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Drug-Specific Risk of Tuberculosis in Patients with Rheumatoid Arthritis Treated with Anti-TNF Therapy: Results from the British Society for Rheumatology Biologics Register (BSRBR)

Dixon, W.G.[1], Hyrich, K.L. [1], Watson, K.D. [1], Lunt, M. [1], Galloway, J. [1], Ustianowski, A.[2], BSRBR Control Centre Consortium and Symmons, D.P.M. [1] on behalf of the BSR Biologics Register.

Corresponding author: Professor Deborah Symmons
deborah.symmons@manchester.ac.uk

Affiliations:
[1] **arc** Epidemiology Unit
Stopford Building
The University of Manchester
Oxford Road
Manchester
M13 9PT

[2] North Manchester General Hospital
Delaunays Road
Crumpsall
Manchester
M8 5RB

Authors' contributions:
Dixon – Study design, analysis, verification, interpretation, writing
Hyrich – Study design, data management, interpretation, writing
Watson – Study design, data management
Lunt – Study design, data analysis
Galloway – Verification, interpretation, writing
Ustianowski - Verification
Symmons - Study design, data management, interpretation, writing

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Abstract

Background
The risk of tuberculosis (TB) in patients with rheumatoid arthritis (RA) is thought to be increased following anti-TNF therapy, with a proposed differential risk between the anti-TNF drugs etanercept (ETA), infliximab (INF) and adalimumab (ADA). We aimed to compare directly the risk between drugs, to explore time to event, site of infection and the role of ethnicity.
Methods and Findings
Using data from the British Society for Rheumatology Biologics Register (BSRBR), a national prospective observational study, we compared TB rates in 10712 anti-TNF treated patients (3913 ETA, 3295 INF, 3504 ADA) and 3232 patients with active RA treated with traditional disease-modifying anti-rheumatic drugs.
Results
To April 2008, 40 cases of TB were reported, all in the anti-TNF cohort. The rate of TB was higher for the monoclonal antibodies ADA (144 events/ 100,000 person years (pyrs)) and INF (136/100,000 pyrs) than ETA (39/ 100,000 pyrs). After adjustment, the incidence rate ratio compared to ETA-treated patients was 3.1 (95% CI 1.0, 9.5) for INF and 4.2 (1.4, 12.4) for ADA. The median time to event was lowest for INF (5.5 months) compared to ETA (13 months) and ADA (18.5 months). 13/40 cases occurred after stopping therapy. 25/40 (62%) cases were extra-pulmonary, of which 11 were disseminated. Patients of non-white ethnicity had a six-fold increased risk of TB compared to white patients treated with anti-TNF therapy.
Conclusion
The rate of TB in patients with RA treated with anti-TNF therapy was 3-4 fold higher in patients receiving INF and ADA compared to ETA.

Introduction

The introduction of anti-tumour necrosis factor (anti-TNF) therapy has significantly advanced the treatment of rheumatoid arthritis (RA). However, despite good efficacy, there have always been concerns about safety. A single case of tuberculosis (TB) was reported in the first anti-TNF randomised controlled trial (1). Since then, there has been accumulating evidence from spontaneous pharmacovigilance studies that anti-TNF therapy increases the risk of TB, with a possible differential risk between the three anti-TNF drugs: infliximab (INF) and adalimumab (ADA) (both monoclonal antibodies) having a higher risk than etanercept (ETA), a soluble TNF receptor (2-5). This proposed differential risk is supported by multiple TB cases being reported in RA clinical trials and open label extension studies of INF (1;6-8) and ADA (9-12) but only once within ETA publications (13).

Although the published data suggest a differential risk between drugs, studies to date do not enable robust direct comparisons between drugs. The aim of this study was firstly to compare directly the influence of the three licensed anti-TNF drugs upon the incidence of TB in patients with RA, and then to explore the magnitude of risk in anti-TNF treated patients compared to patients with RA treated with traditional disease modifying anti-rheumatic drug (DMARD) therapy.

Secondary aims included exploring the time to TB onset, the balance of pulmonary and extra-pulmonary disease, and the ethnicity of TB cases.

Methods

The subjects for this analysis were participating in a large national prospective observational study, the British Society for Rheumatology Biologics Register (BSRBR). The methods have been described in detail elsewhere (14). In brief, the study was established in 2001 in order to examine the long-term safety of biologic drugs. UK national guidelines recommended that “any clinician prescribing these medications must (with the patient’s permission) undertake to register the patient with the [BSRBR] and forward information on dosage, outcome and toxicity on a six-monthly basis” (15). Patients were recruited to the ETA and INF cohorts from 2001 onwards. Recruitment to the ADA cohort started later because of its more recent launch date. Recruitment targets of 4000 patients for the ETA cohort were met in 2005, for INF in 2007 and for ADA in 2008. Before recruitment targets were met, we estimated that >80% of anti-TNF treated patients with RA in the UK were registered on the BSRBR.

Analysis was restricted to patients with a physician diagnosis of RA. All patients had to have at least one returned consultant follow-up questionnaire prior to 31/3/08. The anti-TNF cohort comprised patients commencing an anti-TNF drug as their first biologic drug. A comparison cohort of biologic-naïve patients with active RA was recruited in parallel (see authorship list of the BSR Control Centre Consortium) (14). These patients had active disease despite current treatment with a traditional DMARD and were biologic naïve.

Baseline Assessment

Baseline information included demographics, disease duration, 28 swollen and tender joint counts, inflammatory markers and patient global assessment which enables calculation of a disease activity (DAS28) score

(16). Self-reported ethnicity was captured within the patient baseline questionnaire, then categorised as white or non-white. Details of all previous and current DMARD therapy were obtained, as well as smoking history, co-morbidity and prior TB. Data on screening for latent TB were not requested. Patients completed a Health Assessment Questionnaire (HAQ) adapted for British use (17).

