Risk of septic arthritis in patients with rheumatoid arthritis and the effect of anti-TNF therapy: results from the British Society for Rheumatology Biologics Register

J B Galloway,1 K Hyrich,1 L K Mercer,1 W G Dixon,1 A P Ustianowski,2 M Helbert,3 K D Watson,1 M Lunt,1 D P M Symmons1; on behalf of the BSR Biologics Register

ABSTRACT

Objectives To evaluate the risk of septic arthritis (SA) in patients with rheumatoid arthritis (RA) treated with anti-tumour necrosis factor (TNF) therapy.

Methods Using data from the British Society for Rheumatology Biologics Register, a prospective observational study, the authors compared the risk of SA between 11,881 anti-TNF-treated and 3,673 non-biological disease-modifying antirheumatic drug (nbDMARD)-treated patients.

Results 199 patients had at least one episode of SA (anti-TNF: 179, nbDMARD: 20). Incidence rates were: anti-TNF 4.2/1000 patient years (pyrs) follow-up (95% CI 3.6 to 4.8), nbDMARD 1.8/1000 pyrs (95% CI 1.1 to 2.7). The adjusted HR for SA in the anti-TNF cohort was 2.3 (95% CI 1.2 to 4.4). The risk did not differ significantly between the three agents: adalimumab, etanercept and infliximab. The risk was highest in the early months of therapy. The patterns of reported organisms differed in the anti-TNF cohort. Prior joint replacement surgery was a risk factor for SA in all patients. The rate of postoperative joint infection (within 90 days of surgery) was 0.7%. This risk was not significantly influenced by anti-TNF therapy.

Conclusions Anti-TNF therapy use in RA is associated with a doubling in the risk of SA. Physicians and surgeons assessing the RA patient should be aware of this potentially life-threatening complication.

INTRODUCTION

Septic arthritis (SA) is a serious medical condition that, even with prompt treatment, can lead to irreversible joint damage and has a death rate of around 10%.1 The incidence of SA in the general population is around 4–10 per 100,000 patient years (pyrs) and seems to be rising,2 3 probably due to the combination of an ageing population and larger numbers of orthopaedic interventions.

Important risk factors for SA include increasing age, joint prosthesis, skin infection and pre-existing joint damage.4 5 Patients with rheumatoid arthritis (RA) may have many of these risks combined with the use of immunosuppressive medications. The risk of SA in an RA patient, irrespective of therapy, is increased by 4–15-fold.5 6 Although one might expect immunosuppressive therapy to increase the risk of SA, this has not been well studied. This question has been of increasing interest over the last decade since the emergence of biological therapies. Anti-tumour necrosis factor (anti-TNF) therapies were the first class of biological agents to become established in routine RA care. Data have emerged suggesting that these drugs confer a small but significant risk of serious infections, especially during the first months of treatment.7–9 It is also apparent that this risk differs by anatomical site and that there is increased susceptibility to certain pathogens.9–11

There is very limited information regarding the effect of anti-TNF therapy on the risk of SA. Case reports have described patients on anti-TNF therapy developing SA as a multifocal disease or with unusual causative organisms.12–14 Although case reports are a useful tool for raising questions, they cannot provide information regarding disease incidence or relative risk. An additional important question relates to the risk of SA following joint replacement surgery in anti-TNF-treated patients.

In 2001, the British Society for Rheumatology (BSR) established a national prospective cohort study of patients starting anti-TNF therapy for RA, the BSR Biologics Register (BSRBR). This is the largest register of its kind worldwide and includes detailed records of serious adverse events including SA occurring in patients receiving anti-TNF therapy as well as in a cohort of RA patients not exposed to anti-TNF therapy.

Our primary aim was to test the hypothesis that anti-TNF therapy increases the risk of SA compared with non-biological disease-modifying anti-rheumatic drug (nbDMARD) therapy. Secondary analysis considered whether anti-TNF therapy confers additional risk to patients who have joint replacement surgery either prior to starting therapy or during follow-up.
cohort of patients with active RA (defined as having a 28-joint count disease activity score (DAS28) >4.2) was recruited in parallel. These patients were receiving an nbdMARD and were biologically naive. Patients prescribed biologics were recruited from across the UK (over 250 hospitals) whereas controls were recruited from 29 centres. These control centres reflect a combination of secondary and tertiary care rheumatology centres distributed across the UK and are listed in full in the BSRRB control centre consortium supplementary data file.

