Venous thrombotic events are not increased in patients with rheumatoid arthritis treated with anti-TNF therapy: results from the British Society for Rheumatology Biologics Register

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ABSTRACT

Objectives Past studies have reported conflicting rates of venous thrombotic events (VTEs) in rheumatoid arthritis (RA). The current study aimed to compare (1) the rates of VTEs in patients with RA treated with anti-tumour necrosis factor (anti-TNF) therapy versus those treated with non-biological disease-modifying antirheumatic drugs (nbDMARDs) alone and (2) the rates between each individual anti-TNF agent and nbDMARDs.

Methods Using data from the British Society for Rheumatology Biologics Register, a national prospective observational cohort study of biological safety in patients with RA, the authors compared the incidence of VTEs between 11 881 anti-TNF- and 3673 nbDMARD-treated patients. Analysis was limited to the first VTE per person. HRs were calculated using Cox modelling. Adjustment was made for potential confounders including surgery performed during follow-up.

Results A total of 196 first VTEs were reported (151 anti-TNF, 45 nbDMARD). Overall there was no difference in the rates of VTEs between anti-TNF- and nbDMARD-treated patients (adjusted HR 0.8 (95% CI 0.5 to 1.5)). The risk was similar across all anti-TNF agents. Rates of postoperative VTEs did not significantly differ between groups.

Conclusions These data suggest that anti-TNF therapy is not associated with an increased risk of VTEs in RA patients.

INTRODUCTION

Rheumatoid arthritis (RA) is associated with increased mortality and co-morbidity compared with the general population.[1 2] RA patients may have an increased risk of developing venous thrombotic events (VTEs), based on the high prevalence of many known VTE risk factors.[3 4] Studies examining the incidence of VTEs in patients with RA have been discordant.[5 6]

The introduction of anti-tumour necrosis factor (anti-TNF) drugs for the treatment of RA has improved the outcomes of RA dramatically.[7–9] However, there remain concerns about their long-term safety. Case reports[10 11] and retrospective studies[12–15] looking at VTEs in anti-TNF-treated RA patients have produced conflicting results.

To study this further, the current analysis aimed to compare (1) the rates of VTEs in RA patients treated with anti-TNF and non-biological disease-modifying antirheumatic drugs (nbDMARDs) and (2) the rates between the individual anti-TNF agents and nbDMARDs.

METHODS

A full description of the methods relating to this analysis is available in our publication examining the risk of septic arthritis in this same cohort.[16]

In brief, the British Society for Rheumatology Biologics Register (BSRBR) is a national prospective cohort study that was established in 2001. Patients with active RA who were starting treatment with anti-TNF therapy were enrolled for observational follow-up. Three anti-TNF agents were currently in use during the study period analyses: etanercept (ETN), infliximab (INF) and adalimumab (ADA). A comparison cohort of RA patients with active disease currently receiving an nbDMARD was recruited and followed up in parallel.

Baseline information was collected regarding demographics, disease severity and co-morbidity. There were three sources of data collection during follow-up: consultant questionnaires, patient questionnaires and diaries, and the UK national cancer and death register (National Health Service Information Centre).

Adverse events from these sources were coded using MedDRA (the Medical Dictionary for Regulatory Activities).

Definition of outcome

This analysis limited outcomes to the first VTE per person. All events were verified by a BSRBR physician (JG) according to prespecified criteria (online supplementary table 1). VTEs were classified as postoperative if they occurred within 90 days of any surgery.

Statistical methods

Patients in the anti-TNF cohort were considered to be exposed from the date first treated with an anti-TNF drug until the first VTE, most recent follow-up, first missed dose of anti-TNF therapy or death. We did not include a 90-day lag window after the first missed dose in our primary analysis model as we felt that the effect of anti-TNF therapy upon thrombosis risk would cease after the drug had been eliminated from the body. For patients in the

comparison cohort, follow-up started at the time of registration until first VTE, most recent follow-up form or death. Incidence rates of VTEs are presented as events per 1000 person years (pyrs) with 95% CIs. Survival analyses, performed using a Cox proportional hazards model, were used to compare the rates of VTEs between cohorts. Inverse probability of treatment weighting[16] was used to adjust for confounding between the groups, including age and gender, disease severity (baseline 28-joint Disease Activity Score and Health Assessment Questionnaire), disease duration, year of entry into the study, use of baseline steroids, smoking status and co-morbidity (hypertension, chronic lung disease and diabetes). Surgery was entered into the model as a time-varying covariate, with patients considered to be at risk for 90 days postprocedure. An additional analysis evaluated the risk of postoperative VTEs using logistic regression to compare the risk of VTEs following surgery. Patients could contribute multiple surgeries to this analysis. Adjustment was made for the same confounders used in the main analysis. For all analyses, missing baseline data were replaced using multiple imputations.[16] All analyses were performed using Stata V.10 software (StataCorp, College Station, Texas, USA).

