Association between disease activity and risk of serious infections in subjects with rheumatoid arthritis treated with etanercept or disease-modifying anti-rheumatic drugs

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Abstract

Objective

To determine the risk of serious infection in patients with rheumatoid arthritis (RA) receiving etanercept (ETN) or disease-modifying anti-rheumatic drugs (DMARDs) and to identify factors that predict a higher risk.

Methods

Five-year data from the British Society of Rheumatology Biologics Register (BSRBR), a prospective observational study of patients with active RA treated with ETN, were used. These data were compared with a cohort of patients receiving DMARDs with active RA.

Results

Total follow-up was 19,964 patient-years (py; ETN, 14,381 py; DMARDs, 5583 py). Over the study period, 651 first-recorded serious infections were reported (ETN, 469 [39.9 per 1000 py]; DMARDs, 182 [35.0 per 1000 py]). Overall the risk of serious infection was similar for the 2 treatments; however, in the first 6 months of treatment the hazard ratio (HR) was higher in the ETN than the DMARD group (1.979; p=0.015). A linear association was observed between the serious infection rate and disease-activity score in 28 joints (DAS28) in patients from each treatment group and overall (DAS28 <4, 27.1 per 1000 py; DAS28 ≥8, 64.4 per 1000 py; 7.5% increase in serious infection for each unit increase of DAS28 score at baseline). In a time-dependent analysis, a DAS28 change of 1 unit during follow-up predicted a 27% increase in serious infection rates.

Conclusions

No significant increase in the risk of serious infection was observed with ETN versus DMARDs over the 5-year study; a linear relationship existed between the serious infection rate and disease activity, as measured by DAS28.

Key words

rheumatoid arthritis, etanercept, disease-modifying anti-rheumatic drugs, serious infection

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Introduction

In patients with rheumatoid arthritis (RA), tumour necrosis factor inhibitors (TNF-I) have been shown to reduce disease activity and improve patient outcomes in both clinical trials and observational studies (1-7). However, due to the important role played by TNF in the regulation of immune cells, safety concerns were raised relating to adverse events associated with TNF inhibition. In order to address these concerns, disease registers were established in many countries (8, 9), including the British Society for Rheumatology Biologics Register (BSRBR) in the United Kingdom (10).

Specific safety concerns were raised in relation to the potential impact of TNF-I upon rates of malignancies and serious infections. The incidence of serious infection is increased in patients with RA (11) and meta-analyses of randomised clinical trials signalled that this risk was amplified following initiation with a TNF-I (12, 13). Register studies have supported this association. A study using data from the BSRBR reported an increased risk of serious infection associated with TNF-I with a 20% increased hazard ratio (HR) (14), whereas findings from the RABBIT study found an approximate 2-fold increase (15). In a Swedish study, a 1.4-fold increase was observed in the first year of follow-up, which was reduced in subsequent years (16).

The increased risk of infection observed in these studies may in fact be due to an association with exacerbation of disease severity. Findings from the CORRONA registry have shown that infection risk is associated with increased disease activity (17), and an increase in disease severity may underlie the decision to initiate the patients on TNF-I therapy.

The purpose of this study was to determine if there was an increase in the likelihood of serious infections in subjects who had switched from conventional disease-modifying anti-rheumatic drug (DMARD) therapy to one particular TNF-I, etanercept (ETN), and to investigate other patient risk factors, including disease activity, that determine risk of serious infection.

Methods

This study used data from the BSRBR (10). Briefly, the BSRBR is a national, prospective register established to investigate the safety of biologic agents used in the treatment of rheumatological conditions. It is estimated that during recruitment more than 80% of patients treated with TNF-I in the United Kingdom were included in the register (14). The BSRBR began recruiting in October 2001. A comparative cohort of patients with active RA disease (defined as the disease activity score 28 [DAS28] >4.2) and treated with DMARDs was also recruited from December 2002. Whilst all TNF-I agents are included in the BSRBR, due to the contractual arrangements between the BSRBR and supporting pharmaceutical companies, Pfizer only had access to data relating to ETN and the DMARDs.