Follow-up

Data on changes in therapy, disease activity and the occurrence of adverse events were captured in 3 ways: 6-monthly rheumatologist questionnaire, 6-monthly patient diary and by 'flagging' with the UK Office for National Statistics who provided information on mortality, including cause of death. If active TB was reported from any source, further information including site of infection and supporting evidence for diagnosis (clinical / radiological / microbiological / histopathological) was requested from the rheumatologist. Patient-reported TB cases were only included in the analysis if later verified by a consultant.

Cases were categorised into 'verified' or 'unverified' TB by 3 clinicians, including a consultant in infectious diseases (WGD, JG and AU). Cases were 'verified' if they were culture positive and/or acid fast bacillus (AFB) smear positive, or TB was recorded on the death certificate. Cases of latent TB identified from pre-treatment screening were not included. The site of infection was categorised as pulmonary (including pleural) or extra-pulmonary. All cases of miliary or disseminated TB were categorised as extra-pulmonary.

Statistical Analysis

TB cases were attributed to anti-TNF therapy using two different models: 'on drug' (if the patient was actively receiving that drug at the time of diagnosis) and 'most recent drug' (18). Follow-up was censored at the most recently completed consultant follow-up or death, whichever came first. Patients contributed follow-up time to the 'on drug' model only whilst they were actively receiving the drug (Figure 1). The date of drug discontinuation was taken as the first missed dose. Patients could switch between different anti-TNF drugs and contribute person years (pyrs) to more than one drug. Follow-up was not censored at the time of TB diagnosis. Patients could restart therapy following an episode of TB, either resuming prior therapy or switching drugs. Time following an episode of TB was included to estimate risk reflecting clinical practice. Sensitivity analyses were conducted excluding time after the first diagnosis of TB, and restricting analyses to the first anti-TNF drug.

Comparison patients also contributed pyrs from their registration date until their most recent completed consultant follow-up or death, whichever came sooner. Patients in the comparison cohort who switched to an anti-TNF drug contributed pyrs to the comparison cohort up to the date the anti-TNF drug was started and subsequent follow-up to the anti-TNF cohort. Conversely, patients initially registered in the anti-TNF cohort could not subsequently contribute pyrs to the comparison cohort after stopping anti-TNF therapy.

Incidence rates of TB are presented as events / 100,000 pyrs with 95% confidence intervals (95% CI). Incidence rate ratios (IRR) were calculated using Cox regression, comparing between anti-TNF drugs with ETA as the

referent group. Comparison was then made between the anti-TNF cohort and the DMARD cohort. Adjustment was made for age, gender and calendar year of recruitment. In the absence of cases in the DMARD cohort, an 'expected' number of cases was generated using indirect standardisation: assuming the DMARD cohort shared the same risk as the anti-TNF cohort, allowing for differences in age, gender and calendar year. Analyses examining the influence of ethnicity were performed after adjustment for age, gender and calendar year after exclusion of patients with missing ethnicity data. Multiple variable regression was performed with additional confounders identified from an *a priori* list of possible confounders including smoking, diabetes, chronic obstructive pulmonary disease / asthma, prior TB, disease severity (HAQ, DAS28 and disease duration as continuous variables), number of prior DMARDs, baseline steroid use, and methotrexate use (as a time-varying co-variate). True confounders were identified by sequentially including each confounder in the regression model, and including in the multiple variable regression those confounders that individually changed the estimation post-adjustment by more than 10% (19). All analysis was done using Stata 9.2 (StataCorp, College Station, TX).

Results

13739 patients were included in the analysis: 3232 in the DMARD cohort and 10712 in the anti-TNF cohort. 205 patients switched from the DMARD cohort to the anti-TNF cohort and contributed pyrs to both cohorts. 2552 (24%) patients received two anti-TNF drugs, and 416 (4%) received all three. The baseline characteristics are shown in Table 1. The anti-TNF cohort was younger, comprised proportionally more women and, as expected, had more severe disease than the comparison cohort. Proportionally more patients treated with ETA had prior TB (2.5%) than those treated with INF or ADA (1.5%). Proportionally fewer in the DMARD cohort were of non-white origin.

Total follow-up time was 7345 pyrs for the DMARD cohort and 34025 pyrs for the anti-TNF cohort, with 28447 pyrs spent actively receiving anti-TNF therapy. The median duration of follow-up per patient was 3.21 years for the anti-TNF cohort and 2.30 years for the DMARD cohort. The median duration "on drug" was 2.48 years for ETA, 1.68 years for INF and 1.26 years for ADA.

There were 40 episodes of physician-reported active TB in 39 patients, all in the anti-TNF cohort (detailed in Table S1, on-line supplemental file). There were no cases in the DMARD cohort. 13/40 episodes occurred after discontinuation of the anti-TNF drug. The numbers and rates for the two models of risk attribution are reported in Table 2, with the cumulative incidence shown in Figure 2. Of the 13 cases that occurred 'off drug', 7 were diagnosed within 90 days of stopping treatment. In these cases, the drug was often stopped for symptoms of TB, although the diagnosis was made only after drug discontinuation. One case was diagnosed 6.0 months after stopping ETA, one 11.5 months after stopping INF, and 4 cases after stopping ADA (3.6, 7.3, 12.9 and 13.8 months).

Between drug comparisons

Using the 'on drug' model of attributing risk (upper half of Table 2), the rate of TB was highest for ADA (144 events/ 100,000 pyrs), followed by INF (136/100,000 pyrs) then ETA (39/ 100,000 pyrs). Compared to ETA, the

adjusted IRRs (aIRR) for ADA and INF were 4.2 (1.4, 12.4) and 3.1 (1.0, 9.5), respectively. In the 'most recent drug' model (lower half of Table 2) the aIRRs remained higher for both INF and ADA compared to ETA, although the magnitude of the effect size fell for INF (aIRR 2.2 (0.9, 5.8)). Censoring follow-up at the date of first TB diagnosis did not change the effect size (data not shown). None of the potential confounders changed the point estimate by >10%, and were therefore not included in the regression model. Age and ethnicity were the only potential confounders that were significantly associated with TB (irrespective of their influence upon change in the point estimate).