Baseline assessment
All patients in this study had a physician diagnosis of RA. Baseline information included demographics, disease duration, a measure of self-reported physical function (the Health Assessment Questionnaire (HAQ)\(^{10}\)), DAS28 score,\(^{18}\) baseline steroid use, smoking history, baseline comorbidity and surgery, including prior joint replacement. For the purpose of this analysis, we have considered only large joint replacements (shoulder, elbow, hip and knee) because when reviewing reports of small joint surgery, it was difficult to distinguish between soft-tissue procedures and arthroplasty.

Follow-up
Follow-up information was collected from three sources. First, six monthly questionnaires were sent to the treating rheumatologist for 3 years and annually thereafter. Second, data were collected directly from the patients six monthly for their first 3 years of the study. Patients were provided with a handheld diary card to record details of all hospital attendances as well as new prescriptions. Details of joint replacements during follow-up were collected from these two sources. Third, all patients were flagged with the UK National Health Service Information Centre, which informs the register of any deaths and the causes of deaths. All patients had to have at least one returned consultant follow-up questionnaire prior to 31 December 2009.

Case definition and verification
This analysis was confined to serious cases of SA. ‘Serious’ infections were defined as those requiring intravenous antibiotics or hospitalisation, or those resulting in death. All serious infections reported to the BSRRB were followed up with requests for additional information from the treating clinician to gather information on the site of infection and microbiology results. All reported cases of SA were then verified by a BSRRB clinician (JBG).

Events were ascribed to anti-TNF if they occurred while the patient was receiving anti-TNF therapy or within 90 days of the first missed dose. Events were attributed to the most recent drug exposure in patients who switched anti-TNF therapy. Patients were censored from further follow-up after their first episode of SA. Only one case of articular Mycobacterium tuberculosis was reported to the BSRRB, which has been described in a previous publication and is not included in this analysis.\(^{19}\)

Statistical methods
Crude incidence rates were calculated as the number of episodes of SA per 1000 pyrs of follow-up. Cumulative hazards were compared between the different cohorts using a Nelson–Aalen plot. A Cox model was used to calculate HR between the groups. Changes to the incidence rate over time in the anti-TNF cohort were analysed using a spline model. Potential confounders were identified prior to the analysis as variables that were either unbalanced between the nbdMARD and anti-TNF cohorts (age, gender, disease duration, DAS28, HAQ, steroid exposure, prior joint replacement, calendar year of entry into the study) or significant predictors of infection (chronic obstructive pulmonary disease, diabetes). Adjustment for these potential confounders was made using propensity scores. The use of this method in observational studies has been described in detail previously.\(^{20}\)

In a secondary analysis, the influence of joint replacement was examined. Patients were entered into this analysis when they were at risk of a prosthetic infection (ie, from baseline if they had a prior joint replacement or at the date of surgery if they had a joint replacement during follow-up). An adjusted Cox proportional hazards model was used to compare rates between groups. The risk of postoperative infection following joint replacement surgery during active follow-up was analysed separately using adjusted logistic regression to compare the odds of developing an infection within 90 days of joint replacement surgery between anti-TNF and nbdMARD cohorts. Adjustment was made for the same confounders as identified in the primary analysis. Missing baseline data were replaced using multiple imputations. All analysis was done using Stata 10.1 (StataCorp, College Station, Texas, USA).

Further details of the statistical methodology are presented in a data supplement online.

Ethics approval for this study was obtained in December 2000 from the Multicentre Research Ethics Committee for the Northwest of England.