At registration, patients were seen by a physician or specialist nurse and completed a baseline questionnaire collecting data including duration of RA, DAS28, current and previous medication, comorbidity and demographics. In addition, patients completed a questionnaire including details of occupational history, smoking status, the Health Assessment Questionnaire (HAQ) and the short form (SF)-36.

Physician follow-up was completed at 6-monthly intervals for 3 years and then annually regardless of whether the patient remained on biologic therapy. This included details of changes in anti-rheumatic therapy and current DAS28 status. In addition, patients were sent a questionnaire every 6 months for the first 3 years after registration, including HAQ, and to allow the patient to report any adverse events.

In this study, for both ETN and DMARD cohorts, the following inclusion criteria were applied:

1. A physician diagnosis of RA
2. Registration date on or before 29 September 2005)
3. A minimum of 1 consultant follow-up after baseline registration.

In addition, for the ETN cohort, patients required a maximum window of ± 90 days between treatment initiation and baseline registration whilst for the

DMARD cohort, patients had to have active RA, defined as a DAS28 >4.2.

Serious infection events

Serious infection was defined as that requiring intravenous antibiotics, hospitalisation or resulting in death. All adverse events including serious infections were ascertained either at the physician/nurse follow-up or from the patient questionnaire. In addition, patients were flagged at the UK National Health Service Information Centre (NHS-IC) to allow for the recording of deaths. History of tuberculosis (TB) was recorded.

Analysis

Index date was defined as the date when biologic treatment started for patients receiving ETN and the BSR-BR registration date for those receiving DMARDs. Patients were followed from index date until either the occurrence of the first serious infection or the end of observation (defined as either date of death, date of last follow-up or, for ETN patients, date of discontinuation +90 days). A sensitivity analysis was also performed following patients receiving ETN to the end of the study period.

Statistical analysis

Crude events rates per 1000 patient-years (py) were calculated for the duration of the study. Progression to first serious infection was tested using Cox proportional hazards modelling (CPHM) from the index date to the end of the observation period.

The threshold for inclusion of covariates in the CPHM was set at $p<0.05$. The following *a priori* defined variables were considered for inclusion in each model: age, gender, ethnicity, RA duration, year of enrolment, the number of DMARD drugs used prior to baseline, DAS28 at baseline, baseline HAQ, smoking history at baseline, blood pressure (systolic) and body mass index. Baseline comorbidity was also considered for inclusion and was defined as number of non-RA current prescription drugs recorded and by a comorbidity index derived from the Charlson Comorbidity Index (CCI) (18).

Table I. Baseline characteristics of ETN and DMARDs.

n	ETN 3470		DMARD 1365		*p*-value
Age (Mean, [SD])	55.4	(12.1)	59.5	12.4	<0.001
Gender					
Male n, (%)	797	(23.0%)	341	(25.0%)	0.104
Female n, (%)	2697	(77.2%)	1024	(75.0%)	
Smoking status					
Current	737	(21.1%)	334	(24.6%)	0.025
Ex-smoker	1366	(39.1%)	534	(39.3%)	
Non-smoker	1371	(39.2%)	492	(36.2%)	
Duration of RA (Mean, [SD])	13.6	(9.4)	9.6	10.2	<0.001
Comorbidities					
Diabetes n, (%)	216	(6.2%)	83	(6.1%)	0.893
COPD n, (%)	189	(5.4%)	127	(9.3%)	<0.001
MI n, (%)	116	(3.3%)	63	(4.6%)	0.064
Stroke n, (%)	70	(2.0%)	53	(3.9%)	<0.001
Asthma n, (%)	371	(10.6%)	207	(15.2%)	<0.001
Liver n, (%)	102	(2.9%)	27	(2.0%)	0.066
Cancer n, (%)	120	(3.4%)	86	(6.3%)	<0.001
CCI (Mean, [SD])	0.67	(0.93)	0.80	(1.1)	<0.001
DAS28 (Mean, [SD])	6.6	(0.9)	5.7	(1.0)	<0.001
HAQ (Mean, [SD])	2.07	(0.6)	1.68	(0.7)	<0.001
DMARDs prescribed at baseline, n (%)					
Methotrexate	1207	(34.8)	814	(59.6)	-
Sulphasalazine	394	(11.4)	420	(30.8)	-
Leflunomide	251	(7.2)	192	(14.1)	-
Hydroxychloroquine/chloroquine	210	(6.1)	136	(10.0)	-
Others	288	(8.3)	253	(18.5)	-

