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REVIEW

Incidence density of serious infection, opportunistic infection, and tuberculosis associated with biologic treatment in patients with rheumatoid arthritis – a systematic evaluation of the literature

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Abstract: Summary data on the incidence density (ie, incidence per person-year [PY]) of serious infection, opportunistic infection, and tuberculosis associated with each of the nine biologic therapies currently indicated in rheumatoid arthritis patients are not available. To summarize these data, a systematic review was conducted with searches on PubMed and Embase of literature ranging from January 1998 to November 2011. Incidence density was extracted and reported using the definitions from the respective publications. If the incidence density was not reported, estimation was made using available information. A total of 72 published studies met the inclusion criteria and were reviewed, including 44 clinical trials, open-label extension studies, or meta-analyses, and 28 observational studies. Additional calculation of the incidence density was performed in 12 studies for serious infection and in 13 studies for opportunistic infection or tuberculosis. The incidence of serious infection was consistent across studies and biologic therapies, ranging from 0 to 11/100 PY but mainly clustered from 2 to 6/100 PY. Fewer incidence data were available for opportunistic infection and tuberculosis. The incidence of opportunistic infection and tuberculosis ranged widely, from 0.01 to 3.0/100 PY and 0.01 to 2.6/100 PY, respectively. The data on serious infection may be used to evaluate the public health risk and benefit of biologic treatment. They may also serve as a point of reference for future studies. The limited data on opportunistic infection and the lack of a consistent definition of opportunistic infection invite caution for a benchmark rate for opportunistic infection as a composite category.

Keywords: DMARD, biologic, review, safety, infection, adverse event

Introduction

Rheumatoid arthritis (RA) is a form of inflammatory arthritis characterized by joint and systemic inflammation that can lead to significant disability, morbidity, and increased mortality. Treatment options for RA include nonbiologic (traditional) disease-modifying antirheumatic drugs (DMARDs), often used as a single agent or in combination, and newer biologic DMARDs, which are most commonly used in combination with methotrexate (MTX).[1] As of November 2011, there were nine biologic DMARDs approved in the United States for the treatment of RA, targeting different B- and T-cell pathways, including five tumor necrosis factor (TNF) inhibitors, an anti-interleukin (IL)-1, an anti-CTLA4, an anti-CD20, and an anti-IL-6. The treatment objective is to regulate the activation of the immune system and reduce inflammation.

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However, both traditional and biologic DMARDs can cause some degree of immunosuppression, potentially exposing patients to a higher risk of contracting infections. Therefore, among others, infections can be a significant side effect of RA treatment.[2,3]

Many observational studies, meta-analyses, and literature reviews have examined whether biologic therapies increase the risk of serious infection (SI), although the findings were inconsistent.[2,4–6] Given the rarity of opportunistic infections (OIs), few summary data were available for this outcome. Tuberculosis (TB), sometimes considered an OI, may be associated with biologic therapies.[7,8] Although the majority of studies focused on the association of biologic therapies and the risk of SI, summary data on the absolute incidence of SI, OI, and TB associated with exposure to biologic DMARDs in RA patients are not available. Assessing the absolute incidence of infections associated with biologic DMARDs is important and necessary to guide treatment decisions and facilitate the assessment of each drug's public health risk and benefit. Such data can also provide a benchmark for future studies of existing or new therapies. To achieve this, the analysis that follows focuses on the incidence density (ie, incidence rate per person-time) of SI, OI, and TB in RA patients treated with biologic DMARDs and MTX.

Methods

A systematic review of the literature following the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines was conducted. Searches on PubMed and Embase included the following keywords: rheumatoid arthritis, [incidence or rate or frequency], and [safety or infection or tuberculosis], in combination with each of the following terms: etanercept, infliximab, adalimumab, certolizumab, golimumab, rituximab, abatacept, anakinra, tocilizumab, and methotrexate. A manual search of articles cited in the meta-analyses or review papers was also conducted. For most molecules, only papers published from 2001 and onward were considered. For MTX and older molecules like infliximab or anakinra, papers published from 1998 and onward were included. The search was conducted by the lead author and validated by a librarian. They discussed the search results and came to a consensus on inclusion. From an initial review of the abstracts, the list of articles was then narrowed to meta-analyses, randomized clinical trials (RCTs) or their open-label extensions (OLEs), and observational safety studies. The following criteria were used to exclude articles: lack of an abstract, studies with less than 100 subjects in the treatment group, no English version available, review articles, and case reports. If for a particular molecule there were already five or more clinical trials that reported the incidence density, we excluded those trials that reported only the cumulative incidence (ie, proportions of infected patients), but did not report the incidence density. If there were several articles from the same study, each with varying follow-up, only the most recent article (ie, the longest follow-up) was used, unless the earlier article presented the incidence density and the later article(s) did not. Details of the search and its results are presented in Figure 1.