Comparison between the anti-TNF and DMARD cohorts

No direct comparison between the anti-TNF cohort and the DMARD cohort could be made due to the absence of cases in the DMARD cohort. Indirect standardisation was performed, assuming the DMARD cohort shared the same risk as the anti-TNF cohort. After allowing for differences in age, gender and calendar year, the expected rate in the DMARD cohort was 136 events / 100,000 pyrs (65, 250), equating to 10.0 cases. This was significantly more than the observed 0 cases (one-sided p-value <0.001). Indirect standardisation was also performed assuming the DMARD cohort shared the same risk as the ETA-treated cohort. After allowing for differences in age, gender and calendar year, the expected rate was 41 cases/ 100,000 pyrs (8, 119), equating to 3.1 cases (also significantly increased, p=0.045).

Sensitivity analyses

24/40 (60%) cases were categorised as 'verified and 16 as 'unverified'. Of the 24 verified cases, 2 were most recently treated with ETA, 9 with INF and 13 ADA. Between drug comparisons led to a statistically significantly elevated rate of TB for both monoclonal antibodies compared to ETA, using the 'most recent drug' model.

7 cases of TB occurred following treatment with a second or third anti-TNF drug. Of these, 2 occurred on ADA, 1 on ETA, 3 after discontinuing ADA and 1 after discontinuing ETA. When sensitivity analyses were performed excluding time periods following switching (Table 3), the between-drug aIRRs were largely unchanged.

Time to event

The median time to TB diagnosis from the start of 1st anti-TNF drug was 13.4 months for cases most recently exposed to ETA, 5.5 months for INF and 18.5 months for ADA. Because patients could switch between drugs, the time from start date of first drug does not always reflect time since starting the most recent drug. In the sensitivity analysis excluding time periods after the start of a second anti-TNF drug, the median times to event were 11.0, 5.5 and 15.0 months for ETA, INF and ADA, respectively (Figure 2). The differences in time to diagnosis between the three drugs for both analyses were statistically significant (p<0.05) using a Kruskal-Wallis test.

Site of TB

15/40 cases (38%) were pulmonary and 25 (62%) extra-pulmonary (Table 4). 11 (28%) were disseminated. A lower proportion (50%) of the TB cases after exposure to ETA was extra-pulmonary compared to INF (67%) and ADA (65%). 8/20 (40%) cases in the ADA cohort were disseminated, compared with 2/12 (17%) and 1/8 (13%) in the INF- and ETA-treated cohorts, respectively.

Influence of ethnicity

Ethnicity data were available for 32/39 patients who developed TB. 26 (65%) were white and 6 (15%) non-white. This compared to around 80% patients who were white and 2-3% non-white in the original DMARD and anti-TNF populations. After excluding patients with missing ethnicity data, the age-, sex- and calendar year-adjusted IRR for active TB in non-white compared to white patients was 6.5 (2.8, 15.3).

10/39 patients who developed active TB died within 12 months of diagnosis date. Seven of these had TB listed on their death certificates as the underlying or contributory cause of death (see Table S1, online supplementary file).

One patient had two discrete episodes of TB. A 30 year old white woman developed verified TB in a cervical lymph node 10 months into treatment with ADA. Her ADA was discontinued and she was treated with rifinah, pyridoxine and ethambutol for six months, with confirmed antibiotic sensitivity. Seventeen months later, without any additional anti-TNF therapy, she was diagnosed with verified pulmonary TB. Mycobacterial Interspersed Repetitive Unit (MIRU) typing confirmed this second episode as a relapse of the first.

Discussion

We have confirmed that the monoclonal antibodies INF and ADA are associated with a three- to four-fold higher rate of TB compared to ETA. Although no direct comparison to the DMARD cohort was possible, the expected number of cases (n=10) in the DMARD cohort based on the rate seen in the anti-TNF cohort versus the observed (n=0) suggests that anti-TNF therapy confers a significant risk in patients with active RA. The combined strengths of the large size of the study with the accurate capture of time-dependent drug use and serious adverse event data enabled a robust direct comparison of the rates of TB between the three anti-TNF drugs.

Before concluding that these estimated relative risks represent a true differential risk between the drugs, we should explore alternative explanations. ADA was licensed later, and thus patients receiving ADA may have been more likely to have already received other anti-TNF drugs. Some risk of TB may be carried over from the previous drug, and sequential drug use may have a multiplicative risk. However, the sensitivity analysis censoring follow-up at switching did not change the results. Other factors that may influence the drug-specific rates include calendar year of drug start in parallel with the increasing background UK population rate of TB (12.3 to 14.7 events/ 100,000 pyrs from 2001-2005 (20)) and increasing awareness of, and changing UK guidelines for, TB screening (21). This was addressed by adjusting all analyses for calendar year of recruitment. Nonetheless, there may be some residual confounding.

It has been suggested that there may be a time-varying risk of TB with anti-TNF therapy, with a higher early increased risk for INF compared to ETA (5). Different average durations of follow-up by drug may influence our rate estimates if the risk of TB is non-linear. However, limiting analysis to the first year of follow-up would result in too few cases to allow meaningful comparison between the drugs.

The early belief that the risk of TB was greater for INF- versus ETA-treated patients may have led to a selection bias, where clinicians preferentially prescribed ETA to patients at higher risk of TB. Indeed, proportionally more patients treated with ETA had prior TB, supporting this hypothesis. Assuming no effect of anti-TNF therapy, we might thus expect a higher rate of TB in ETA-treated patients. Our results show the opposite, meaning such a treatment bias does not account for our findings.