RESULTS

This analysis included 15 554 patients (11 881 anti-TNF, 3673 nbDMARD cohort). The anti-TNF cohort comprised 4139 patients starting ETN, 3475 patients starting INF and 4267 patients starting ADA. The baseline characteristics are displayed in table 1, which shows that the anti-TNF cohort was younger and comprised proportionally more women. The anti-TNF cohort also had more severe disease of a longer duration and had greater exposure to steroids at baseline.

There were 196 verified VTEs (anti-TNF: 151, nbDMARD: 45) with an overall crude incident rate of 3.7 (95% CI 3.1 to 4.3)/1000 pyrs and 3.9 (95% CI 2.9 to 5.3)/1000 pyrs, respectively. The unadjusted HR was 1.1 (95% CI 0.8 to 1.6) and fully adjusted HR was 0.8 (95% CI 0.5 to 1.5) (table 2). We conducted sensitivity analyses to calculate HRs in those on drugs with a 90-day lag window, which did not alter the results (online supplementary table 2). Supplementary data are available detailing univariate predictors of VTEs and HRs for unimputed data (online supplementary tables 3–5).

When comparing the anti-TNF agents, the crude incidence of VTEs was highest in the INF group at 4.7 events per 1000 pyrs, compared with 3.3 for ADA- and ETN-treated patients. After adjusting for confounders, none of the hazard estimates for the individual anti-TNF agents differed significantly from the nbDMARD cohort (table 2). Analyses comparing individual anti-TNF agents with each other also showed no significant differences.

In total (allowing multiple surgeries per patient), 5584 surgical operations were reported during follow-up (table 3). Orthopaedic procedures accounted for 3948 (71%) of the surgeries performed. Twenty-one surgeries were complicated by a VTE (anti-TNF: 18/4572, nbDMARD: 3/1012). The fully adjusted OR for postoperative VTEs in the anti-TNF cohort compared with the nbDMARD cohort was 1.9 (95% CI 0.5 to 7.4) (table 3). A sensitivity analysis limited to orthopaedic procedures showed similar findings (results not shown).

DISCUSSION

The data from this BSRBR cohort have shown that treatment with ETN, INF or ADA was not associated with a change in the risk of first VTE, either de novo or in the postoperative period.

This cohort had over 90% power to detect a doubling in the risk of VTEs but only 60% power to detect a 50% increase in the anti-TNF cohort compared with the DMARD cohort. Therefore, although we are confident that we can exclude a doubling in risk of VTEs with the TNF inhibitors studied here, differences of a smaller magnitude cannot be excluded. However, given the incidence of VTEs was 3.7/1000 pyrs in the nbDMARD cohort, smaller differences would be of questionable clinical relevance. For example, a 50% increase in relative risk would represent a small risk in absolute terms, equivalent to a number needed to treat one additional event of 540.

Comparing rates of events between the three anti-TNF cohorts must be done with caution. For example, it is important to acknowledge that differences exist relating to recruitment of patients to the anti-TNF cohorts by calendar year.[17] This could be of particular relevance if we were to compare differences in the rates of postoperative VTEs when variations in rates could be partly explained by changes in the prescribing of anticoagulants following high-risk procedures. However, accepting the limitations of between-drug comparisons, our data show that the risk between ETN, INF and ADA for VTEs is broadly comparable.

The rates of postoperative VTEs in this cohort were reassuring, with approximately 4 out of every 1000 procedures being complicated by VTEs in all cohorts. Although the OR for postoperative VTEs for the anti-TNF cohort was 1.9, the 95% CI was wide and this result should not be interpreted as a significant finding. Research into this possible association could be explored further in countries with access to national registers of surgical procedures.