The overall incidence density of SI, OI, and TB was extracted and reported using the definitions from the respective publications. If the overall incidence density was not available, the range of incidence by doses was reported instead. The definition of SI and OI was noted for each study if available. In clinical trials that did not report the incidence density, the incidence density was estimated as the ratio of the number of cases over the total person-time of follow-up. If the exact total person-time was not provided, it was calculated as the product of the number of subjects at the beginning of the follow-up and the average duration of follow-up. In some cases in which only the patient-disposition information was available, an assumption had to be made that withdrawals from the trial were evenly distributed during the follow-up to be able to estimate the total person-time. The following formula was used:

$$PT = T \times (N_1 + N_2)/2$$

where PT was the person-time, N_1 was the number of subjects at the beginning of the follow-up, N_2 was the number of subjects at the end of the follow-up, and T was the duration of the follow-up period. The results were grouped into two main categories, namely evidence from clinical trials and from observational studies.

Results

In total, 72 literature articles met the inclusion criteria and were reviewed. Among them, 44 were RCTs, OLEs, or meta-analyses of clinical trials, and 28 were observational studies. In RCT or OLE studies, SI was often defined as an infection that required hospitalization or intravenous (IV) antibiotics or that met the regulatory definition of a serious adverse event (SAE, ie, events that are fatal, life-threatening, requiring or prolonging hospitalization, resulting in persistent or significant disability, or other events that are medically significant) (Table 1). In observational studies, the majority

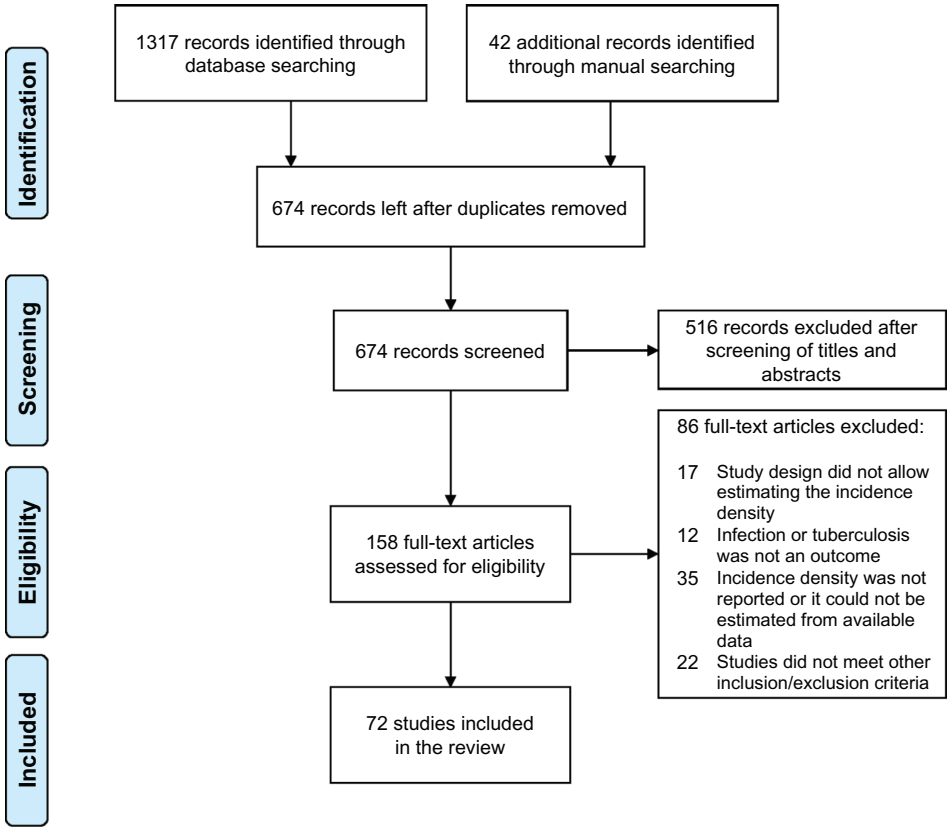

Figure 1 Flow diagram of the systematic search.

of studies defined SIs as those requiring hospitalization. Some observational studies defined an SI as one requiring hospitalization, IV antibiotics, having a fatal outcome, or used a physician diagnosis of SI (Table 2). The definition of OI was often not presented in published studies. In some clinical trials, OIs were defined using the US Centers for Disease Control and Prevention's criteria.[9]

In most RCTs with biologics in RA, MTX is used as a stable background medication in all treatment groups including the controls. The majority of RCTs did not report the incidence of infections in the control group. Available data for MTX mostly came from the control group in clinical trials or from observational studies with biologic DMARDs. Among the 72 articles reviewed, additional analyses were conducted to estimate the incidence density of SI in 12[10–21] articles and of OI or TB in 13[10,12–16,22–28] articles, of which all were reporting results from clinical trials or their extensions (estimated figures are noted in Table 1). The calculated incidence density was generally consistent with the range of incidence density from studies that provided the exact incidence. Among the molecules, infliximab and golimumab were the two biologics that required the majority of calculations for the incidence density.