DAS28: disease-activity score in 28 joints; CCI: Charlson Comorbidity Index; COPD: chronic obstructive pulmonary disease; DMARD: disease-modifying anti-rheumatic drugs; ETN: etanercept; HAQ: Health Assessment Questionnaire; MI: myocardial infarction; RA, rheumatoid arthritis; SD: standard deviation.

Two models were created. Model 1 included baseline DAS28 as a predictor of serious infection; Model 2 also included a 6-monthly time-dependent variable representing actual change in DAS28 from the previous time segment. Where no change occurred or values were missing, the value was set to 0. CPHMs were also created for 4 time-frames: 0–6 months, 7–12 months, 13–24 months and 25–36 months.

In addition to the CPHM, parametric models were fitted to the survival data based on 4 different distributions (Weibull, exponential, log-normal and log-logistic). These 4 models were compared using Akaike's information criterion (AIC). Appropriateness of the log-logistic assumption was further evaluated by visually comparing expected *versus* observed plots, *i.e.* comparing resulting survival times from the parametric models against those obtained from the Kaplan-Meier and CPHM fits. This model was run with different values for DAS28 and different ages. Other covariates were entered at the mean value.

Results

Baseline characteristics

Total follow-up was 19,964 py; 14,381 years in the ETN group (mean 4.1; median 4.9), and 5583 years in the DMARD group (mean 4.1; median 4.9). Table I shows the baseline characteristics of patients treated with ETN and DMARDs. Significant differences were observed between the groups: ETN subjects were significantly younger (55.4 years *vs*. 59.5 years; $p<0.001$) but with a longer duration of RA (13.6 years *vs*. 9.6 years; $p<0.001$) compared with DMARD subjects. Patients receiving ETN reported greater disability (HAQ 2.07 *vs*. 1.68; $p<0.001$) but significantly less non-RA baseline morbidity than those treated with DMARDs, as measured by the following indi-

vidual conditions: chronic obstructive pulmonary disorder (COPD; 5.4% *vs*. 9.3%; $p<0.001$), stroke (2.0% *vs*. 3.9%; $p<0.001$), asthma (10.6% *vs*. 15.2%; $p<0.001$) and cancer (3.4% *vs*. 6.3%; $p<0.001$), and by CCI (0.67 *vs*. 0.80; $p<0.001$). History of TB was recorded, with 90 (2.6%) cases reported in the ETN group *versus* 29 (2.1%) cases for the DMARD group.

Figure 1A shows the distribution of DAS28 at baseline. Patients treated with ETN had significantly greater disease activity (6.5 *vs*. 5.7; $p<0.001$). One ETN patient had a DAS28 score indicative of remission.

DAS28 change and crude infection rates by DAS28

At 6 months, there was a decrease in DAS28 from baseline for both groups but this was significantly greater in those initiated with ETN (–2.29 [SD 1.48] for ETN and –0.96 [SD 1.7] for DMARDs, $p<0.001$; Fig. 1B-1C).

Over the study period, there were 651 first recorded serious infections; 469 in the ETN cohort and 182 in the DMARD cohort, with respective rates of 39.9 and 35.0 per 1000 py. The most common specific infection was pneumonia, with 172 cases (14.1 per 1000 py) in the ETN cohort and 108 (20.1 per 1000 py) in the DMARD cohort.

