.35).

Storage et al.,<sup>4</sup> in a systematic review of eight (randomized and open-label) clinical trials, identified severe infection in up to 2.3% in cases of exclusive use of abatacept and from 1.3 to 12.7% with the use of abatacept associated with synthetic DMARDs.

Although performing a meta-analysis of observational studies on the safety of biological DMARDs, Bernatsky et al.<sup>12</sup> studied only TNF- $\alpha$  antagonists. Thus, we emphasize that except for abatacept, systematic reviews of observational studies on the risk of severe infection associated with non-TNF- $\alpha$  antagonists (anakinra, rituximab, and tocilizumab) have not yet been carried out.

The aim of this study was to evaluate the risk of severe infection associated with the use of anakinra, rituximab, abatacept, and tocilizumab in RA patients, using only observational studies.

## Method

The description of this systematic review was conducted according to a pre-specified protocol, based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline.<sup>13</sup> The following are the main definitions and steps described in the protocol. Severe infections were defined as those in which there is a risk for the patient's life, and the necessity of parenteral antibiotics or of hospitalization in adult patients with RA users of anakinra, rituximab, and abatacept. Only longitudinal observational studies were selected, including post-marketing evaluation studies and clinical trial follow-up studies (e.g., open-label clinical trials).

The following electronic databases were searched: PubMed, Literatura Latino-Americana e do Caribe em Ciências da Saúde (LILACS), Scopus, Web of Science, Science Direct, Excerpta Medica Database (EMBASE), SciELO, and Scirus. For each base search, a strategy combining the following descriptors – infection, bacterial infections, antirheumatic agents, adverse effects, therapeutic use, rheumatoid arthritis, and drug therapy – were developed. There were no restrictions on language. The strategy used in Pubmed was: ((infection [MeSH Terms] OR bacterial infections [MeSH Terms]) AND (antirheumatic agents/adverse effects [MeSH Terms] OR antirheumatic Agents/therapeutic use [MeSH Terms])) AND (arthritis, rheumatoid/drug therapy [MeSH Terms]). Equivalent strategies have been formulated for the other bases. The Scirus base also covered gray literature. Searches included studies published up to July 2010, covering prior periods without limitation of publication date. The reference lists of all articles were manually investigated, in a pursuit of new articles (cross-references).

A database for the electronic searches was created with the help of the EndNote X1 program. Duplicate quotations were deleted. Potentially relevant titles and abstracts were selected independently by peer reviewers VPC/CAFA and VPC/SRLP, who also took the readings of the full text, extracted information, and assessed the quality of studies. Disagreements were resolved by consensus and, where necessary, the opinion of the third auditor (external to the pair of peer reviewers) was requested.

The extraction of independent data was based on completing a standard form with relevant data about each study (full reference, country of its production, sample size, design, duration, clinical and demographic characteristics of patients, the results for the risk of severe infection, and quality assessment scores). The authors were contacted for data request needed and not contained in the published version of articles.

As to the interpretation of the frequency of severe infections, we used the classification proposed by Meyboom and Egberts<sup>14</sup> for adverse drug reactions: commonly, when they happen in 1–10% of users; unusually, 0.1–1%; and rarely, in less than 0.1%.

To evaluate the quality of observational studies, an instrument adapted, based on the Newcastle-Ottawa Scale,<sup>15</sup> was used. Three items were considered; each received one point when the required standard was met: (1) manner of selection of participants – a described sample, representative of the target population by being complete, random or systematic;

(2) percentage of losses – with description, and under 20.0%; and (3) manner of outcome assessment – an available or described measuring instrument. In those articles that were scored for the three items, the study was considered as being of high quality; articles that received points for two items were considered of intermediate quality; and when only one item was scored, the study was considered of low quality.

This study was approved by the Research Ethics Committee of the Instituto Nacional de Infectologia Evandro Chagas, Oswaldo Cruz Foundation (Opinion 017/2010).