Serious infections

The incidence of SI across biologic DMARDs ranged from 0 to 11.1 per 100 person-years (PY). Excluding one trial that reported no SIs,[29] all studies were in the range of ~2–11 per 100 PY, and the majority of studies reported a narrower range of ~2–6/100 PY (Tables 1 and 2). Results from observational studies were consistent with those from clinical trials. Regarding TNF inhibitors or biologic DMARDs as a group, observational studies produced results that were similar to the data for individual molecules. Among observational study participants, the ranges of incidence of SI associated with TNF inhibitors and biologic DMARDs (including TNF inhibitors and non-TNF inhibitors) were 2.2–10.4/100 PY and 4.6–7.0/100 PY, respectively (Table 2). The former was also consistent with results of a meta-analysis of 18 RCTs in more than 8800 RA patients that reported the incidence of SI associated with TNF inhibitors to be 3.6/100 PY.[4] The corresponding incidence associated with MTX ranged from 1.0 to 8.8/100 PY (Table 1), which was not different from the range observed for nonbiologic DMARDs as a group (1.3–9.6/100 PY). (Table 2)

Among RCTs or OLEs and excluding meta-analyses, there was no important difference in the distribution of

Table 1 Incidence of SIs, OIs, and TB in RA patients receiving biologic DMARDs and methotrexate among clinical trial participants

Source of information	Study information	Definition of SI and OI[a]	Number of subjects (n)[b]	Incidence per 100 PY	
				SI	OI or TB
Etanercept (TNF inhibitor)					
Klareskog et al[49]	5-year OLE study	SI: infection that meets criteria for SAE	549	6.4	No OI, no TB
Weinblatt et al[22]	OLE study, up to 10 years of follow-up	SI: infection that results in death, requires hospitalization or IV antibiotics OI: CDC's definition for AIDS[9]	558 early RA, 714 long-lasting RA	2.6 for early RA, 4.4 for long-lasting RA	OI: 0.03[c] for early RA; 0.09[c] for long-lasting RA; no TB
Gottlieb et al[47]	Meta-analysis of 49 clinical trials of etanercept	SI: infection that meets criteria for SAE OI: CDC's definition for AIDS[9]	6973	3.75	OI: 0.12[d]
Weisman et al[50]	RCT safety in RA patients with at least 1 comorbidity, 16 weeks follow-up	SI: hospitalized infection or requires IV antibiotics	266	11.1	No OI
Moreland et al[51]	Pooled analysis of 7 RCTs and 1 OLE, up to 7 years follow-up	SI: hospitalized infection or requires IV antibiotics	714	4.2	No OI, no TB
Infliximab (TNF inhibitor)					
Delabaye and De Keyser[10]	OLE, 74 weeks follow-up	SI: infection that meets criteria for SAE	575	7.8[c]	OI: 1.32[c] TB: 0.66[c]
Schiff et al[41]	RCT, 52 weeks follow-up		165	9.2	OI: 2.6[d]
Maini et al[11]	RCT, 30 weeks follow-up	SI: life-threatening or requiring hospital treatment	340	3.9[c]	
St Clair et al[12]	RCT, 54 weeks follow-up		749	5.5[c]	TB: 0.55[c]
Westhovens et al[13]	RCT, 54 weeks follow-up		721	6.3[c]	TB: 0.88[c]
Adalimumab (TNF inhibitor)					
Schiff et al[48]	Pooled analysis of clinical trial safety database of RCT and OLE	SI: infection that meets criteria for SAE OI: using the MedDRA terms	10050	5.1	OI: 0.03; TB, prior to routine TB screening, 1.3; after screening, 0.33 in Europe, 0.08 in US
Keystone et al[23]	52-week RCT	SI: hospitalized infection or requires IV antibiotics	419	3.0–6.0 depending on doses	OI: 1.12[c] TB: 0.56[c]
Weinblatt et al[52]	4-year OLE study	SI: infection that meets criteria for SAE	147	2.0	No OI; no TB
Keystone et al[53]	5-year OLE study		553	4.4	TB: 0.11
Burmester et al[54]	Meta-analyses of 19 trials of adalimumab in RA		12345	4.65	OI: 0.09 TB: 0.29
Burmester et al[24]	12-week open-label study with extension up to 60 weeks		6610	5.5	OI: 0.14[c] TB: 0.5
Certolizumab pegol (TNF inhibitor)					
Fleischmann et al[55]	RCT, 6 months follow-up		111	4.0	No OI, no TB
Smolen et al[14]	RCT, 6 months follow-up	AE classified using the MedDRA	492	6.9[c]	TB: 2.5[c]
Keystone et al[56]	RCT, 1 year follow-up	AE classified using the MedDRA	781	5.3–7.3 depending on dose	No OI, TB 0.7–1.0 depending on dose
Golimumab (TNF inhibitor)					
Keystone et al[57]	RCT, 1 year follow-up		354	3.0–10.0 depending on dose	
Kremer et al[15]	RCT, 48 weeks follow-up		626	4.5[c]	TB: 0.46[c]
Emery et al[16]	RCT, 24 weeks follow-up		317	6.2[c]	TB: 1.4[c]
Kay et al[17]	RCT, 1 year follow-up		137	2.5[c]	No OI, no TB