Table 1 Baseline characteristics of the nbDMARD- and anti-TNF-treated patients

Characteristic	nbDMARD n=3673	Anti-TNF n=11 881	p Value	ETN n=4139	INF n=3475	ADA n=4267	p Value
Age, mean (SD)	60 (12)	56 (12)	0.0001	56 (12)	56 (12)	57 (12)	0.0184
Gender, % female	72	76	<0.0001	77	76	76	0.203
Disease duration, median (IQR) years	6 (1–15)	11 (6–19)	0.0001	12 (6–19)	12 (6–19)	10 (5–18)	0.0001
DAS28 score, mean (SD)	5.1 (1.3)	6.6 (1.0)	0.0001	6.6 (1.0)	6.6 (1.0)	6.5 (1.0)	0.0001
HAQ score, mean (SD)	1.5 (0.8)	2.0 (0.6)	0.0001	2.1 (0.6)	2.1 (0.5)	2.0 (0.6)	0.0001
Corticosteroids, no. (%)	837 (23)	5, 252 (44)	<0.0001	1979 (48)	1609 (46)	1664 (39)	<0.0001
Diabetes, no. (%)	247 (7)	685 (6)	0.033	255 (6)	169 (5)	261 (6)	0.026
Hypertension, no. (%)	1171 (32)	3563 (30)	0.041	1283 (31)	966 (28)	1314 (31)	0.002
Smoking history, no. (%)			0.001				0.056
Current smoker	868 (24)	2580 (22)		846 (21)	757 (22)	977 (24)	
Former smoker	1454 (40)	4510 (38)		1576 (38)	1314 (38)	1620 (38)	
Never smoked	1333 (36)	4714 (40)		1691 (41)	1386 (40)	1637 (39)	

ADA, adalimumab; Anti-TNF, anti-tumour necrosis factor; DAS28, 28-joint Disease Activity Score; ETN, etanercept; HAQ, Health Assessment Questionnaire; INF, infliximab; nbDMARD, non-biological disease-modifying antirheumatic drug.

Table 2 Crude incidence rates and hazard rates of verified first VTE in nbDMARD and anti-TNF-treated patients

	nbDMARD n=3673	Anti-TNF n=11 881	ETN n=4139	INF n=3475	ADA n=4267
Exposure (person years)	11 424	41 235	17 977	10 484	12 773
Total VTEs, n	45	151	60	49	42
VTE incidence rate/1000 person years (95% CI)	3.9 (2.9 to 5.3)	3.7 (3.1 to 4.3)	3.3 (2.5 to 4.3)	4.7 (3.5 6.2)	3.3 (2.4 to 4.4)
Unadjusted HR (95% CI)	Ref	1.1 (0.8 to 1.6)	1.0 (0.7 to 1.6)	1.4 (0.9 to 2.1)	1.0 (0.6 to 1.5)
Adjusted HR (95% CI)*	Ref	0.8 (0.5 to 1.5)	0.8† (0.4 to 1.4)	1.1† (0.6 to 1.9)	0.8† (0.4 to 1.4)

ADA, adalimumab; Anti-TNF, anti-tumour necrosis factor; ETN, etanercept; INF, infliximab; nbDMARD, non-biological disease-modifying antirheumatic drug; VTE, venous thrombotic event.
*Inverse probability of treatment weighting model adjusted for age, gender, diabetes, baseline steroid exposure, smoking, hypertension, disease duration, disease severity, year of first anti-TNF drug and year of entry into study, with surgery as a time-varying covariate.
†Differences between INF and ETN rates were non-significant (p=0.186). Differences between INF and ADA rates were non-significant (p=0.105).

Table 3 Surgery table

	nbDMARD	Anti-TNF	ETN	INF	ADA
Total surgeries (n)	1012	4572	2074	1170	1328
Total orthopaedic (n)	599	3349	1535	859	955
No. of patients having surgery (n)	699	2816	1184	743	889
Orthopaedic (n)	424	2104	908	546	650
Patients with more than one surgery (n)	227	1051	486	266	299
Orthopaedic (n)	129	726	334	178	214
No. postoperative VTEs (n)	3	18	6	6	6
Postop VTE crude rates (95% CI)	3.0 (0 to 6.3)	4.0 (2.1 to 5.8)	2.9 (0.6 to 5.2)	5.1 (1.0 to 9.3)	4.5 (0.9 to 8.2)
Unadjusted OR (95% CI)	Referent	1.3 (0.4 to 4.5)	–	–	–
Fully adjusted OR (95% CI)*	Referent	1.9 (0.5 to 7.4)	–	–	–

*Adjusted for age, gender, diabetes, baseline steroid exposure, smoking, hypertension, disease duration, disease severity, year of first anti-TNF drug and year of entry into study.
ADA, adalimumab; Anti-TNF, anti-tumour necrosis factor; ETN, etanercept; INF, infliximab; nbDMARD, non-biological disease-modifying antirheumatic drug; VTE, venous thrombotic event.