RESULTS
The baseline characteristics of the 15 554 patients included in the analysis are shown in table 1. Although both anti-TNF and nbdMARD groups had active RA, there were significant differences at baseline. The patients receiving anti-TNF therapy were younger and proportionally more were women. The anti-TNF group had significantly longer disease duration as well as higher disease activity. History of joint replacement was higher in the anti-TNF cohort (24% vs 14% (p<0.001)).

 incident SA was reported in 199 patients during the follow-up period (179 anti-TNF; 20 nbdMARD). In univariate analysis, increasing age, longer disease duration, higher HAQ, higher DAS28 score, baseline steroid exposure, prior orthopaedic surgery and diabetes were associated with SA irrespective of anti-TNF exposure. The strongest association was with a history of large joint orthopaedic surgery at baseline irrespective of whether the SA developed in a prosthetic joint: HR 2.45 (1.90–3.17).

The incident rate for SA was significantly higher in the anti-TNF cohort (4.2/1000 follow-up pyrs) than in the nbdMARD group (1.8/1000 pyrs) (table 2). The cumulative incidence over time is presented in figure 1. The unadjusted HR for SA in the anti-TNF cohort was 2.5 (95% CI 1.6 to 4.0). After full adjustment, patients on anti-TNF therapy were more than twice as likely to develop SA as the nbdMARD controls: adjusted HR 2.3 (95% CI 1.2 to 4.4).

Hazard estimates for the first year of follow-up were increased in all three anti-TNF agents; however, beyond 1 year, the hazard in the ETN cohort increased more than in the ADA and INF cohorts (figure 1). The adjusted HR was highest within the ETN cohort and lowest for ADA (table 2) although there were no differences between the three individual drugs or between the monoclonal antibody class and ETN that achieved statistical significance (results not shown).

The pattern of joint involvement was similar in the two cohorts with the knee being the most frequent site of infection.
Extended report

Table 1 Baseline patient characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>nbDMARD (n=3673)</th>
<th>All TNF (n=11881)</th>
<th>p Value*</th>
<th>Etanercept (n=4139)</th>
<th>Infliximab (n=3475)</th>
<th>Adalimumab (n=4267)</th>
<th>p Value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD)</td>
<td>60 (12)</td>
<td>56 (12)</td>
<td>&lt;0.001</td>
<td>56 (12)</td>
<td>56 (12)</td>
<td>57 (12)</td>
<td>0.018</td>
</tr>
<tr>
<td>Sex (% female)</td>
<td>2652 (72)</td>
<td>9053 (76)</td>
<td>&lt;0.001</td>
<td>3193 (77)</td>
<td>2626 (76)</td>
<td>3234 (76)</td>
<td>0.203</td>
</tr>
<tr>
<td>DAS28 (mean (SD))</td>
<td>5.1 (1.3)</td>
<td>6.1 (1.0)</td>
<td>&lt;0.001</td>
<td>6.6 (1.0)</td>
<td>6.6 (1.0)</td>
<td>6.5 (1.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HAQ score (mean (SD))</td>
<td>1.5 (0.8)</td>
<td>2.1 (1.5)</td>
<td>&lt;0.001</td>
<td>2.1 (0.6)</td>
<td>2.1 (0.5)</td>
<td>1.9 (0.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Disease duration (years (median (IQR)))</td>
<td>6 (1, 15)</td>
<td>11 (6–19)</td>
<td>&lt;0.001</td>
<td>12 (6–19)</td>
<td>12 (6–19)</td>
<td>10 (5–19)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Baseline steroid use (n (%))</td>
<td>845 (23)</td>
<td>5228 (44)</td>
<td>&lt;0.001</td>
<td>1979 (48)</td>
<td>1609 (46)</td>
<td>1664 (39)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diabetes (n (%))</td>
<td>234 (6.7)</td>
<td>675 (5.8)</td>
<td>0.033</td>
<td>255 (6)</td>
<td>169 (4)</td>
<td>261 (6)</td>
<td>0.026</td>
</tr>
<tr>
<td>COPD (n (%))</td>
<td>304 (8)</td>
<td>570 (5)</td>
<td>&lt;0.001</td>
<td>222 (5)</td>
<td>165 (5)</td>
<td>183 (4)</td>
<td>0.070</td>
</tr>
<tr>
<td>Smoking (n (%))</td>
<td>Current</td>
<td>868 (24)</td>
<td>2500 (22)</td>
<td>0.001</td>
<td>846 (21)</td>
<td>757 (22)</td>
<td>977 (23)</td>
</tr>
<tr>
<td>Ex</td>
<td>1454 (40)</td>
<td>4510 (38)</td>
<td></td>
<td>1576 (38)</td>
<td>1314 (38)</td>
<td>1620 (38)</td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>1333 (36)</td>
<td>4714 (40)</td>
<td></td>
<td>1691 (41)</td>
<td>1386 (40)</td>
<td>1637 (39)</td>
<td></td>
</tr>
<tr>
<td>Prior large joint replacement (n (%))</td>
<td>521 (14)</td>
<td>2837 (24)</td>
<td>&lt;0.001</td>
<td>1090 (26)</td>
<td>846 (24)</td>
<td>901 (21)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Large joint replacement during follow-up (n (%))</td>
<td>481 (13)</td>
<td>4390 (37)</td>
<td>&lt;0.001</td>
<td>1907 (46)</td>
<td>1111 (32)</td>
<td>1372 (32)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*Represents the significance of differences between the DMARD and anti-TNF cohorts using χ² tests for categorical outcomes and Wilcoxon rank sum tests for continuous variables.
†Represents the significance of differences between the three anti-TNF drugs using χ² tests for categorical outcomes and Kruskal–Wallis rank tests for continuous variables.

