

Concise report

Opportunistic infections in rheumatoid arthritis patients exposed to biologic therapy: results from the British Society for Rheumatology Biologics Register for Rheumatoid Arthritis

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Abstract

Objectives. This analysis set out to estimate the risk of opportunistic infection (OI) among patients with RA by biologic class.

Methods. The British Society for Rheumatology Biologics Register for Rheumatoid Arthritis is a prospective observational cohort study established to evaluate safety of biologic therapies. The population included adults commencing biologic therapy for RA. The primary outcome was any serious OI excluding tuberculosis (TB). Event rates were compared across biologic classes using Cox proportional hazards with adjustment for potential confounders identified *a priori*. Analysis of the incidence of TB was performed separately.

Results. In total, 19 282 patients with 106 347 years of follow-up were studied; 142 non-TB OI were identified at a rate of 134 cases/100 000 patient years (pyrs). The overall incidence of OI was not significantly different between the different drug classes; however, the rate of *Pneumocystis* infection was significantly higher with rituximab than with anti-TNF therapy (adjusted hazard ratio = 3.2, 95% CI: 1.4, 7.5). The rate of TB fell dramatically over the study period (783 cases/100 000 pyrs in 2002 to 38 cases/100 000 pyrs in 2015). The incidence of TB was significantly lower among rituximab users than anti-TNF users, with 12 cases/100 000 pyrs compared with 65 cases/100 000 pyrs.

Conclusions. The overall rate of OI was not significantly different between drug classes; however, a subtle difference in the pattern of OI was seen between the cohorts. Patient factors such as age, gender and comorbidity were the most important predictors of OI.

Key words: opportunistic, infection, biologic, rheumatoid, tuberculosis

Rheumatology key messages

- Opportunistic infections affect ~0.1% of RA patients receiving biologic therapy each year.
- Tuberculosis rates have fallen among biologic users with RA since pre-screening guidelines were introduced.
- The incidence of tuberculosis is significantly lower with rituximab than with anti-TNF in RA.

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Introduction

Modern treatment of RA has been revolutionized by the advent of biologic therapies. For most patients, these drugs represent a safe and efficacious treatment strategy; however, serious infections associated with biologic therapies are a significant concern for patients and clinicians. Registry data from the UK and Sweden have shown an increased risk of serious infection in new anti-TNF starters, especially in the first 6–12 months of therapy [1, 2].

Many of these infections will be due to the same organisms seen commonly in the general population but a small proportion will be due to opportunistic organisms that would not typically cause infections in an immunocompetent individual.

Much of the early literature on opportunistic infections (OI) comes from patients with HIV or cancer. In this setting, OI are often defined as infections that are more frequent or more severe because of immunosuppression in HIV-infected persons [3]. However, it could be argued that according to this definition all infections are OI. Winthrop *et al.* [4] published evidence-driven consensus recommendations for the reporting of OI in rheumatology clinical trials and surveillance studies, identifying 24 infections as definite OI and 11 infections as probable OI.

Clinical trials are not powered to detect a change in the incidence of rare events such as OI. The original British Society for Rheumatology Biologics Register for Rheumatoid Arthritis (BSRBR-RA) TNF inhibitor (TNFi) recruitment target was chosen to provide adequate statistical power to ascertain a doubling in the incidence of lymphoma between the cohorts. This was based on lymphoma having an incidence of approximately 1 in 1000. As such, the BSRBR-RA is powered to detect differences in the rates of other rare events following TNFi with a similar incidence.

The primary outcome of this analysis was to estimate the incidence of serious (defined as requiring hospitalization, intravenous antimicrobial therapy or resulting in death) OI among individuals with RA treated with biologic therapy.

Methods

We used data from the BSRBR-RA, a prospective observational cohort study established in 2001, to evaluate the safety of biologic therapies. Initially, there were just three cohorts of patients (etanercept, infliximab and a comparator group of patients treated with existing DMARDs). Further cohorts studying adalimumab, rituximab, certolizumab-pegol and tocilizumab have since been recruited. The BSRBR-RA methodology has been described previously [5].