Our study did not capture data on all the known risk factors for TB. We did not have data on nutritional status, substance misuse, living environment (e.g. residential care), contact with TB, vitamin D deficiency or immunodeficiency states such as HIV (22). However, it is unlikely that these factors were more prevalent in the monoclonal antibody treated patients than the ETA cohort.

Comparing our results to the published literature, there are few studies attempting to address the question of drug-specific risk. Limitations of prior studies include imprecise estimates of rates in spontaneous pharmacovigilance studies resultant from under-reporting of cases and an unknown denominator (4;5) and low numbers of events in observational studies (23;24). The French RATIO study recently attempted to address drug-specific risk by calculating event "rates" from spontaneously reported cases of TB and estimates of national anti-TNF drug use across all indications (25). Our findings support the original suggestion that the rate of TB may be higher in INF- compared to ETA-treated patients (3;26) although to a lesser extent than the French study (25). Our finding that TB rates are highest in patients treated with ADA is supported by a high rate of TB in the ADA open label extension study (12). The possible mechanisms underlying this differential risk of TB have been elegantly reviewed elsewhere (27).

Active TB was diagnosed only in patients treated with anti-TNF therapy. If patients in the DMARD cohort had an equal risk to those in the anti-TNF cohort, we would have expected to see 10 TB cases in the DMARD cohort. The magnitude of difference between the observed and expected cases strongly suggests that anti-TNF therapy is associated with significant risk of TB above and beyond the risk conferred by RA alone. The indirect standardisation data also support an increased risk for ETA, where the expected number of cases in the DMARD cohort would have been 3.1. This finding suggests that, whilst the rates of TB are higher in patients treated with the monoclonal antibodies, patients treated with ETA are not without risk. The average annual incidence of TB for the period of the study in the UK general population was 13.2 events / 100,000 pyrs (20). The anti-TNF rate was therefore 8 times higher than the UK general population. The magnitude of increased risk is higher than the estimated four-fold increased risk conferred by RA in the pre-biologic era from non-UK sources (24). Unfortunately there are no previously published rates of TB in UK RA populations from the pre-biologic era. Because of widely varying international TB incidence, it is not valid to compare our rates to those in other national RA cohorts. Nonetheless, the magnitude of risk in the anti-TNF cohort compared with the general population fits with prior estimates from other countries (23;28).

All TB cases in the analysis were confirmed by a physician. The 'gold standard' for diagnosing TB is culture of *Mycobacterium tuberculosis* bacilli. However, in clinical practice, physicians diagnose and treat TB based on

weaker criteria such as the presence of acid fast bacilli, caseating granulomata, suggestive radiological findings, or even clinical suspicion. We categorised our cases as verified or unverified. Our tight classification for verified TB led to the exclusion of 16 cases. Nonetheless, restriction to verified cases generated the same pattern of drug-specific risk.

Prior estimates of the frequency of extra-pulmonary TB in patients treated with anti-TNF therapy have ranged from 28-75%, with most reporting >50% cases as extra-pulmonary. Our study replicates these findings, but in addition shows a greater increased risk of extra-pulmonary disease with the monoclonal antibodies, a finding not previously described. Our finding of a significant risk conferred by non-white ethnicity in patients treated with anti-TNF therapy also reflects similar findings in the RATIO study (25).

There are a number of clinically important points to take from this analysis. Firstly, although the relative risk of TB is 3-4 times higher for the monoclonal antibodies compared to ETA, the actual number of cases is low. After a total follow-up time of nearly 35,000 pyrs, we identified only 40 cases of TB. The 'number needed to harm' for 1 year's therapy with ADA compared to ETA in this study is around 600. That said, the UK is a country with a relatively low prevalence of TB. Such a differential risk would likely have greater implications in countries with higher background prevalence. Secondly, the lower rate with ETA compared to the other anti-TNF drugs does not mean that there is a negligible risk with this drug. Although relatively safer than the monoclonal antibodies, clinicians should be aware that ETA still confers an increased risk. Thirdly, the high prevalence of disseminated TB should remind clinicians that TB may present atypically in patients treated with anti-TNF therapy. Lastly, nearly half of the disseminated TB cases in patients most recently treated with ADA occurred after therapy had been stopped, with 13 of the total cases being diagnosed after stopping therapy (6/13 >3 months after stopping). This should remind clinicians to remain vigilant for TB even after discontinuing anti-TNF therapy.

*** BSRBR Control Centre Consortium**

Antrim Area Hospital, Antrim (Dr Nicola Maiden)
Cannock Chase Hospital, Cannock Chase (Dr Tom Price)
Christchurch Hospital, Christchurch (Dr Neil Hopkinson)
Derbyshire Royal Infirmary, Derby (Dr Sheila O'Reilly)
Dewsbury and District Hospital, Dewsbury (Dr Lesley Hordon)
Freeman Hospital, Newcastle-upon-Tyne (Dr Ian Griffiths)
Gartnavel General Hospital, Glasgow (Dr Duncan Porter)
Glasgow Royal Infirmary, Glasgow (Prof Hilary Capell)
Haywood Hospital, Stoke-on-Trent (Dr Andy Hassell)
Hope Hospital, Salford (Dr Romela Benitha)
King's College Hospital, London (Dr Ernest Choy)
Kings Mill Centre, Sutton-In Ashfield (Dr David Walsh)
Leeds General Infirmary, Leeds (Prof Paul Emery)
Macclesfield District General Hospital, Macclesfield (Dr Susan Knight)
Manchester Royal Infirmary, Manchester (Dr Ian Bruce)
Musgrave Park Hospital, Belfast (Dr Allister Taggart)
Norfolk and Norwich University Hospital, Norwich (Prof David Scott)
Poole General Hospital, Poole (Dr Paul Thompson)