Table 2 Risk of septic arthritis in patients with rheumatoid arthritis

<table>
<thead>
<tr>
<th>Exposure time (years)</th>
<th>nbDMARD</th>
<th>All anti-TNF</th>
<th>Etanercept</th>
<th>Infliximab</th>
<th>Adalimumab</th>
</tr>
</thead>
<tbody>
<tr>
<td>Events (n)</td>
<td>11 426</td>
<td>42 671</td>
<td>18 554</td>
<td>10 827</td>
<td>13 289</td>
</tr>
<tr>
<td>Incident rate/1000 pyrs (95% CI)</td>
<td>1.8 (1.1 to 2.7)</td>
<td>4.2 (3.6 to 4.8)</td>
<td>4.6 (3.7 to 5.7)</td>
<td>3.8 (2.7 to 5.1)</td>
<td>3.9 (2.9 to 5.1)</td>
</tr>
<tr>
<td>Unadjusted HR (95% CI)</td>
<td>Ref</td>
<td>2.5 (1.6 to 4.0)</td>
<td>3.0 (1.8 to 4.8)</td>
<td>2.2 (1.3 to 3.8)</td>
<td>2.3 (1.4 to 3.8)</td>
</tr>
<tr>
<td>Adjusted HR (95% CI)</td>
<td>Ref</td>
<td>2.3 (1.2 to 4.4)</td>
<td>2.5 (1.3 to 4.9)</td>
<td>2.4 (1.0 to 5.8)</td>
<td>1.9 (0.9 to 4.0)</td>
</tr>
</tbody>
</table>

Anti-TNF, anti-tumour necrosis factor; nbDMARD, non-biological disease-modifying antirheumatic drug; pyrs, patient years.

Fig. 1 Nelson–Aalen plot comparing nbDMARD and anti-TNF cohorts. Anti-TNF, anti-tumour necrosis factor; nbDMARD, non-biological disease-modifying antirheumatic drug.

DISCUSSION

Key questions remain unanswered from clinical trial data regarding the safety of anti-TNF therapy, particularly with respect to rare outcomes including SA. This is the first study to specifically examine the rate of SA in patients treated with anti-TNF therapy. We confirmed our primary hypothesis that SA is increased in patients on anti-TNF therapy. However, these results must be interpreted with some important caveats. First, the absolute risk of SA remains very small, with an incident rate of only 4.2 per 1000 pyrs of

(anti-TNF 51%; nbDMARD 22%). Microbiological confirmation was available for 94 (53%) of the anti-TNF cases and 7 (35%) of the DMARD cases. Staphylococcus aureus was the most frequently reported organism in both cohorts (anti-TNF 57%; DMARD 45%). Six (11%) of the S aureus cases in the anti-TNF cohort were reported as being methicillin resistant. Also, within the anti-TNF cohort, several species that seldom cause joint infections were reported. These included five cases of intracellular infection (two Listeria, three Salmonella) and four cases of Pseudomonas aeruginosa infection. Analysis of results limited to only culture-proven SA yielded an adjusted HR of 2.7 (95% CI 1.0 to 6.9) for anti-TNF.