The population studied were adults commencing biologic therapy for RA. Subjects were considered at risk from treatment start until the date of OI, five half-lives after drug stop, death or last follow-up before June 2016, whichever came first. For the rituximab cohort patients were considered at risk until 270 days after the last infusion. If two infusions were separated by >270 days, the subject was considered to have been continuously exposed, reflecting the varying dosing frequency of rituximab.

We chose to analyse all anti-TNF drugs together, as given that they share a common mode of action we would expect to see a similar pattern of OI across the drugs and to increase the power of the study. Sensitivity analyses were performed to see if there was any in-class variation in the rates of OI.

The primary outcome was any serious OI as defined by Winthrop *et al.* [4], excluding tuberculosis (TB). Both definite

and probable OI were included in analysis, although a sensitivity analysis was performed including only definite OI.

We made an *a priori* decision to exclude TB from the main analysis, for two reasons. First, it has previously been reported within the BSRBR-RA [6]. Secondly, guidelines and pre-screening for TB have changed over time with increasing availability of IFN γ release assays, thus comparison of newer cohorts of biologic-treated patients with older cohorts would lead to biased results. A separate analysis looking only at TB was performed.

All OI were validated independently by two clinicians (A.I.R. and E.P.) who were blinded to the treatment exposure. Differences in coding were resolved by discussion or, if consensus could not be reached, by a third clinician (J.B.G.).

Event rates were compared across biologic classes using Cox proportional hazards with adjustment for age, gender, disease severity and duration, smoking, seropositivity and polypharmacy (as a surrogate for comorbidity). Missing baseline data were imputed using the Imputation by Chained Equations, ICE package in Stata 14 (StataCorp, College Station, TX, USA).

The BSRBR-RA was approved by the North-West Multicentre Research Ethics Committee (MREC 00/8/053, IRAS: 64202) and all patients gave written informed consent; this analysis did not require additional ethical approval.

Results

In total, 19 282 patients with 106 347 years of follow-up were studied. There were 85 331 years of patient follow-up in the anti-TNF cohort comprising of 36 663 years on etanercept, 17 670 years on infliximab, 28 751 years on adalimumab and 2247 years on certolizumab-pegol. Some 5072 patients were exposed to rituximab with 17 154 years of follow-up and 2171 patients were exposed to tocilizumab with 3861 years of follow-up. No patients receiving a biosimilar product were included in this analysis. Baseline characteristics are presented in supplementary Table S1, available at *Rheumatology* online.

One hundred and sixty-one events were identified, of which 142 were validated as OI by the two blinded assessors. The remaining 19 events did not meet criteria for inclusion. The overall incidence of non-TB OI was 134 cases/100 000 patient years (pyrs). The most common OI seen with anti-TNF therapy were herpes zoster (HZ) infection (54/114 cases), *Pneumocystis jirovecii* pneumonia (PJP, 15/114 cases) and legionella (11/114 cases). With rituximab therapy, PJP was the most frequently observed OI (9/25 cases) followed by HZ (7/25 cases). The follow-up was shorter in the tocilizumab cohort with just three OI recorded, all with different organisms.

There was no difference in overall rates of OI across biologics in the unadjusted or fully adjusted model. Male gender, increasing age, DAS28, HAQ, steroid usage and polypharmacy were all predictors of OI in a univariate model. Age, gender and polypharmacy remained significant predictors in the multivariable model.

Pattern of non-TB OI by drug

HZ was the most common OI seen in the register, with an incidence of 59 cases/100 000 pyrs. There was no difference in the rate of serious HZ by drug class.

PJP infections were rare, with 23 cases/100 000 pyrs (95% CI: 16, 35) though a higher rate was observed in the rituximab cohort at 52 cases/100 000 pyrs (95% CI: 27, 100). The increased rate observed with rituximab compared with anti-TNF was statistically significant in both unadjusted (HR = 3.7, 95% CI: 1.6, 8.6) and adjusted models (adjusted HR = 3.2, 95% CI: 1.4, 7.5).