Queen Alexandra Hospital, Portsmouth (Dr Fiona McCrae)
Royal Glamorgan Hospital, Glamorgan (Dr Rhian Goodfellow)
Russells Hall Hospital, Dudley (Prof George Kitas)
Selly Oak Hospital, Selly Oak (Dr Ronald Jubb)
St Helens Hospital, St Helens (Dr Rikki Abernethy)
Weston General Hospital, Weston-super-Mare (Dr Shane Clarke)
Withington Hospital, Manchester (Dr Paul Sanders)
Withybush General Hospital, Haverfordwest (Dr Amanda Coulson)

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Table 1. Baseline characteristics

	DMARD n=3232[†]	All Anti-TNF n=10712[†]	p-value*	First anti-TNF drug:			p-value**
				ETA n=3913	INF n=3295	ADA n=3504	
Mean age: years (sd)	60 (12)	56 (12)	<0.001	56 (12)	56 (12)	57 (12)	0.012
Females: %	72	76	<0.001	77	76	75	0.108
Mean DAS28 (sd)	5.1 (1.3)	6.6 (1.0)	<0.001	6.6(1.0)	6.6(1.0)	6.5(1.0)	<0.001
Mean HAQ (sd)	1.5 (0.8)	2.0 (0.6)	<0.001	2.1(0.6)	2.1(0.5)	2.0(0.6)	<0.001
Median disease duration: years (IQR)	6 (1-15)	11 (6-19)	<0.001	12 (6-19)	12 (6-19)	10 (5-18)	<0.001
Number of prior DMARDs: median (IQR)	2 (1-3)	4 (3-5)	<0.001	4 (3-5)	4 (3-5)	3 (3-5)	<0.001
Baseline steroid use: n (%)	744 (23)	4753 (44)	<0.001	1860(48)	1520(46)	1373(39)	<0.001
Diabetes: n (%)	212 (6.6)	596 (5.6)	0.034	236 (6.1)	156 (4.8)	204 (5.9)	0.042
COPD / Asthma: n (%)	590 (18.4)	1429 (13.5)	<0.001	558 (14.4)	423 (13.0)	448 (12.9)	0.104
Prior TB: n (%)	74 (2.3)	201 (1.8)	0.193	96 (2.5)	53 (1.5)	52 (1.5)	0.05
Smoking:							
- Current: n (%)	751 (23)	2334 (22)	0.013	805 (21)	718 (22)	811 (23)	0.057
- Former: n (%)	1273(40)	4067 (38)		1485(38)	1247(38)	1335(38)	
- Never: n (%)	1191(37)	4249 (40)		1599(41)	1314(40)	1336(38)	
Ethnicity: n (%)							
- white	2509(78)	8873 (83)	<0.001	3228(82)	2704(82)	2941(84)	0.363
- non-white	59 (2)	366 (3)		124 (3)	124 (4)	118 (3)	
- missing	664 (21)	1473 (14)		561(14)	467 (14)	445 (13)	
Entry year: n (%)							
- pre-2003	11 (0)	1322 (12)	<0.001	181 (5)	1112(34)	29 (1)	<0.001
- 2003	306 (9)	2924 (27)		1440(37)	1063(32)	421 (12)	
- 2004	886 (27)	3092 (29)		1876(48)	485 (15)	731 (21)	
- 2005	925 (29)	1537 (14)		412 (11)	326 (10)	799 (23)	
- 2006 +	1104(34)	1837 (17)		4 (0)	309 (10)	1524(43)	

sd: standard deviation, IQR: interquartile range, TB: tuberculosis, HAQ: Health assessment questionnaire, COPD: chronic obstructive pulmonary disease, DMARDs: disease modifying anti-rheumatic drugs

[†] 205 patients switched from the DMARD cohort to the anti-TNF cohort and contributed pyrs to both cohorts

* p-value represents the significance of differences between the DMARD and anti-TNF cohorts using chi-squared tests for categorical outcomes and Wilcoxon rank sum tests for continuous variables

** p-value represents the significance of differences between the three anti-TNF drugs using chi-squared tests for categorical outcomes and Kruskal-Wallis rank tests for continuous variables

Table 2. Numbers and rates of incident tuberculosis, switchers included

Number of patients ever received the drug	DMARD n=3232	All Anti-TNF n=10712	ETA n=5521	INF n=3718	ADA n=4857
On drug*					
Person years	7345	28447	12744	8069	7634
Cases of TB	0	27	5	11	11
Rate / 100,000 pyrs (95% CI)	0	95 (63, 138)	39 (13, 92)	136 (68, 244)	144 (72, 258)
IRR, adjusted for age, gender and entry year (95% CI)			Referent	3.1 (1.0, 9.5)	4.2 (1.4, 12.4)
Most recent drug*					
Person years	7345	34025	15070	9730	9224
Cases of TB	0	40	8	12	20
Rate / 100,000 pyrs (95% CI)	0	118 (84, 160)	53 (23,105)	123 (64,215)	217 (132,335)
IRR, adjusted for age, gender and entry year (95% CI)			Referent	2.2 (0.9, 5.8)	4.2 (1.8, 9.9)

Patients could switch between anti-TNF therapies, but all TB cases were attributable to 1 drug only

*The two models of risk attribution are illustrated in Figure 1

Table 3. Numbers and rates of incident tuberculosis, limited to first anti-TNF drug (Follow-up censored at date of commencing 2nd anti-TNF drug.)