The hazard for SA in the anti-TNF cohort was greatest in the early months of therapy (figure 2). This risk then decreased steadily over the remainder of the follow-up period. The 30-day all-cause mortality following SA was 6% (10/178) in the anti-TNF cohort and 10% (2/20) in the DMARD cohort.

Forty-seven (24%) of the 199 cases were in prosthetic joints. In the patients with a history of large joint replacement (either at baseline or during follow-up), the incidence of prosthetic joint SA was not different between nbDMARD and anti-TNF cohorts (table 3). Thirty of the 47 prosthetic joint SA cases occurred postoperatively (within 90 days of the joint replacement surgery). In total, 4871 large joint replacements were performed during the follow-up (nbDMARD 481; anti-TNF 4390). This equates to an incidence of SA within 90 days of surgery of 0.7% in the whole cohort. The adjusted OR for postoperative joint infection in the anti-TNF cohort compared with nbDMARD was 0.8 (0.2–3.5).

Downloaded from http://ard.bmj.com/ on June 4, 2017 - Published by group.bmj.com
host defence and is in keeping with our previous reports of an 
Listeria aetiological organisms were 
about between-drug differences from these data. 
Dar year. 21 Therefore, it is not possible to draw firm conclusions 
on ETN. However, this was not a hypothesis that we had set 
out to test. After adjusting for confounders, the 95% CIs for 
the risk of SA in patients with RA. This risk seen in 
this study was greatest in the first year of treatment. Joint pros-
thesis is a key risk factor for infection. Careful vigilance for joint 
infections in anti-TNF patients remains important, especially in 
the early months of therapy, with awareness of the potential 
range of pathogens that may be responsible. Antibiotic guide-
lines should incorporate this information and consider giving 
specific advice for patients being actively treated with anti-TNF 
agents. Current evidence does not support any one anti-TNF 
agent having a safer profile with regard to SA.

As in the general population of RA patients, the most common 
aetiological organisms were Staphylococcal species. It is important 
to note that the organisms within the anti-TNF cohort included 
Listeria and Salmonella, both intracellular pathogens that rarely 
cause SA. This fits current understanding of the role of TNF in 
host defence and is in keeping with our previous reports of an 
increased risk of intracellular organisms (including M tuberculosis) 
at all sites. 9 19 In the nbDMARD cohort, gram-negative species 
accounted for 50% of the organisms, which may reflect the older 
age of the nbDMARD cohort, whereas in the anti-TNF cohort, only 
10% of the reported species cultured were gram negative. This is 
of relevance when considering antibiotic choices for patients with 
RA on anti-TNF therapy. Many guidelines for SA recommend 
antimicrobial therapy primarily aimed at Staphylococcal species and 
that lack activity against gram-negative organisms.
The risk of SA appeared to vary over time in the anti-TNF 
cohort. The finding of a greater risk early on in therapy has been 
described with other infections in our data as well as data from 
other cohorts. 22 There are a number of potential explanations for 
this early increased risk. First, it may reflect a depletion of sus-
ceptible individuals from the exposed cohort. Second, it may 
reflect a true reduction in risk of joint infection in patients who 
achieve better control of their RA. However, the data presented 
here do not allow definite conclusions to be made about these 
possibilities.

We also addressed the influence of orthopaedic surgery on the 
risk of SA. The BSR recommends that patients on anti-TNF 
therapy stop their treatment temporarily for 2–4 weeks prior to 
major surgical procedures and do not recommence therapy until 
joint healing is satisfactory. 23 Although it is not known with 
certainty how strictly physicians and patients adhere to these 
guidelines, in the context of this practice, it is very reassuring to 
see no evidence of an increased risk of prosthetic joint SA.