There was no statistically significant difference in the rates of *Aspergillus* infection between the drugs classes. The remaining OI were too rare to allow any comparative analysis between drug classes. No cases of progressive multifocal leukoencephalopathy (PML) were recorded with any of the drugs. The breakdown of each individual type of OI is shown in supplementary Table S2, available at *Rheumatology* online.

Tuberculosis infections

Fig. 1A shows the incidence of TB across all biologic users in the BSRBR-RA by calendar year. The rate has fallen from 783 cases/100 000 pyrs in 2002 to 38 cases/100 000 pyrs in 2015, the latest year that complete data were available for. Data from Public Health England were extracted to allow comparison of the rate from the BSRBR-RA with that seen in the general population in England, and the results are shown in Fig. 1 [7].

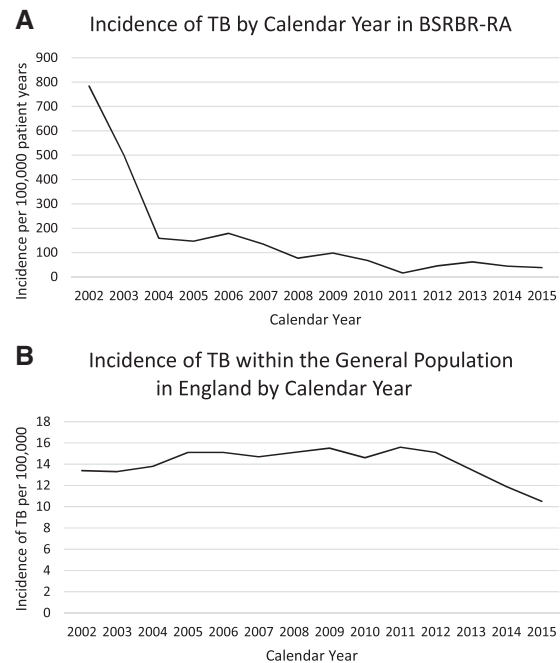
The incidence of TB was significantly lower among rituximab users than anti-TNF users, with 12 cases recorded per 100 000 pyrs compared with 65 cases/100 000 pyrs (see Table 1). The difference remained statistically significant in a sensitivity analysis looking at individuals who started biologic therapy after the year 2005.

The rate of TB by each individual anti-TNF drug is shown in supplementary Table S3, available at *Rheumatology* online. Etanercept had the lowest incidence of TB of all the anti-TNF drugs but the rate was still significantly higher than the rate with rituximab with an adjusted HR = 4.63 (95% CI: 1.06, 20.2).

Discussion

This study is reassuring, showing that the overall incidence of OI is low at just over 1 case in 1000 pyrs. This is similar to results from the French Research Axed on Tolerance of Biotherapies registry, which found that the incidence of OI was 152 cases/100 000 years among anti-TNF users [8]. There appeared to be no difference in the overall rate of non-TB OI between the drugs, although

Fig. 1 Incidence of TB by calendar year in the BSRBR-RA compared with the general population



(A) Falling rate of TB by calendar year among all biologic users within the BSRBR-RA. (B) Rate of TB in the general population over the same time period—data provided by Public Health England. TB: tuberculosis; BSRBR-RA: British Society for Rheumatology Biologics Register for RA.

TABLE 1 Incidence of OI and TB by drug class

	All biologics	Anti-TNF	Rituximab	Tocilizumab
Opportunistic infections excluding TB				
Survival time follow-up, years	106 347	85 331	17 154	3861
Number of OI	142	114	25	3
Unadjusted OI incidence rate per 100 000 pyrs (95% CI)	134 (113, 157)	134 (111, 161)	146 (98, 217)	78 (25, 241)
Unadjusted hazard ratio (95% CI)	N/A	Ref.	1.18 (0.76, 1.83)	0.56 (0.18, 1.76)
Adjusted hazard ratio (95% CI)	N/A	Ref.	0.96 (0.62, 1.50)	0.52 (0.17, 1.65)
TB infections				
Number of TB cases	59	56	2	1
Incidence of TB per 100 000 pyrs (95% CI)	55 (43, 71)	65 (50, 85)	12 (3, 46)	26 (4, 183)
Adjusted HR for TB (95% CI)	N/A	Ref.	0.16 (0.04, 0.67)	0.35 (0.05, 2.55)

OI: opportunistic infections, TB: tuberculosis, HR: hazard ratio, pyrs: patient years.

given the small size of the tocilizumab cohort it is difficult to draw firm conclusions.