Number of patients ever received the drug	**DMARD n=3232**	**All Anti-TNF n=10712**	**ETA n=3913**	**INF n=3295**	**ADA n=3504**
On drug*					
Person years	7345	23286	10111	7459	5716
Cases of TB		24	4	11	9
Rate / 100,000 pyrs (95% CI)		103 (66, 153)	40 (11, 101)	147 (74, 264)	157 (72, 299)
IRR, adjusted for age, gender and entry year (95% CI)			Referent	3.7 (1.1, 12.7)	4.4 (1.3, 15.2)
Most recent drug*					
Person years	7345	27624	11926	8963	6735
Cases of TB		33	6	12	15
Rate / 100,000 pyrs (95% CI)		119 (82, 168)	50 (18, 110)	134 (69, 234)	223 (125, 367)
IRR, adjusted for age, gender and entry year (95% CI)			Referent	2.7 (0.9, 7.8)	4.4 (1.6, 12.1)

*The two models of risk attribution are illustrated in Figure 1

Table 4. Classification and sites of TB infection, by drug

		ETA n=8 [5]	INF n=12 [11]	ADA n=20 [11]	All anti-TNF n=40 [27]
Pulmonary n=15 (38% total)	Lower respiratory tract	4 [2]	2 [2]	6 [3]	12 [7]
	Pleural	-	2 [2]	1 [1]	3 [3]
	Total pulmonary	4 [2]	4 [4]	7 [4]	15 [10]
Extra-pulmonary (including disseminated) n=25 (62% total)	Bone & joint	1 [1]	-	-	1 [1]
	Gastrointestinal	-	3 [3]	-	3 [3]
	Lymph node	2 [2]	2 [2]	2 [2]	6 [6]
	Central nervous system	-	1 [1]	2 [1]	3 [2]
	Pharyngeal wall	-	-	1 [1]	1 [1]
	Disseminated	1 [0]	2 [1]	8 [3]	11 [4]
	Total extra-pulmonary	4 [3]	8 [7]	13 [7]	25 [17]

Numbers represent number of cases attributable to most recent drug [number of cases whilst 'on drug']

Figure 1. Models for attributing TB to drug therapy
Model A: 'on drug'. Pyrs and adverse events were attributed to each drug only whilst the patient was actively receiving that drug. Event A was not attributed to any drug, whilst event B was attributed to drug 2. Model B: 'most recent drug'. Pyrs were accrued for each drug from the start date of that drug until the date of switching to the next anti-TNF drug irrespective of drug discontinuation. Follow-up was censored at the most recently completed consultant follow-up or death, whichever came first, for all models.

Figure 2. Cumulative incidence of TB following first exposure to anti-TNF therapy (most recent drug model, with pyrs censored at death, last returned follow-up form, or date of switching to 2nd anti-TNF).

Numbers in table represent the number of patients eligible for follow-up at the specified follow-up time points.

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Table S1. Clinical table of TB cases in patients who ever received anti-TNF therapy, grouped by most recent anti-TNF exposure

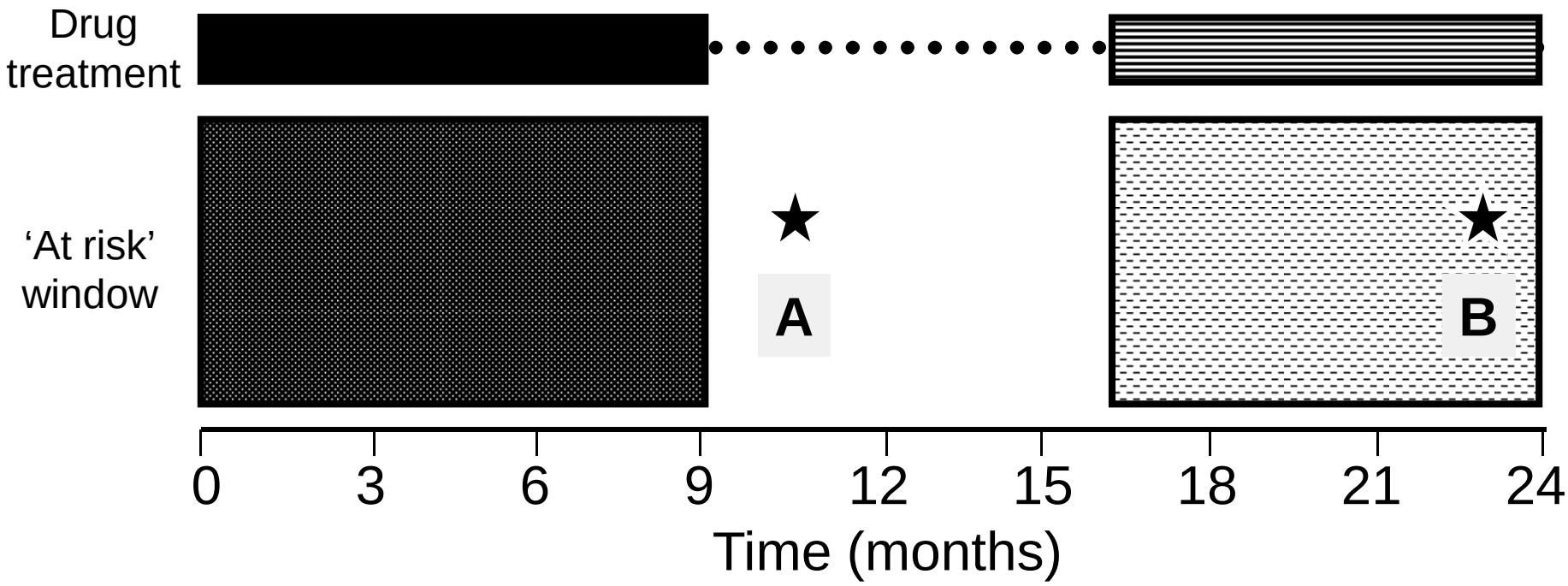
Patient number	Age group	Ethnicity	Prior TB	Biologic history (months from registration treated)	Time of TB diagnosis (months from registration)	Site	Verification	Outcome[§]
ADALIMUMAB								
1	61-70	Chinese	No	ADA 0-3 ETA 9-20	2	Lymph node	Verified	Alive
2	61-70	Indian	No	ADA 0-15	5	Lower respiratory tract	Unverified	Alive
3	51-60	White	Scarring on baseline CXR and CT highly suggestive	ADA 0-6	7**	Disseminated	Verified	Died [†]
4*	21-30	Missing	No	ADA 0-12	10	Lymph node	Verified	Alive
5	71-80	White	No	ADA 0-11	11**	Disseminated	Verified	Died [†]
6	71-80	White	No	ADA 0-13	11	Pharyngeal wall	Unverified	Alive
7	31-40	Other	No	ADA 0-13	12	Disseminated	Unverified	Alive
8	51-60	Missing	No	ETA 0-5 ADA 6-13	14**	Disseminated	Unverified	Alive
9	71-80	White	No	ADA 0-15	15	Lower respiratory tract	Verified	Alive
10	51-60	Missing	No	ADA 0-14	18**	Central nervous system	Verified	Alive
11	51-60	White	No	ETA 0-7 ADA 8-11 RTX 36	19**	Lower respiratory tract	Verified	Alive
12	71-80	White	No	ADA 0-7	19**	Lower respiratory tract	Verified	Died
13	61-70	White	No	ADA 0-22	22**	Disseminated	Verified	Alive
14	71-80	Missing	No	ADA 0-23	23	Disseminated	Verified	Died [†]