In summary, exposure to TNF inhibitor therapy is associated 
with an increased risk of SA in patients with RA. This risk seen in 
this study was greatest in the first year of treatment. Joint pros-
thesis is a key risk factor for infection. Careful vigilance for joint 
infections in anti-TNF patients remains important, especially in 
the early months of therapy, with awareness of the potential 
range of pathogens that may be responsible. Antibiotic guide-
lines should incorporate this information and consider giving 
specific advice for patients being actively treated with anti-TNF 
agents. Current evidence does not support any one anti-TNF 
agent having a safer profile with regard to SA.

Acknowledgements The authors acknowledge the enthusiastic collaboration of all consultant rheumatologists and their specialist nurses in the UK in providing the data. In addition, the authors acknowledge the support from Dr Ian Griffiths (Past) and Professor David Isenberg (Current), Chairs of the BSRBR Management Committee, Professor Gabriel Panayi, Professor David G I Scott, Dr Andrew Bamji and Professor Deborah Bax, presidents of the BSR during the period of data collection, for their active role in enabling the Register to undertake its tasks and to Samantha Peters (BSR) and Nia Taylor and members of the BSRBR Scientific 
Steering Committee. The authors also acknowledge the seminal role of the BSR 
Clinical Affairs Committee for establishing national biological guidelines and recom-
endations for such a register. Finally, the authors would like to acknowledge the 
substantial contribution of Andy Tracey, Katie McGoerther and Dr Mark Lunt in data-
base design and manipulation and Professor Alan Silman in his prior role as a principal 
investigator of the BSRBR.

Funding The BSR commissioned the BSRBR as a UK-wide national project to 
investigate the safety of biological agents in routine medical practice. BSR receives 
restricted income from UK pharmaceutical companies, principally Abbott Laboratories, 
Amen, Schering Plough (now MSD) and Wyeth Pharmaceuticals (now Pfizer). This 
income finances a wholly separate contract between the BSR and the University 
of Manchester, who provide and run the BSRBR data collection, management and 
analysis services. The principal investigators and their team have full academic 
freedom and are able to work independently of pharmaceutical industry influence. All 
decisions concerning analyses, interpretation and publication are made autonomously 
of any industrial contribution.

Competing interests MH has received payment for advisory work for Shire, CSL, 
and GSK, as well as receiving financial support for attending conferences from GSK, 
Octopharma, Biorad, BPL, Phadia, GSK and CSL. All other authors have declared no 
conflict of interests.

Ethics approval Ethics approval for this study was obtained in December 2000 from 
the Multicentre Research Ethics Committee (MREC) for the Northwest of England.

Provenance and peer review Not commissioned; externally peer reviewed.
REFERENCES


Risk of septic arthritis in patients with rheumatoid arthritis and the effect of anti-TNF therapy: results from the British Society for Rheumatology Biologics Register


Ann Rheum Dis 2011 70: 1810-1814 originally published online July 21, 2011
doi: 10.1136/ard.2011.152769

Updated information and services can be found at:
http://ard.bmj.com/content/70/10/1810

These include:

Supplementary Material
Supplementary material can be found at:
http://ard.bmj.com/content/suppl/2011/06/23/ard.2011.152769.DC1

References
This article cites 22 articles, 9 of which you can access for free at:
http://ard.bmj.com/content/70/10/1810#BIBL

Open Access
This paper is freely available online under the BMJ Journals unlocked scheme, see http://ard.bmj.com/info/unlocked.dtl

Email alerting service
Receive free email alerts when new articles cite this article. Sign up in the box at the top right corner of the online article.

Topic Collections
Articles on similar topics can be found in the following collections

Open access (602)
Connective tissue disease (4253)
Degenerative joint disease (4641)
Immunology (including allergy) (5144)
Musculoskeletal syndromes (4951)
Rheumatoid arthritis (3258)
Biological agents (545)
Drugs: musculoskeletal and joint diseases (700)

Notes

To request permissions go to:
http://group.bmj.com/group/rights-licensing/permissions

To order reprints go to:
http://journals.bmj.com/cgi/reprintform

To subscribe to BMJ go to:
http://group.bmj.com/subscribe/