## Results

A flow chart (Fig. 1) describing the results of bibliographic search performed was prepared. Initially, these searches in eight databases provided 1583 abstracts, of which 19 were selected for full-article reading. Apart from these abstracts, we selected 44 of the 49 abstracts obtained by cross-references, resulting in 63 full studies. Of these studies, only seven were approved and included in the systematic review: five open-label articles (Nuki et al.,<sup>16</sup> Fleischmann et al.,<sup>17</sup> Keystone et al.,<sup>18</sup> Genovese et al.,<sup>19</sup> and Schiff et al.<sup>20</sup>), one cohort-nested case-control study,<sup>21</sup> and one cohort study<sup>22</sup> (Fig. 1).

Table 1 presents the general characteristics of each study. The seven observational studies included in this review had a total duration of follow-up periods from six to 63 months, were conducted in European countries, in the United States (USA) and Mexico, and addressed 5166 patients diagnosed with RA treated with one of three drugs (anakinra, rituximab, abatacept). A meta-analysis was not performed due to the presence of multiple sources of heterogeneity among studies, and also to the limited number of publications for the studied drugs (different types of study designs, eligibility criteria, and medicines).

### Anakinra

In total, 2896 patients were treated with anakinra and evaluated in four studies lasting from 12 to 63 months: one cohort study,<sup>22</sup> two open-label articles,<sup>16,17</sup> and one cohort-nested case-control study<sup>21</sup> (Table 1).

Among the evaluated patients, the female gender prevailed, with a mean age from 52.8 to 54.8 years, with RA duration ranging from four to 13 years, and with a very active disease, according to the number of swollen or painful joints, C-reactive protein, and a disease activity index based on 28 joints (DAS28 > 5.1). In those two articles that reported on comorbidities,<sup>21,22</sup> their authors observed mainly chronic lung disease and diabetes mellitus. Concomitant use of corticosteroids ranged from 45.9% to 87.0%, and the use of various synthetic DMARDs ranged from 71.4% to 80.5% (Table 2).

Brassard et al.<sup>21</sup> only evaluated the risk of tuberculosis, adding demographic data from the use of three biological DMARDs (infliximab, etanercept, and anakinra). Despite the establishment of a contact with the author, there were no specific demographic data for anakinra, as well as for the sites of infection.

Table 3 lists the four studies in which 147 episodes of severe infection were reported in 129 (5.1%) of 2896 patients