Table 1 (*Continued*)

Source of information	Study information	Definition of SI and OI[a]	Number of subjects (n)[b]	Incidence per 100 PY	
				SI	OI or TB
Cohen et al[58]	RCT, 24 weeks follow-up		308	5.2	No OI, no TB
van Vollenhoven et al[59]	Pooled/meta-analysis of 9 clinical trials including 2 OLE studies	SI: infections that meet criteria for SAE or require IV antibiotics OI: using the MedDRA terms	2578	4.3 (95% CI 3.8–4.9)	No OI, no TB
Keystone et al[60]	OLE up to >3 years follow-up	SI: infections that meet criteria for SAE or require IV antibiotics	1039	5.0	No OI, no TB
Emery et al[61]	RCT different doses of rituximab, safety measure at week 48		337	2.0 or 2.6 depending on doses	
Abatacept (anti-CTLA4)					
Schiff et al[41]	RCT, 1 year, and OLE, 1 year follow-up		156 (RCT) 399 (OLE)	2.0 (RCT) 1.6 (OLE)	OI: 0 (RCT) 0.2 (OLE)
Genovese et al[18]	RCT, 6 months follow-up	AE classified using the MedDRA	1457	2.1[c]	No OI, no TB
Westhovens et al[19]	RCT, 1 year follow-up	AE classified using the MedDRA	256	2.0[c]	No OI, no TB
Kremer et al[62]	OLE, 2 years follow-up	AE classified using the MedDRA	593	4.3	
Kremer et al[25]	RCT, 1 year, and OLE, 3 years follow-up	AE classified using the MedDRA	433 (RCT) 594 (OLE)	4.2 (RCT) 3.2 (OLE)	TB: 0.18[c] (OLE)
Simon et al[42]	Pooled analysis of 7 RCTs or OLEs	SI: hospitalized infection	1955 (RCT) 4134 (OLE)	3.1 (RCT) 2.7 (OLE)	TB: 0.06 (RCT) and 0.04 (OLE)
Anakinra (anti-IL-1)					
Fleischmann et al[26]	OLE, up to 3 years follow-up	SI: hospitalized infection or requires IV antibiotics	1346	5.4	OI: 0.13[c,d]
Cohen et al[29]	RCT, 24 weeks follow-up		419	0	
Fleischmann et al[20]	RCT, 6 months follow-up		1116	5.0[c]	No OI, no TB
Tocilizumab (anti-IL-6)					
Yazici et al[63]	RCT, 6 months follow-up		412	7.9	No OI, no TB
Schiff et al[27]	Pooled analysis of 5 RCTs, 2 OLEs, 1 clinical study	AE classified using the MedDRA; SAE, events fulfilled regulatory seriousness criteria	4009	4.7	OI: 0.15[c] TB: 0.08[c]
Kremer et al[64]	RCT, 1 year follow-up		797	3.7–4.0 depending on dose	
Nishimoto et al[28]	Pooled analysis of 6 RCTs and 5 OLEs	SAE, events that were fatal, life-threatening, leading to permanent or significant disability, requiring prolonged hospitalization; AE classified using the MedDRA	601	6.2	OI (HZ): 0.64 TB: 0.09[c]
Nishimoto et al[65]	OLE, 5 years follow-up	Same as Nishimoto et al[28]	143	5.7	OI (HZ): 1.1
Smolen et al[66]	RCT, 6 months follow-up		418	3.1–6.1 depending on dose	
Methotrexate					
Rigby et al[67]	RCT of ocrelizumab vs placebo in patients with stable MTX, 48 weeks follow-up		320	3.5	No OI, no TB

(*Continued*)

Table 1 (*Continued*)