Table II shows the serious infection rates by DAS28 score for all patients and for patients receiving ETN and DMARDs. For both treatment groups and overall, there was a positive relationship between DAS28 and serious infection rate. For the combined cohort, there was an increase from 27.1 per 1000 py for those with DAS28 <4 to 64.4 per 1000 py for those with DAS28 ≥8.

Adjusted infection rates

In the first adjusted CPHM (Model 1; Table IIIA), each integer increase in baseline DAS28 was associated with a 17.5% increase in hazard ratio (HR) for serious infection (HR=1.175; 95% confidence interval [CI] 1.077 to 1.282; $p<0.001$). Other significant variables were age, gender, non-RA current prescription drugs, baseline steroid use, baseline HAQ score and CCI (Table IIIA). Treatment was not a significant variable (ETN *vs*. DMARDs HR=1.047; 95% CI 0.839–1.306; $p=0.686$).

In sensitivity analysis, including serious infections occurring during the entire period of follow-up, baseline DAS28 remained significant (HR=1.160; 95% CI 1.063–1.266; $p=0.001$). Treatment was not significant (ETN *vs*. DMARDs HR=0.992; 95% CI 0.795–1.237; $p=0.942$).

In the second model (Model 2; Table IIIB), which included DAS28 escalation, baseline DAS28 was associated with a similar increase in HR as in Model 1 (HR=1.183; 95% CI 1.084–1.290; $p<0.001$). The time-dependent

Fig. 1A. Comparison of DAS28 at baseline, ETN *vs*. DMARDs.

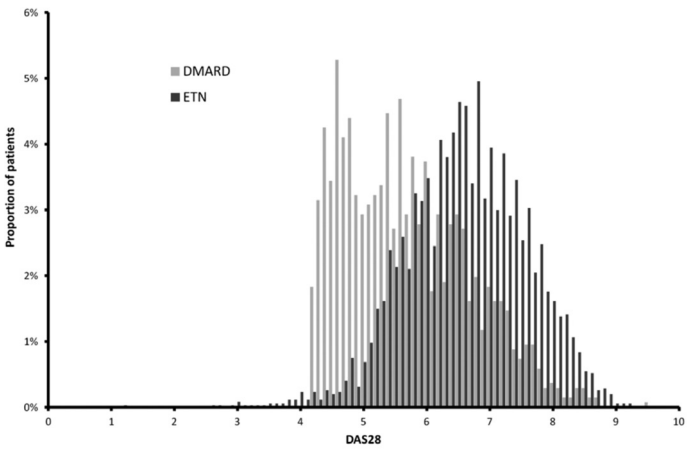


Fig. 1B. Change in DAS28 from baseline for patients initiated on treatment with DMARDs and ETN.

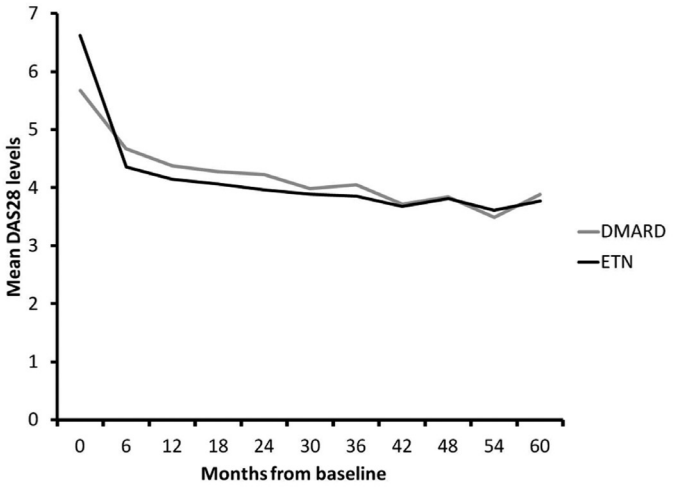
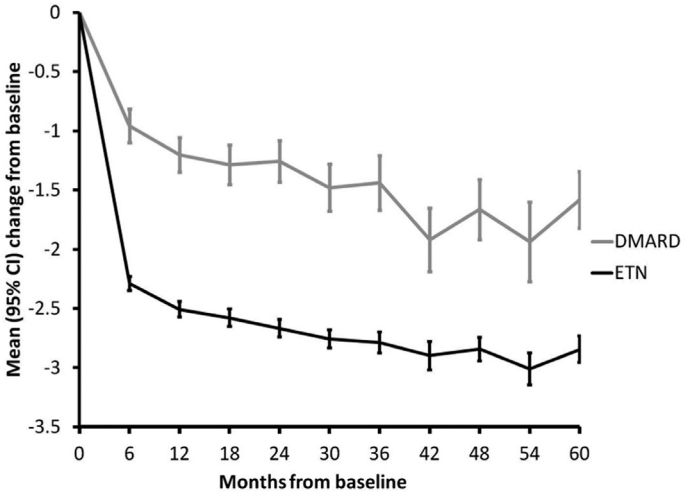