Subtle differences were seen in the pattern of non-TB OI seen between drug classes. Most striking was the higher incidence of PJP observed with rituximab. Animal models have shown that B cells play a vital role in generation of CD4⁺ memory T cells in response to PJP infection in the lungs [9]. The link between PJP and rituximab has been described before, although the majority of documented cases come from the lymphoma treatment population [10]. Corticosteroid exposure is a strong predictor of developing PJP. In our cohort, 64% of PJP cases were on oral steroids at the time of infection. A meta-analysis of rituximab-treated lymphoma patients demonstrated that PJP prophylaxis is highly effective at preventing subsequent infection [11]. It is important to remember that PJP infection is rare, and while these data would not support PJP prophylaxis for all rituximab users it may be appropriate in certain high-risk individuals.

No cases of PML were recorded despite over 100 000 pyrs of follow-up. This supports previous literature that PML is extremely rare among biologic users with RA [12].

The incidence of TB in biologic-treated patients has fallen dramatically since the inception of the BSRBR-RA. This is not reflected in the general population, where the rate of TB has remained stable over the same period. The falling incidence observed in the BSRBR-RA is likely to reflect improved screening and treatment of latent TB following the introduction of British Thoracic Society Guidelines in 2005 [13]. Even in recent years the rate of TB appears higher in the BSRBR-RA than that observed in the general population, although the figures are obtained using different methodology so it is difficult to draw strong conclusions about relative risk. The link between TNFi and TB has previously been established [6]. Keane *et al.* [14] showed that patients with TB infection on infliximab failed to form granulomas and had reduced macrophage apoptosis, hinting at a potential mechanism for why a higher rate of TB is seen with anti-TNF when compared with other biologics with different modes of action.

Previous studies using registries have mostly compared the risk of starting a biologic with the risk of continuing current DMARDs in patients with severe disease. This is an increasingly irrelevant comparison, as most clinicians faced with a patient who has not responded to DMARDs will opt to start a biologic. When choosing a biologic, safety is an important consideration, particularly in high-risk groups. It is therefore vital to have directly comparative studies of safety between biologic drugs.

The main strengths of this study are the use of real world data from a large sample of biologic-treated patients with a long follow-up. It was interesting to note that 58% of OI and 55% of TB occurred among individuals who had been on a biologic for >1 year. These cases might not have been detected in many clinical trials that have shorter follow-up periods.

The main limitations of this study are those that will affect any observational study. As the patients are not randomized to each treatment arm there will be an element

of bias introduced. Most rituximab (93%) and tocilizumab (89%) users in our cohort had already been exposed to another biologic, including TNFi, and it is unclear what impact sequential biologic exposure has on infection risk. Conversely, patients who experienced an OI on a TNFi may not have progressed on to sequential biologic therapy, thus identifying a so-called healthier user cohort, at least in terms of infection risk. There is likely to be channelling bias, with rheumatologists more likely to use a drug that they perceive to be safe in individuals who are at risk of infection. Whilst we have tried to adjust for patient factors in the model, there will always be some unmeasured confounders that we cannot adjust for.

Conclusions

OI are rare among individuals with RA treated with biologics. In this analysis, drug choice was not a significant predictor of the overall rates of OI, although subtle differences in the type of OI observed were seen between drug classes. The strongest predictors of OI were unmodifiable patient factors such as age, gender and comorbidity.

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Supplementary data

Supplementary data are available at *Rheumatology* online.

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