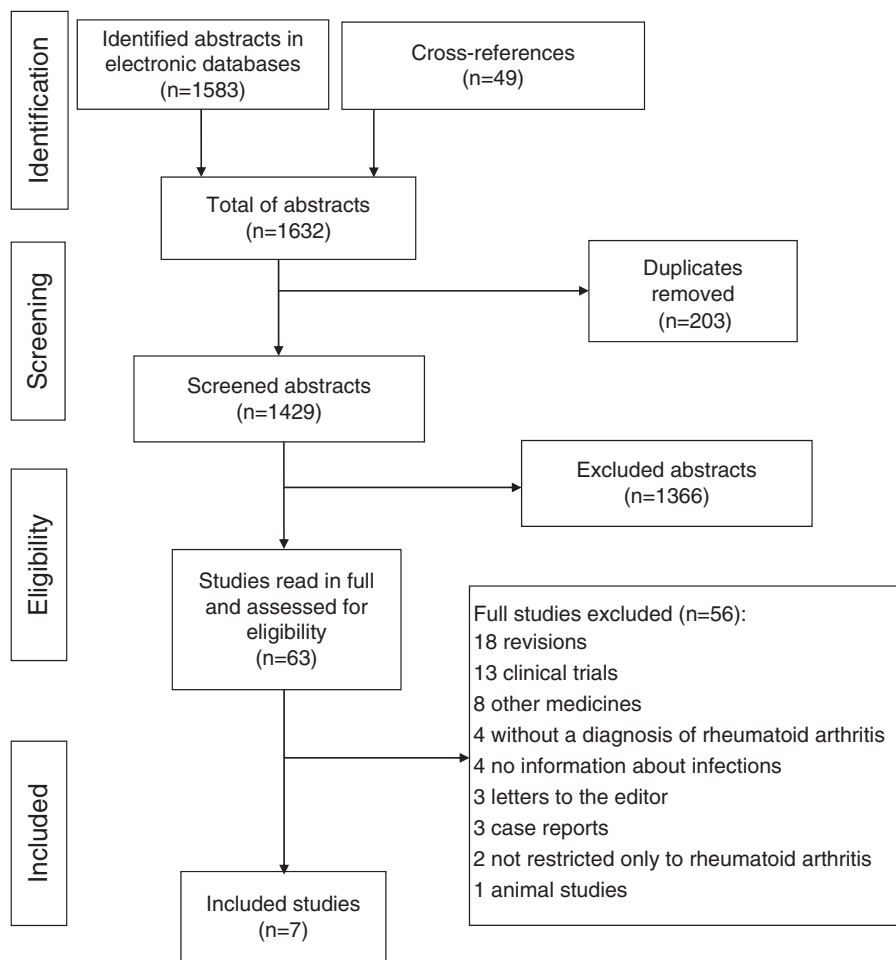


Fig. 1 – Flowchart of selection of studies for the systematic review.

treated with anakinra, along with their respective incidences (frequencies and rates).

The frequency of infection for anakinra ranged from 1.3 to 11.1%. Nuki et al.<sup>16</sup> and Brassard et al.<sup>21</sup> showed similar frequencies (1.3%). Fleischmann et al.<sup>17</sup> reported pneumonia

(23.8%) and cellulitis (14.8%) as the most frequent infections, but without detailing their clinical aspects. These authors were the only ones who reported deaths related to the use of anakinra. Nuki et al.<sup>16</sup> did not specify the sites of the four cases of severe infection and although these authors have informed

Table 1 – Description of the seven publications (2002-2009) on the risk of severe infections in patients with rheumatoid arthritis associated with use of non-anti-TNF- $\alpha$  biological DMARDs.

First author, year	Drug	Design	Place	Sample size	Duration of study in months
Nuki, <sup>a</sup> 2002 <sup>16</sup>	Anakinra	Open label	Europe (11 countries)	309	12-18
Listing, 2005 <sup>22</sup>	Anakinra	Cohort	Germany	70	18
Brassard, <sup>b</sup> 2006 <sup>21</sup>	Anakinra	Case-control nested in cohort	USA	1414	63
Fleischmann, <sup>c</sup> 2006 <sup>17</sup>	Anakinra	Open label	USA	1103	36
Keystone, 2007 <sup>18</sup>	Rituximab	Open label	-	1039	6
Genovese, 2009 <sup>19</sup>	Rituximab	Open label	9 international studies	185	12
Schiff, 2009 <sup>20</sup>	Abatacept	Open label	USA, Europe and Mexico	1046	6

DMARDs, Disease Modifying Antirheumatic Drugs; USA, United States of America.

<sup>a</sup> 218 in use of anakinra and 71 with placebo in the first six months of the double-blind clinical trial, all included in the extension phase with open label (12 months).

<sup>b</sup> The outcome was tuberculosis.

<sup>c</sup> Patients who participated in the first six months of the double-blind clinical trial and in the open-label phase for 30 months were included.

**Table 2 – Clinical and demographic characteristics of the samples of patients with rheumatoid arthritis in studies on the risk of severe infections associated with the use of non-anti-TNF- $\alpha$  biological DMARDs.**