Fig. 1C. Mean change from baseline in DAS28 for patients initiated on treatment with DMARDs and ETN.



variable measuring DAS28 escalation was also significantly associated with a 30% increase in HR for each integer increase in DAS28 score between adjacent time segments (HR=1.278; 95% CI 1.168–1.399; $p<0.001$). Treatment was not significant (HR=1.098; 95% CI 0.880–1.369; $p=0.409$).

Risk of serious infection over time

Over the 4 time-windows, the rate of serious infection varied between those treated with ETN *versus* DMARDs (Table II). The adjusted HR was significantly greater for ETN between baseline and 6 months (HR=1.979; 95% CI 1.143–3.428; $p=0.015$) but there was no significant difference after this time.

Parametric survival analysis

Goodness of fit for the model was assessed graphically and confirmed by AIC value. The AIC values for the assessed distributions were log-normal=11722.75, Weibull=11756.31, exponential=11783.61, and log logistic=11743.88. The best fit for the data by AIC value was the log-normal distribution. Table IV shows the parameter estimates based on this model. Figure 2 shows the hypothetical serious infection rates for ETN *versus* DMARDs for different DAS28 values and ages.

Table II. Time segmented rates of serious infection and adjusted HRs for patients treated with ETN *versus* DMARDs.

DAS28	Rate per 1000 py		
	ETN	DMARD	Combined
<5	15.9 (7.4–30.1)	30.3 (23.0–39.2)	27.1 (21–34.5)
5	30.6 (24.5–37.9)	29.3 (22.2–38.1)	30.1 (25.3–35.6)
6	40.9 (35.4–47.1)	50.0 (36.1–62.6)	42.2 (37.1–47.9)
7	43.3 (36.6–50.9)	42.7 (26.8–64.7)	43.2 (36.9–50.3)
>7	66.1 (49.9–86.1)	48.1 (15.3–116)	64.4 (49.1–83.0)

Time window	Rate per 1000 py		HR	95% CI		*p*-value
	ETN	DMARD				
0–6 months	72.3 (60.2–86.0)	40.2 (27.0–57.7)	1.979	1.143	3.428	0.015
7–12 months*	54.7 (43.5–68.0)	46.7 (31.9–66.2)	0.785	0.460	1.339	0.375
13–24 months**	39.5 (32.6–47.6)	38.3 (28.5–50.6)	0.985	0.641	1.512	0.943
25–36 months***	27.1 (21.3–34.1)	31.4 (22.6–42.7)	0.877	0.513	1.498	0.630

DAS28: disease-activity score in 28 joints; DMARD: disease-modifying anti-rheumatic drugs; ETN: etanercept; py: patient-year.
*ETN n: 3,077; DMARDS n: 1,297; **ETN n: 2,616; DMARDS n: 1,183; ***ETN n: 2,196; DMARDS n: 1,022.

Table IIIA. Cox proportional hazards modelling for time to serious infection without time-dependent DAS28 escalation.