4*	21-30	Missing	No	ADA 0-12	26**	Lower respiratory tract	Verified	Alive
15	41-50	White	No	ADA 0-26	26	Central nervous system	Unverified	Alive
16	51-60	White	No	ADA 0-34	33	Disseminated	Unverified	Alive
17	51-60	White	No	ETA 0-26 ADA 26-36	37**	Disseminated	Verified	Died †
18	51-60	White	No	INF 0-7 ADA 7-46	46	Lower respiratory tract	Unverified	Died
19	61-70	Missing	Missing	INF 0-40 ADA 41-53	53	Lower respiratory tract	Verified	Alive
ETANERCEPT								
20	31-40	White	No	ETA 0-5	5	Lymph node	Unverified	Alive
21	41-50	White	No	ETA 0-7	6	Lower respiratory tract	Unverified	Alive
22	61-70	Black-Caribbean	No	ETA 0-9	9	Lower respiratory tract	Unverified	Alive
23	41-50	White	Yes Spinal TB 1956	ADA 0-6 ETA 6-14 ETA 21-24	13	Bone and joint	Unverified	Alive
24	51-60	Missing	No	ETA 0-31	13	Lymph node	Unverified	Alive
25	71-80	White	No	INF 0-4 ETA 6-8	14**	Disseminated	Verified	Alive
26	71-80	White	No	ETA 0-24	24**	Pleural	Unverified	Alive
27	61-70	White	No	ETA 0-41 RTX 50-?	42**	Lower respiratory tract	Verified	Alive
INFLIXIMAB								
28	61-70	Missing	No	INF 0-4	2	Central nervous system	Unverified	Alive
29	41-50	White	No	INF 0-3 ETA 30-present	2	Gastrointestinal	Verified	Alive
30	41-50	White	No	INF 0-10	3	Pleural	Unverified	Died
31	71-80	White	No	INF 0-4	3	Gastrointestinal	Verified	Alive
32	41-50	Pakistani	No	INF 0-3	3	Lymph node	Verified	Alive
33	51-60	Indian	No	INF 0-6	4	Pleural	Unverified	Alive

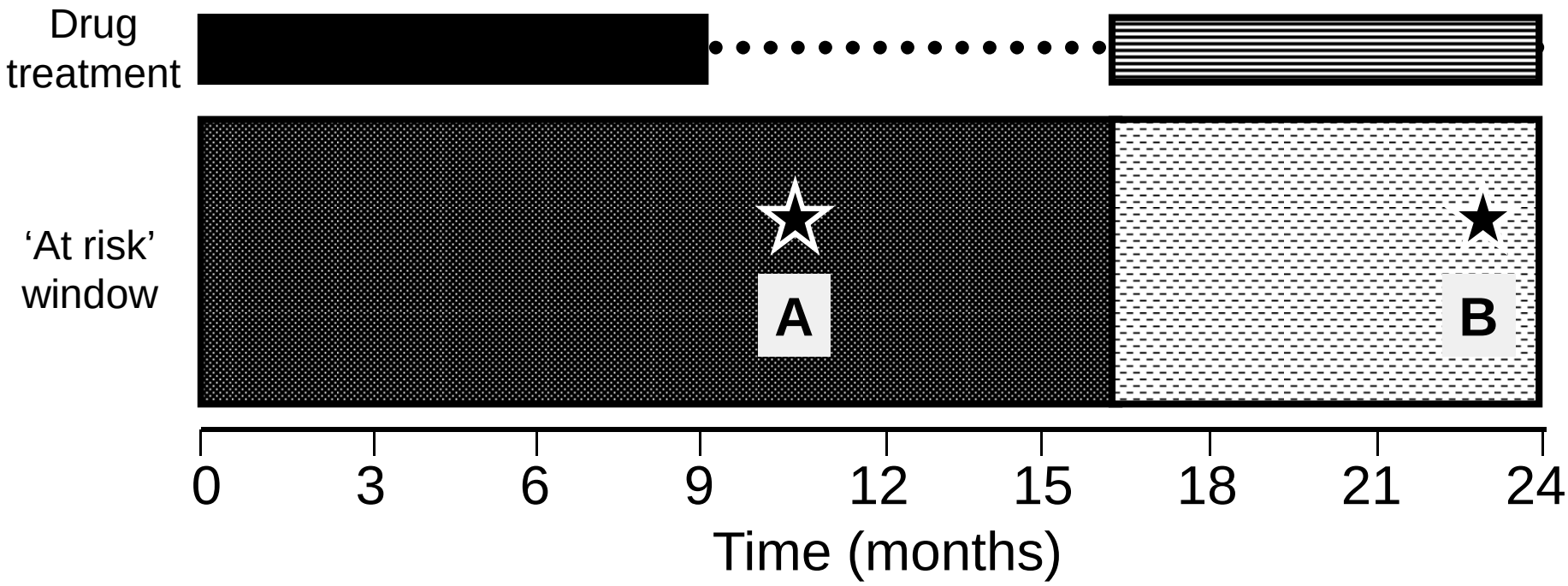
34	51-60	White	No	INF 0-9	7	Lymph node	Verified	Alive
35	71-80	White	No	INF 0-8	8	Disseminated	Verified	Died †
36	61-70	White	No	INF 0-11 ADA 28-31	11	Lower respiratory tract	Verified	Died †
37	61-70	White	No	INF 0-2 INF 3-12 INF 18-present	14	Lower respiratory tract	Verified	Alive
38	61-70	White	No	INF 0-14	14	Gastrointestinal	Verified	Alive
39	71-80	White	No	INF 0-3	15 **	Disseminated	Verified	Died †