First author, year	Drug	Sample, n	Women (%)	Mean age (SD)	Rheumatoid arthritis activity	Years of disease (SD)	Comorbidities (%)	Corticosteroids, n (%)	Use of synthetic DMARDs, n (%)	Use of synthetic DMARDs, n (SD)
Nuki, 2002 <sup>16</sup>	Anakinra	309	75.1	52.8 (13.0)	NPJ 33.5 (13.1) NSJ 25.9 (9.3) CRP 3.9 (3.8)	4.0 (2.4)	–	142 (45.9)	223 <sup>c</sup> (72.2)	1.2 <sup>c</sup> (1.0)
Listing, 2005 <sup>22</sup>	Anakinra	70	77.1	54.3 (11.6)	6.1 (1.2) <sup>a</sup>	13.0 (7.0–22.0) <sup>b</sup>	Chronic lung disease (12.9) Diabetes (11.4) Psoriasis (1.4)	61 (87.0)	50 <sup>d</sup> (71.4)	4.2 (1.9)
Brassard, 2006 <sup>21</sup>	Anakinra	1414	–	–	–	–	Diabetes. Silicosis CKD. Solid organ transplant and carcinoma (...)	–	–	–
Fleischmann, <sup>e</sup> 2006 <sup>17</sup>	Anakinra	1103	74.3	54.8 (19–85) <sup>f</sup>	NPJ 22.2 (0–68) NSJ 18.2 (0–66) CRP 2.7 (0.1–25.6)	10.3 (0.2–59.5) <sup>f</sup>	– <sup>g</sup>	654 (59.3)	888 <sup>d</sup> (80.5)	–
Keystone, 2007 <sup>18</sup>	Rituximab	1039	80.0	51.9 (11.4)	6.8 (1.0) <sup>a</sup>	11.2 (8.2)	– <sup>h</sup>	–	–	2.5 <sup>e</sup> (1.6)
Genovese, 2009 <sup>19</sup>	Rituximab	185	78.4	51.2 (12.3)	7.0 (0.9) <sup>a</sup>	11.9 (9.2)	–	–	–	4.0 <sup>f</sup> (2.4)
Schiff, 2009 <sup>20</sup>	Abatacept	1046	81.2	54.4 (12.4)	6.2 (0.7) <sup>a</sup>	11.6 (9.5)	–	611 (58.4)	1003 <sup>e</sup> (96.2)	–

DMARDs, Disease Modifying Antirheumatic Drugs; SD, standard-deviation; NPJ, number of painful joints; NSJ, number of swollen joints; CRP, C-reactive protein; n, number.

<sup>a</sup> Arthritis rheumatoid activity by DAS28 (SD) – index of activity of the disease with 28 joints.

<sup>b</sup> Interquartile range.

<sup>c</sup> Prior use of non-biological DMARDs

<sup>d</sup> Concomitant use of non-biological DMARDs.

<sup>e</sup> Patients who participated in the first six months of placebo-controlled clinical trial were included.

<sup>f</sup> (minimum and maximum).

<sup>g</sup> Diabetes and cancer excluded.

<sup>h</sup> Exclusion: changes in blood count, liver enzymes and creatinine.

**Table 3 – Results relative to the risk of severe infections associated with the use of non-anti-TNF- $\alpha$  biological DMARDs in patients with rheumatoid arthritis.**

First author, year	Drug	Sample, n	Infected patients (number of episodes)	Severe infections % (95% CI) <sup>b</sup>	Rate of severe infections/100 person-years (95% CI)	Infection sites, n (%)	Deaths, n
Nuki, 2002 <sup>16</sup>	Anakinra	309	4 (4)	1.3 (0.4–3.3)	–	–	0 <sup>c</sup>
Listing, 2005 <sup>22</sup>	Anakinra	70	1 (2)	2.9 (0.4–9.9)	3.2 (0.4–11.5)	Arthritis: 1 Acute osteomyelitis: 1	0
Brassard, 2006 <sup>21</sup>	Anakinra	1414	19 (19)	1.3 (0.8–2.1)	–	–	0
Fleischmann, <sup>a</sup> 2006 <sup>17</sup>	Anakinra	1103	105 (122)	11.1 (9.3–13.1)	5.4 (4.5–6.4)	Pneumonia: 29 Cellulitis: 18 Sepsis: 5 Other: 70	3 (sepsis)
Keystone, 2007 <sup>18</sup>	Rituximab	1039	– (59)	5.7 (4.4–7.3)	5.1 (4.0–6.6)	UTI: – Bronchitis: – Sepsis: –	2 (bronchopneumonia and sepsis)
Genovese, 2009 <sup>19</sup>	Rituximab	185	12 (13)	7.0 (3.8–11.7)	7.0 (4.1–12.0)	UTI: – Gastroenteritis: 4 Pneumonia: 2 Diverticulitis: 2 Bronchitis: 1 UTI: 2 Cellulitis: 1 Septic arthritis: 1	0
Schiff, 2009 <sup>20</sup>	Abatacept	1046	25 (25)	2.4 (1.6–3.5)	–	Pneumonia: 6 Bronchitis: 3	0