	HR	95% CI		*p*-value
Female	0.712	0.595	0.853	0.000
Age	1.026	1.018	1.033	0.000
Baseline steroid	1.236	1.044	1.465	0.014
Baseline DAS28	1.175	1.077	1.282	0.000
Previous non-RA drugs	1.102	1.068	1.137	0.000
CCI	1.122	1.038	1.213	0.004
Baseline HAQ	1.301	1.106	1.529	0.001
Therapy (ETN:DMARD)	1.047	0.839	1.306	0.686

Table IIIB. Cox proportional hazards modelling for time to serious infection with time-dependent DAS28 escalation.

	HR	95% CI		*p*-value
Female	0.707	0.591	0.846	<0.001
Age	1.026	1.018	1.034	<0.001
Baseline steroid	1.228	1.036	1.454	0.018
Baseline DAS28	1.191	1.092	1.299	<0.001
Previous non-RA drugs	1.102	1.068	1.137	<0.001
CCI	1.117	1.033	1.207	0.006
Baseline HAQ	1.285	1.092	1.511	0.002
Therapy (ETN:DMARD)	1.098	0.880	1.369	0.409
DAS28 change	1.278	1.168	1.399	<0.001

The figures for HAQ, DAS and CI refer to an integer increase. CCI: Charlson Comorbidity Index; CI: confidence interval; DAS28: disease-activity score in 28 joints; DMARD: disease-modifying anti-rheumatic drugs; ETN: etanercept; HAQ: Health Assessment Questionnaire; HR: hazard ratio; RA, rheumatoid arthritis.

Discussion

This study used data from a large, prospective UK patient register to evaluate the correlation between the risk of serious infection and disease activity for patients with RA, with the aim of identifying factors predicting a higher risk. When studying the relationship between TNF-I therapy and serious infection, several questions are raised. Firstly, does TNF-I increase the risk of serious infection? Meta-analyses of randomised control trials (12, 13), an analysis of claims data (19) and observational data (14-17) have all found an increased rate of serious infection with TNF-I therapy compared with conventional DMARD therapy. Therapy with the DMARD methotrexate has historically been considered to come with an increased risk of varicella zoster virus and herpes zoster infections but a systematic review of the literature showed no substantial evidence existed to support this (20).

The risk of serious infection in RA patients treated with TNF-I was previously evaluated using shorter (3-year) follow-up data from the BSRBR, with a special emphasis on the risk across different ages (14). In this analysis, Galloway *et al*. found a higher risk of serious infections associated with TNF-I overall, with no significant differences between the 3 agents studied (adalimumab, ETN and infliximab). This point is supported by van Dartel *et al*. (21). When Galloway *et al*. analysed by individual TNF-I, all 3 agents

Table IV. Parametric model (log-normal) for rate of serious infection.

Parameter	Estimate	SE	Z	*p*-value
Intercept	14.0149	0.50071	27.99	0.000
ETN	–0.1381	0.14854	–0.93	0.353
Female	0.4605	0.12476	3.69	0.000
Age	–0.0305	0.00501	–6.1	0.000
Baseline DAS28	–0.1906	0.05994	–3.18	0.001
Baseline HAQ	–0.3713	0.10477	–3.54	0.000
CCI	–0.1426	0.05608	–2.54	0.011
Baseline steroid	–0.3336	0.11342	–2.94	0.003
Other previous non-RA drugs	–0.1346	0.02239	–6.01	0.000
Log(scale)	0.8073	0.03276	24.64	0.000

CCI: Charlson Comorbidity Index; DAS28: disease-activity score in 28 joints; HAQ: Health Assessment Questionnaire; RA: rheumatoid arthritis.