Source of information	Study information	Definition of SI and OI[a]	Number of subjects (n)[b]	Incidence per 100 PY	
				SI	OI or TB
Keystone et al[23]	RCT of adalimumab vs placebo + MTX, 52 weeks follow-up	SI: hospitalized infection or requires IV antibiotics	200	1.0	
Weinblatt et al[22]	RCT of etanercept vs MTX or placebo in early or long-lasting RA patients	SI: infection associated with hospitalization or IV antibiotics	217	3.0 in early RA 5.0 in long-lasting RA	
Emery et al[61]	RCT of rituximab vs placebo + MTX, safety for MTX measured at week 24		172	8.8	
St Clair et al[12]	RCT of infliximab vs MTX + placebo, 54 weeks follow-up		291	2.1[c]	No TB
Schiff et al[21]	RCT of abatacept and infliximab vs MTX + placebo, 28 weeks follow-up for MTX + placebo		110	5.2[c]	

Notes: [a]Definition of serious and opportunistic infection is presented if available; [b]number of RA subjects exposed to the molecule; [c]estimated; [d]including TB cases.

Abbreviations: AE, adverse event; CI, confidence interval; CDC, Centers for Disease Control and Prevention; DMARDs, disease-modifying antirheumatic drugs; HZ, herpes zoster; IV, intravenous; MedDRA, Medical Dictionary for Regulatory Activities; MTX, methotrexate; OI, opportunistic infection; OLE, open-label extension; PY, person-year; RA, rheumatoid arthritis; RCT, randomized clinical trial; SAE, serious adverse event; SI, serious infection; TB, tuberculosis.

incidence density of SI by durations of follow-up, ie, 26 weeks or less, from more than 26 weeks to 54 weeks, and more than 54 weeks (Figure 2).

Opportunistic infections and tuberculosis

Incidence data for OI and TB were reported far less frequently than for SI. Among trials that reported OI and TB, the incidence of OI and TB ranged from 0.03 to 2.6/100 PY and 0.04 to 2.5/100 PY, respectively (Table 1). Two observational studies reported an incidence of OI (including TB) of 2.5–3.0/100 PY[30] and of non-TB OI of 0.15/100 PY[31] among those receiving TNF inhibitors. Several observational studies reported an incidence of TB of 0.01–0.10/100 PY,[32] 0.05–0.38/100 PY,[33–35] and 0.01–2.6/100 PY[36–38] during the period before, after, and both before and after 2001, respectively (data not shown), when TB was first recognized as a potential adverse event in patients receiving biologic therapy.[39] Among the studies that reported an incidence of TB, one was conducted in South Korea, where TB may be endemic;[36] all other studies were from the US or Western European countries.

Discussion

Despite a large number of studies on the safety of biologic treatment in RA patients, to our knowledge few summaries of the absolute incidence of SI, OI, and TB associated with biologic DMARD treatment in RA patients were available. The majority of literature reviews and meta-analyses focused on whether biologic DMARDs increased the risk of SI (ie, focused on the relative risk), but did not discuss the absolute incidence of infections. An earlier review by Furst[40] looked at the absolute incidence of infections associated with six biologics in RA patients that did not include newer biologics such as certolizumab, tocilizumab, and golimumab. Furst's review[40] presented cumulative incidence estimates or incidence-density estimates. To our knowledge, our analysis is the first that discusses incidence-density estimates of SI, OI, and TB associated with each of the nine biologics indicated in RA patients as of November 2011. The incidence of SI was relatively consistent across biologic DMARDs and between clinical trials and observational studies, ranging from ~0 to 11/100 PY. The majority of studies clustered a narrower range, approximately 2.0–6.0/100 PY. There was only one study, a 24-week clinical trial of anakinra, where no cases of SI were reported.[29] The findings of this study are inconsistent with results from the other two studies of anakinra reporting an incidence of 5.0–5.4/100 PY[20,26] (Table 1). Even though this analysis is not meant to discuss the difference in

Table 2 Incidence of serious infections in RA patients receiving biologic and nonbiologic DMARDs among observational study participants