CI 95%, confidence interval of 95%; URTI, upper respiratory tract infection; UTI, urinary tract infection.

<sup>a</sup> Patients who participated in the first six months of the placebo-controlled clinical trial were included.

<sup>b</sup> The WinPepi program was used for calculations, with 95% CI, Fisher's exact test.

<sup>c</sup> The author of this article reported the occurrence of two deaths not attributed to anakinra.

two deaths, they did not consider anakinra as a causal factor. Listing et al.<sup>22</sup> reported a patient who developed septic arthritis, which progressed to osteomyelitis.

Three studies<sup>17,21,22</sup> were classified as of intermediate quality, and a fourth study received a low-qualification<sup>16</sup> (Table 4).

### Rituximab

Rituximab was administered in 1224 patients evaluated in two open-label clinical trials with durations from six<sup>18</sup> to 12<sup>19</sup> months (Table 1). Here too female gender prevailed, with a mean age of 51.8 years, with high RA activity, according to DAS28 (>5.1), and with a mean disease duration ranging from 11 to 12 years (Table 2).

Table 3 lists the two studies related to rituximab in which 72 episodes of severe infection (5.9%) were reported in the total number of patients treated, and the highest incidence was noted in the study by Genovese et al.<sup>19</sup> These infections occurred in various sites, particularly upper respiratory tract (URT), urinary tract, and gastrointestinal tract.

Although Keystone et al.<sup>18</sup> have not specified all severe infection sites, these authors reported two deaths attributed to the use of rituximab: one of them due to bronchopneumonia and the other due to neutropenic sepsis after the use of trimethoprim.

Both studies<sup>18,19</sup> were classified as high-quality trials (Table 4).

### Abatacept and tocilizumab

Only an open-label clinical trial lasting six months evaluated abatacept.<sup>20</sup> The authors included 1046 patients with similar characteristics as to gender, age, and RA duration and activity reported in the studies related to anakinra and rituximab. Pneumonia and bronchitis were the main types of infection observed (Tables 2 and 3). The quality of the Schiff et al.<sup>20</sup> study was considered intermediate (Table 4). In the period of the review, no observational study evaluated infections in RA patients taking tocilizumab.

## Discussion

This revision compiled information of 5166 RA patients taking anakinra, rituximab, or abatacept, of which at least 166 had severe infections – 5.1% with anakinra, 5.9% with rituximab, and 2.4% with abatacept, with events characterized as common.<sup>14</sup> Only one study included<sup>16</sup> was considered of low quality, and the remaining trials had scored for at least two of the three evaluated quality criteria.

**Table 4 – Quality assessment of selected studies on the risk of severe infections in patients with rheumatoid arthritis associated with the use of non-anti-TNF- $\alpha$  biological DMARDs using an instrument based on the Newcastle-Ottawa Scale. Assessment of each item (selection of participants, losses, outcome, and selection of variables) and of the total score.**

First author, year	Selection of participants <sup>a</sup>	Losses <sup>b</sup>	Outcome <sup>c</sup>	Total score
Nuki, 2002 <sup>16</sup>	1	0	0	1
Listing, 2005 <sup>22</sup>	1	0	1	2
Brassard, 2006 <sup>21</sup>	1	0	1	2
Fleischmann, 2006 <sup>17</sup>	1	0	1	2
Keystone, 2007 <sup>18</sup>	1	1	1	3
Genovese, 2009 <sup>19</sup>	1	1	1	3
Schiff, 2009 <sup>20</sup>	1	1	0	2

DMARDs, Disease Modifying Antirheumatic Drugs.