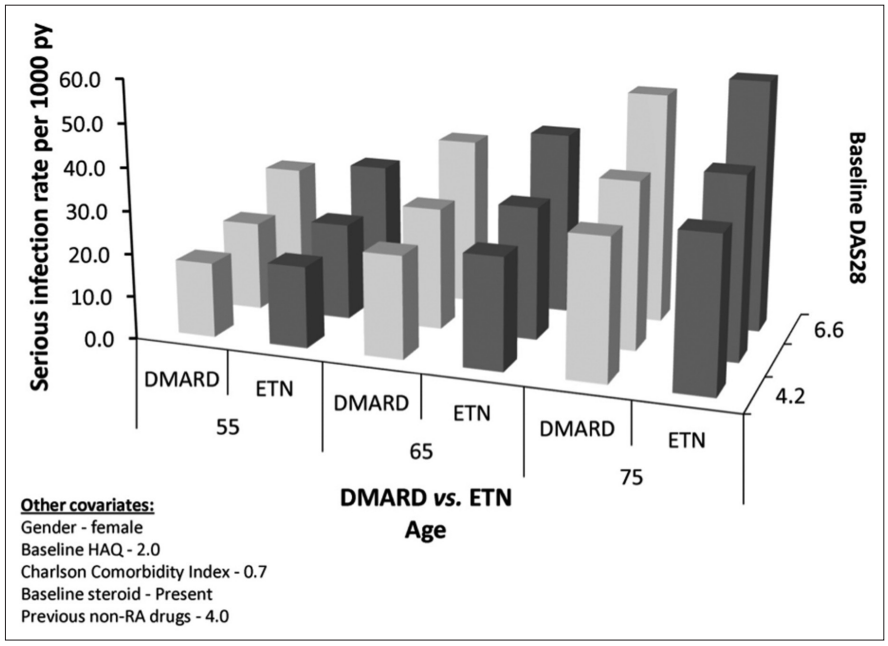


Fig. 2. Serious infection risk per 1000 py for patients treated with ETN *versus* DMARDs by age and DAS28 score.
The data presented are based on predictions generated from a parametric model.

had elevated risks of serious infections compared to DMARD therapy, with the adjusted HR reaching statistical significance for adalimumab and infliximab, but not ETN. After adjustment for disease severity and other covariates, we found no significant increased risk of serious infection for patients initiated with ETN compared with DMARDs over the entire 5 years of observation.

The second question in relation to this subject is whether this elevation in risk is constant over time. Several studies have reported that after an initial increased risk was observed in the first 6 months of therapy, a relative reduction in the infection risk occurs over time in patients treated with TNF-I (14, 16, 19). In an open-label ETN extension study, the rates of serious infections in patients decreased over the course of 5 years, the same length of study as ours (22). Our study confirms that the risk of serious infection between TNF-I and DMARD patients dissipates over time; the significant 2-fold increase in risk we observed in the first 6 months of treatment reached unity after 12 months. Strangfeld *et al*. (23) suggest that the relative decrease in risk over time associated with TNF-I can be attributed largely to the depletion of susceptible cases from the TNF-I cohort, in addition to improvement in clinical status and reduction in glucocorticoid treatment as a result of response to TNF-I.

Another possible explanation for the increase in infection rates for patients treated with ETN in the first 6 months, and subsequent decrease, is that the therapy may be initiated in response to an escalation of disease activity. As shown in our time-dependent analysis, DAS28 escalation over time is associated with increased risk of infection, therefore ETN initiation may be a confounding factor. As DAS28 data were not available prior to baseline, it is not possible to test this hypothesis fully with the existing data. Over the course of the study, mean DAS28 for all patients fell, with the biggest decrease occurring in the first 6 months following baseline. This decrease was significantly greater for those patients treated with etanercept (–2.3) compared with those treated with conventional DMARD therapy (–1.0).

The third question, which we focused on in this analysis, is whether the increased risk of serious infection observed in patients treated with TNF-I is related only to therapy, or is associated with the greater disease activity in this patient group. This question is complicated by the fact that disease activity is a factor that influences both risk of infection and the decision to initiate treatment with TNF-I. This is particularly relevant to patients enrolled in the BSRBR as TNF-I initiation in the UK is restricted by the National Institute of Health and Clinical Excellence (NICE) to RA patients with a DAS28 >5.1 (24); however, no such restriction applies to initiation of DMARDs.