Studies	Study information	Definition of SI	Drugs	Incidence per 100 PY[a]
Lacaille et al[68]	Retrospective cohort study using administrative data, Canada, n = 27,710, 1996–2003	Requiring hospitalization	MTX	4.5
			Immunosuppressive DMARDs	5.1
			Nonimmunosuppressive DMARDs	4.6
Lane et al[43]	Retrospective cohort study, VA system (US), n = 20,814, 1998–2005	Requiring hospitalization	Etanercept, infliximab, adalimumab	3.6
			MTX, leflunomide, azathioprine, cyclophosphamide, cyclosporine, anakinra	3.5
			Hydroxychloroquine, sulfasalazine, auranofin, injectable gold, penicillamine	3.0
Listing et al[69]	Retrospective cohort study using biologic registry, Germany, 2001–2003, n = 512 receiving etanercept, 346 infliximab, 70 anakinra	Physician diagnoses	Nonbiologic DMARDs	2.3 (1.3–3.9)
			Etanercept	6.4 (4.5–9.1)
			Infliximab	6.2 (4.0–9.5)
			Anakinra	3.2
Askling et al[44]	Cohort study using national biologic registry in Sweden, 1999–2003, n = 4167	Requiring hospitalization	TNF inhibitors	4.7 overall 4.5 1st TNF inhibitor 7.0 2nd TNF inhibitor
Dixon et al[45]	Prospective follow-up, UK (BSRBR), n = 10,755, 8659 with TNF inhibitor, 2170 with traditional DMARDs	Requiring hospitalization; IV antibiotics or death	Nonbiologic DMARDs	3.9 (3.2–4.7)
			Etanercept	5.1 (4.6–5.7)
			Infliximab	6.3 (5.6–7.0)
			Adalimumab	5.0 (4.2–6.1)
			TNF inhibitors	5.6 (5.2–6.0)
Dixon et al[70]	Prospective follow-up, UK BSRBR, n = 7666 TNF inhibitor and 1354 for traditional DMARDs	Requiring hospitalization; IV antibiotics or death	Non-biologic DMARDs	4.1 (3.1–5.4)
			Etanercept	5.1 (4.5–5.9)
			Infliximab	5.5 (4.9–6.2)
			Adalimumab	5.2 (4.0–6.6)
			TNF inhibitors	5.3 (4.9–5.8)
Favalli et al[71]	LORHEN registry (Italy), 36 months of FU after first use of TNF inhibitors, n = 1064	Requiring hospitalization; IV antibiotics, death, or significant medical risk	Etanercept	2.6 (1.0–4.1)
			Infliximab	3.9 (2.7–5.1)
			Adalimumab	3.8 (2.1–5.5)
			All	3.6 (2.8–4.4)
Galloway et al[72]	BSRBR UK, prospective FU, n = 11,798 TNF inhibitors and 3598 nonbiologic DMARDs	Requiring hospitalization; IV antibiotics or death	Nonbiologic DMARDs	3.2 (2.8–3.6)
			TNF inhibitors	4.2 (4.0–4.4)
			Etanercept	3.8 (3.5–4.2)
			Infliximab	4.6 (4.2–5.0)
			Adalimumab	4.3 (3.9–4.7)
Curtis et al[73]	Retrospective FU, claims data, US, hospitalized infections were abstracted and confirmed, incidence within 6 months of index	Requiring hospitalization	TNF inhibitors	2.9
			MTX	1.4
Curtis et al[74]	Retrospective cohort study in claims database	Requiring hospitalization	Biologic DMARDs (previous biologic-free)	4.6
			Biologic DMARDs (biological switcher)	7.0
Salliot et al[75]	Retrospective review at 1 center, 1997–2004, France, n = 709	Requiring hospitalization or life-threatening	TNF inhibitors	3.4 prior to TNF inhibitor 10.4 after TNF inhibitor
den Broeder et al[76]	Cohort study at 6 centers, 2002–2004, n = 146, Netherlands		Anakinra	0.97
Koike et al[77]	Postmarketing surveillance, Japan, n = 3881	Clinically important events	Tocilizumab	9.1
Mariette et al[78]	TNF inhibitor registries, France	Requiring hospitalization; IV antibiotics or death	TNF inhibitors	4.5–5.0 depending on registry
Komano et al[79]	Longitudinal RA registry, n = 1144; Japan	Infections meeting definition of SAE	Infliximab or etanercept	6.4
			Nonbiologic DMARDs	2.6

(*Continued*)

Table 2 (*Continued*)

Studies	Study information	Definition of SI	Drugs	Incidence per 100 PY[a]
Grijalva et al[80]	Multicenter cohort study, US, n = 10,484	Requiring hospitalization	TNF inhibitors	8.2
			Nonbiologic therapy	7.8
			Infliximab	10.3
			Adalimumab	8.7
			Etanercept	6.8
Strangfeld et al[46]	Longitudinal RA registry, Germany, n = 5044		TNF inhibitors	2.2–4.8 depending on time since treatment start
Bernatskyl 2007[81]	Nested case-control study, n = 23,733, 1980–2002, Canada	Requiring hospitalization	DMARDs (including mostly nonbiologic)	1.3
Doran et al[82]	Retrospective cohort study, 1955–1994, n = 609	Requiring hospitalization	Corticoid and nonbiologic DMARDs	9.6