<sup>a</sup> Selection of participants – 1 point for described sample representative of the population (complete, random or systematic).

<sup>b</sup> Losses – 1 point for proportion of described losses under 20.0%.

<sup>c</sup> Outcome evaluation – 1 point for available or described outcome measurement instrument.

The strengths of this review consist of the wide search conducted, of the broad definition of severe infections, and of its originality, taking into account that, although other SRs from observational studies have been published, such studies do not separately evaluate these same drugs. We detected only one review<sup>23</sup> of observational studies that, although assessing the safety of the therapeutic drugs evaluated in this study, presented their results collectively, also including TNF- $\alpha$  antagonists.

Curtis et al.<sup>24</sup> described a cohort (1998–2011) in which the rates of severe bacterial infections associated with the use of rituximab were 4.4 (95% CI 3.1–6.4) and, for abatacept, 2.8 (95% CI 1.7–4.7), per 100 patient-years. Our results were similar since the frequency of infection was also higher for rituximab versus abatacept.

A meta-analysis published by Singh et al.,<sup>25</sup> which evaluated severe infection in patients with RA treated with nine biologic drugs, included these three medications studied in our SR, but the authors did not include observational studies and presented collective results for the nine drugs, showing an increase in severe infections with the use of biologicals in conventional doses (OR = 1.90; 95% CI 1.50–2.39).

The incidence of infections related to the use of abatacept in this study (2.4%), possibly due to the short follow-up period (six months) of the single identified trial,<sup>20</sup> was similar to the incidence found by Salliot et al.<sup>11</sup> (2.5%) in a randomized trial lasting 12 months.<sup>26</sup>

In this SR, severe infection rates for anakinra were heterogeneous, ranging from 1.3% in the smaller follow-up studies (Nuki et al.<sup>16</sup> – 12 months, and Listing et al.<sup>22</sup> – 18 months) to 11.1% in the study with the largest sample (1103 patients) and with a 36-month follow-up.<sup>17</sup> In an SR that included four clinical trials with a six-month duration, Salliot et al.<sup>11</sup> found only 1.4% of severe infections.

In the studies included in our SR which evaluated rituximab,<sup>18,19</sup> the follow-up times, of six to 12 months, were similar to those of the three trials included by Salliot et al.<sup>11</sup> Thus, the highest frequency of severe infections attributed by us to rituximab could be partially credited to the inclusion criterion of Keystone et al.,<sup>17</sup> who admitted patients diagnosed with diabetes mellitus, unlike the case in Salliot et al.'s SR.<sup>11</sup>

In the comparison of our SR versus SRs published by Salliot et al.<sup>11</sup> and Storage et al.,<sup>4</sup> we observed that the respiratory

tract is the main site of infection with respect to anakinra and abatacept. However, with the use of rituximab, urinary and gastrointestinal tracts (in addition to the respiratory tract) are also main sites of severe infection, both in our SR as in Salliot et al.<sup>11</sup>

The number of published observational studies on adverse events with the use of non-TNF- $\alpha$  antagonist DMARDs is scarce. This is a limitation that affects the present review and also other published reviews on this topic.<sup>11,27</sup>

We emphasize that in addition to the fact that severe infections have occurred with a frequency considered as common, these infections have resulted in deaths (three in 125 severe infections with anakinra, two in 72 with rituximab, and zero with abatacept). If we take into account that the maximum follow-up time in most of the studies analyzed was only about three years, not allowing the observation of a greater number of fatal cases, we emphasize the importance of SRs to the clinical practice of rheumatology. Considering the risk of severe infections brought about by these drugs, patients should have their respiratory and urinary tracts regularly monitored with an active surveillance for infections, particularly those more severe ones, in order to prevent conditions such as bronchopneumonia or sepsis.

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## Conflicts of interest

The authors declare no conflicts of interest.

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