Recently, the CORRONA study assessed the relationship between DAS28 and infection (17) and found that a unit increase in DAS28 correlated with a 25% increase in the rate of hospitalised infections and a 4% increase in the rate of outpatient infections. Analyses from the BSRBR and Italian LORHEN registry showed the increase to be 20% and 23%, respectively, in univariate analysis across TNF-I agents, although the Italian estimate did not reach significance (25). These results contrast with those from other European registers, which suggested that higher disease activity as measured by DAS28 was not directly associated with an increased

infection risk, but rather that there may be an indirect association through the use of glucocorticoids (23) and decline in function (HAQ) (16).

Our analysis has shown that disease activity, as measured using the DAS28, has a linear relationship with rates of serious infection and in analysis adjusted for other covariates; each unit increase of DAS28 score at baseline (treatment initiation) was associated with a 17.5% increase in serious infection. Our study also found, using a time-dependent analysis, that increases in disease activity over time were associated with an increase in serious infections such that a DAS28 change of 1 unit during follow-up predicted a 27% increase in serious infection rates.

It should be noted that there were significant differences in the profile of ETN and DMARD patients at baseline. Patients receiving DMARDs were older, had a higher proportion of smokers, and had greater general morbidity in terms of the prevalence of non-RA individual conditions, the CCI and number of non-RA drugs at baseline. Although these baseline characteristics favour the ETN arm, with greater relevance to this study, the ETN patients had worse RA-specific morbidity as measured by DAS28 (see Fig. 1A) and HAQ. Whilst the multivariate modelling strategies adjust for these differences, it should be recognised that the comparison is between 2 distinct populations. It should also be noted that the DMARD patients were not "control" patients in that they were not necessarily initiated on any therapeutic change at baseline whereas, by definition, the ETN patients were initiated on new treatment. Therefore, data on serious infections that occurred in DMARD patients prior to study registration were not collected and patient years prior to the index date were not included in analyses. Confounding by indication is therefore inherent within the register.

It is also important to consider the impact of different analytical approaches to similar data sources. Dixon *et al*. have shown the impact of using different scenarios to define patient follow-up for those treated with TNF-I (26). By defining different scenarios 'on-treatment', 'on-treatment +90 days' and 'ever-treated', they report respectively increasing HRs. In this study, we defined patients as 'on-treatment +90 days' and also included ever treated as a sensitivity analysis. Interestingly, whilst using the same data source, we report a lower, non-significant HR for the ever treated scenario than on treatment +90 days. This difference is presumably due to the longer follow-up period in our study.

Several predictive factors for risk of serious infections have previously been reported to help identify the patients at higher risk (23); however, in clinical practice it is still difficult to translate this evidence into treatment choices for individual patients. Furthermore, most existing algorithms assessing the risk for serious infections have included TNF-I agents, but always as a class.

The parametric analysis confirmed the importance of DAS28 and age in driving the risk of serious infection. From the hypothetical example (Fig. 2), using mean values for other significant covariates for a patient aged 75 with DAS28 score of 6.6, the estimated rate of serious infection per 1000 py would be 58.5 for patients initiating with ETN *versus* 53.9 for those treated with DMARDs. It can be seen that risk of serious infection is driven by several factors, including age and disease severity. For example, for a 65-year-old DMARD-treated patient with DAS28 of 5.1, the estimated rate of serious infection is 28.5 per 1000 py compared with 39.4 for a 65-year-old patient with a DAS28 of 6.6, or 39.0 for a patient with DAS28 of 5.1 but aged 75.

Whilst there remains a lack of consensus regarding the effect of TNF-I therapies on the risk of serious infection, it may be argued that other patient risk factors have a greater impact and these should be considered when initiating a patient on TNF-I.

Authors' *contributions*

All co-authors were involved in the design of this study and interpretation of these data. C. Morgan and C. Poole were responsible for the data analysis. All co-authors were involved with the writing process and drafting elements of the manuscript. The original parametric modelling was performed by Christian Bannister from the School of Medicine, Cardiff University, Cardiff, United Kingdom.

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