Note: [a]Values in parentheses are the 95% confidence intervals.
Abbreviations: BSRBR, British Society for Rheumatology Biologics Register; DMARDs, disease-modifying antirheumatic drugs; FU, follow-up; IV, intravenous; LORHEN, Lombardy Rheumatology Network; MTX, methotrexate; PY, person-year; RA, rheumatoid arthritis; SI, serious infection; TNF, tumor necrosis factor; UK, United Kingdom; US, United States; VA, Veterans Affairs.

incidence of SI among individual biologics or between different classes of biologic DMARDs, the relative consistency of findings among the majority of approved therapies suggests that any differences, if they exist, may be small. Our review showed that there was a lack of incidence data on OI and TB, especially from observational studies. Even for clinical trials, available data on OI and TB were scarce. The ranges of incidence for OI and TB were wide – 0.01–3.0/100 PY and 0.01–2.6/100 PY, respectively (Table 3) – reflecting the limited amount of data and high variability among studies.

Estimates of the absolute incidence reported from clinical trials and observational studies may differ, given their different designs. Study subjects included in the clinical trials are often highly selected. Trials are often of small size and with short duration, making it difficult to obtain stable estimates, especially for rare outcomes. On the other hand, observational studies are conducted in less selected populations, of larger size, and with longer duration. However, follow-up procedure for adverse events in observational studies is often not as rigorous as in clinical trials, potentially leading to an underestimation of certain types of adverse event. On the other hand, capture of broadly defined or unconfirmed events may lead to overestimation. In this review, the incidence of SI reported from observational studies was relatively consistent with that from clinical trials, suggesting that infections requiring hospitalization is a reasonable definition of SIs in the observational setting. This suggests that infections requiring IV antibiotics, which were life-threatening or fatal,

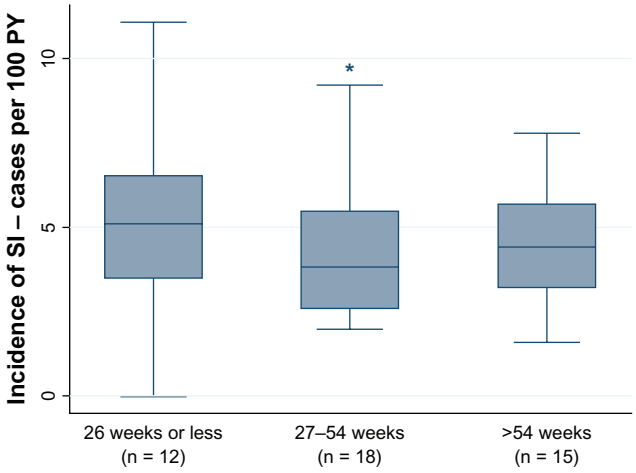

Figure 2 Incidence density of serious infections after biologic treatment by duration of follow-up – data from RCT and OLE studies only.
Abbreviations: OLE, open-label extension; PY, person-year; RCT, randomized controlled trial; SI, serious infection.

Table 3 Range of incidence density of SIs, OIs, and TB in RA patients receiving biologic DMARDs – data from RCT, OLE, and observational studies

Drugs	Incidence per 100 PY (range)		
	SI[a]	OI	TB
Rituximab	2.0–5.2	–	–
Etanercept	2.6–11.1	0.01–0.12[a]	0.01–0.11[a]
Adalimumab	2.0–8.7	0.03–1.12[a]	0.08–0.56[a]
Abatacept	1.6–4.3	0.2	0.18
Infliximab	3.9–10.3	0.29–2.6[a]	0.05–2.6[a]
Anakinra	1.0–5.4	0.13	–
Certolizumab	4.0–7.3	–	0.7–2.5
Tocilizumab	3.1–9.1	0.15–1.1	0.08–0.09
Golimumab	2.5–10.0	–	0.46–1.4
TNF inhibitors	2.2–10.4	0.15–3.0[a]	–
Biologic DMARDs	4.6–7.0	–	–
Methotrexate	1.0–8.8	–	–
Nonbiologic DMARDs and corticoid	1.3–9.6	–	–

Note: [a]Data were also from observational studies.
Abbreviations: DMARDs, disease-modifying antirheumatic drugs; OI, opportunistic infection; OLE, open-label extension; PY, person-year; RA, rheumatoid arthritis; RCT, randomized clinical trial; SI, serious infection; TB, tuberculosis; TNF, tumor necrosis factor.

or those resulting in significant medical risk, ie, the other components of the SI definition used in clinical trials, may occur relatively rarely outside the hospital setting.