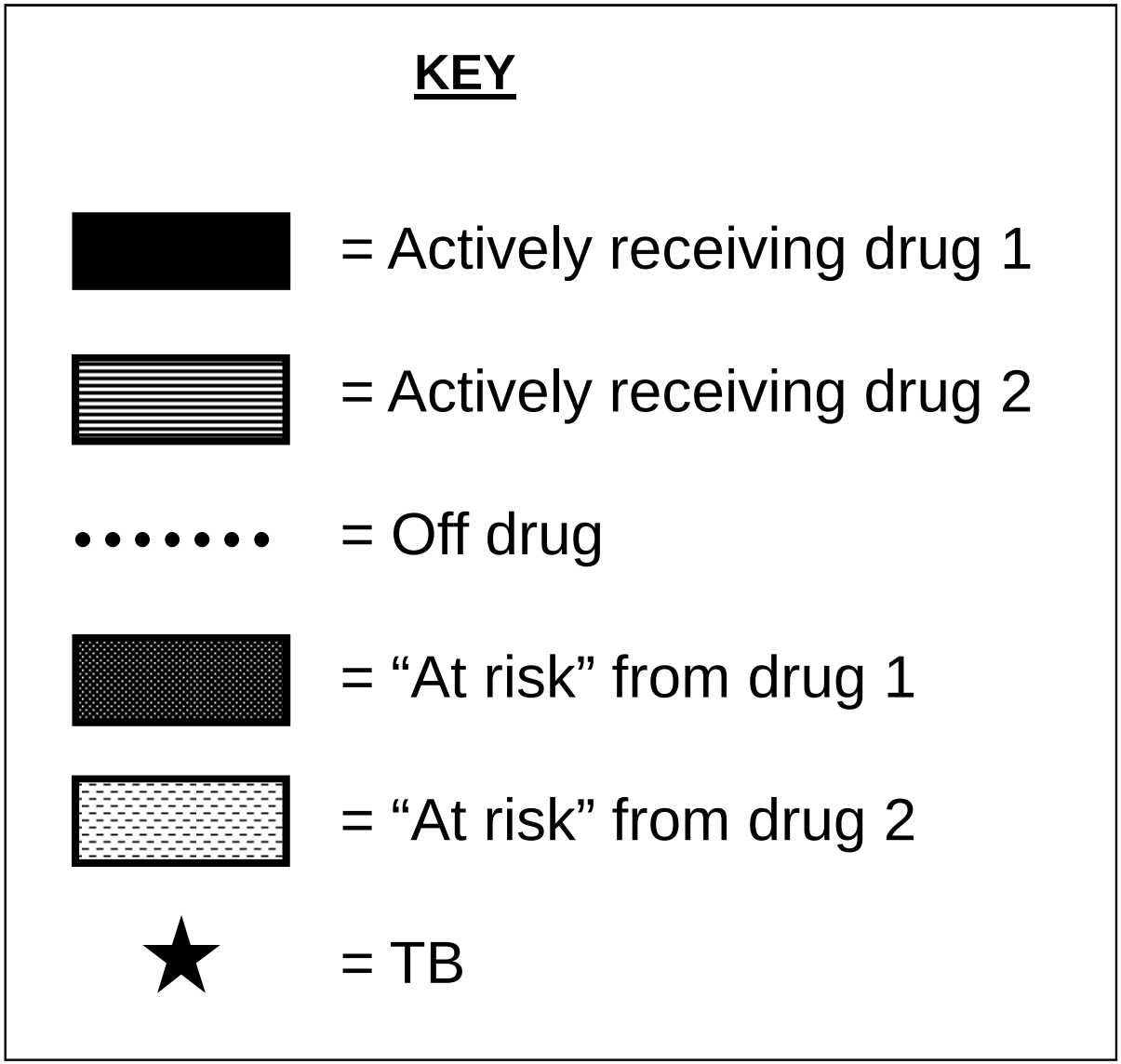
§ Outcome = survival to 12 months following TB diagnosis, or most recent returned follow-up, whichever comes sooner
† = Deaths where TB was reported on the death certificate
* Patient 4 had 2 episodes of TB (microbiological identification confirmed identical organism)
** Episodes where TB developed after the patient had stopped anti-TNF therapy

A) On drug



B) Most recent drug





Drug	Registration (entry to study)	1 year (365 days)	2 years (730 days)	3 years (1095 days)	4 years (1460 days)
DMARD	3232	2652	1839	742	213
ETA	3913	3474	3051	2363	1020
INF	3295	2694	1918	1392	918
ADA	3504	2457	1531	729	247