In this review, we did not observe any important difference in the distribution of incidence of SI in RA patients by duration of follow-up in clinical trials or their long-term extensions. The first two categories, ie, 26 weeks or less and 26–54 weeks, were the two most common follow-up periods of RCTs; the third category, ie, more than 54 weeks, often corresponded to OLE studies. This finding is in agreement with several OLE studies that observed negligible differences in incidence of SI between the main randomized studies and the extension periods.[15,41,42] However, this qualitative assessment of the distribution of SI incidence should be interpreted with caution, because we are not comparing the statistics in a controlled setting. A meta-regression of data from 18 RCTs in RA patients suggested that the odds ratios of SI are inversely correlated with duration of the trials.[4] Several observational studies have also suggested that the risk of SI was highest within the first year after the initiation of a biologic therapy.[43–46] The larger size of observational studies and of the meta-analysis might have helped observe the trend by time on treatment, whereas smaller individual extension studies did not. This may be due to a true higher risk of SI in the first few months of therapy, but may also be in part due to the depletion of susceptible patients. Those at high risk of SI may not be prescribed treatment, or those experiencing SI may have stopped the treatment, thus leaving a healthier cohort that remains on treatment.[46]

Due to the relatively rare occurrence of OI and TB in a clinical trial setting, only a few studies reported OI and TB. Even in trials that reported OI, the definition of OI was often not presented and may vary among different reports. This lack of a consistent definition may contribute to the broad variation of incidence density reported in this area. Although some studies considered TB an OI and included TB cases in the overall calculation of OI incidence,[26,30,41,47] others did not. TB is relatively common compared to other OI; thus the inclusion of TB as an OI could artificially inflate the incidence of OI when compared to studies that do not include TB in this class. Therefore, a benchmark rate for OI as a composite category should be interpreted with caution. It is important that future studies consistently define and report OI and TB. The reported incidence of TB associated with biologic treatment in RA patients also varied greatly, in part due to the small size of studies, the rarity of TB, the difference in background incidence of TB in specific geographical regions,[36] and the intrinsic difference in the risk for TB associated with the mechanism of action of a specific agent. Given the limited data, little is known of the temporal distribution of OI and TB in RA patients treated with biologic DMARDs. It is unfortunate that larger observational studies with longer follow-up have not been able to detect OI reliably, considering that OI is not adequately captured in routine practice. Prospective registries of RA patients may be an appropriate setting to study the risk of rare events like OI and TB in RA patients, but this will require improved methods of capturing this information validly and consistently.

For the first time, we summarize here the absolute incidence density of SI, OI, and TB associated with each of the nine biologic DMARDs currently available for treatment of RA. In clinical trials, the incidence of events was reported either as a cumulative incidence or an incidence density. Because the cumulative incidence is directly related to the duration of the follow-up – ie, the longer the follow-up is, the higher the cumulative risk of experiencing the event – it is not an optimal measure to compare the risk between studies of different lengths of follow-up. In contrast, the incidence density, which takes into account the difference in follow-up time among individuals, is likely to be a better measure of disease frequency to compare between studies. Our effort to estimate the incidence density using available data in some studies that did not present incidence density helped provide information for some molecules (infliximab, golimumab).

This analysis has several limitations. The summarized range of incidence data does not discuss specifics on study inclusion/exclusion criteria, quality of the included studies, background characteristics of the study population, or variation across geographic regions. Therefore, the range of incidence presented here may not be applicable to all populations. The reported incidence density was likewise not adjusted for doses of the molecules under study. Some previous studies have suggested a dose-dependent increase in the risk of SI.[43] However, this review showed that the reported incidence densities of SI were rather consistent across studies. Most trials included patients receiving both a biologic DMARD under study and MTX, making it difficult to sort out the incidence of infections in patients receiving the molecule under study as a monotherapy. This also applied to observational studies, most of which could not obtain an incidence among those who received biologic monotherapy treatment. Thus, the incidence of infections reported in this review is not directly applicable to treatment with biologic DMARDs as monotherapy. Appropriate screening might mitigate the risk of TB reactivation in RA patients.[33,48] Earlier trials may not have had their patients screened for TB, and it was not clear what proportion of clinical trials reviewed had their patients

screened for TB prior to enrollment. The small number of studies per molecule, the limited amount of information available for infections or TB from each study, and the heterogeneity of the study designs and populations did not allow us to perform a meta-analysis with the available data.

In conclusion, this review discussed the absolute incidence density of SI, OI, and TB associated with biologic treatment in RA patients. The SI data may be used to evaluate the public health risk and benefit of each biologic treatment, as well as serving as a point of reference for future studies. The limited data on OI and TB and the lack of a consistent definition of OI invite caution for a benchmark rate for OI as a composite category.

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Disclosure

TNT and HC are employees of MedImmune, LLC. FM is a former employee of MedImmune, and is a current employee of Eli Lilly and Company.

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