The main strengths of the BSRBR data have been detailed previously[18] and relate to the prospective nature of the study, the large size of the cohort and the detailed data collection during follow-up. Several important limitations must also be considered when interpreting these results. The observational nature of the BSRBR predisposes to channelling bias, whereby patients with more severe disease are more likely to be enrolled into the anti-TNF cohort. Although we have made extensive efforts to adjust for this, we must acknowledge that it is likely some unmeasured confounding persists. In particular, we have only made adjustment for confounders that we record at baseline. Disease severity and steroid exposure are examples of variables that we would predict to change significantly during follow-up. Higher disease activity may well represent a prothrombotic state and would be likely to correlate to immobility; therefore, correct adjustment for this factor is clearly important. Further research is needed to establish how best we should take these factors into account.

In conclusion, this study found no evidence that anti-TNF therapy is associated with an increased risk of VTEs in RA patients, with no difference in risk observed between the anti-TNF drugs. Although this is a negative study, it has important implications. These results strengthen the evidence base and will help enable patients and healthcare professionals to make informed choices regarding therapy.

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Competing interests DPMS and KLH are principal investigators on the BSRBR. BSR receives restricted income from UK pharmaceutical companies, presently Abbott Laboratories, Biovitrum, Merck Sharp & Dohme, Pfizer and Roche. This income finances a wholly separate contract between the BSR and the University of Manchester. 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. Members of the Manchester team, BSR trustees, committee

members and staff complete an annual declaration in relation to conflicts of interest. The authors declare no other conflicts of interest.

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

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Appendix A: BSRBR Control Centre Consortium

The BSRBR Control Centre Consortium consists of the following institutions (all in the UK): 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/Dr Sandra Green), Withington Hospital, Manchester (Dr Paul Sanders), Withybush General Hospital, Haverfordwest (Dr Amanda Coulson), North Manchester General Hospital (Dr Bev Harrison), Royal Lancaster Infirmary (Dr Marwan Bukhari) and The Royal Oldham Hospital (Dr Peter Klimiuk).

Supplementary Table 1 – Validation of VTE events.

Validation stages	***Validation criteria***
Stage 1 *N.B. events coded to any of the terms were included for validation*	Coded to medDRA Higher Level Group Term 'Embolism & Thrombosis'
Stage 2 *N.B. evidence of at least 1 of these must have been present for verification to be completed*	Presence of positive Doppler ultrasound scan for DVT Or Pulmonary Ventilation/Perfusion (VQ) or Computed Tomography Pulmonary Angiogram (CPTA) scan for PE Or Consultant reported event Or Listed as cause of death on Office of National Statistics (ONS) death certificate Or Patient reported event with a prescription for warfarin

Supplementary Table 2 – Hazard rates of verified first VTE in nbDMARD and anti-TNF treated patients.

Univariate predictor	***nbDMARD***	***Anti-TNF***	***ETN***	***INF***	***ADA***
Unadjusted HR	referent	1.1 [0.8, 1.6]	1.0 [0.7, 1.6]	1.4 [0.9, 2.1]	1.0 [0.6, 1.5]
Sensitivity analyses (unadjusted)*	referent	1.2 [0.8, 1.7]	1.1 [0.7, 1.7]	1.4 [0.9, 2.1]	1.2 [0.8, 1.8]
Adjusted HR 1**	referent	0.9 [0.6, 1.4]	0.9 [0.5, 1.4]	1.0 [0.6, 1.6]	0.9 [0.6, 1.5]
Adjusted HR 2***	**referent**	**0.9 [0.5, 1.5]**	**0.8 [0.4, 1.5]**	**1.1 [0.6, 2.0]**	**0.8 [0.4, 1.4]**
Adjusted HR 3******	**referent**	**0.8 [0.5, 1.5]**	**0.8 [0.4, 1.4]**	**1.1 [0.6, 1.9]**	**0.8 [0.4, 1.4]**

* anti-TNF patients on drug with a 90 day lag window.
** adjusted for age, gender, diabetes, baseline steroid exposure, smoking, hypertension, disease duration, disease severity, year of first anti-TNF drug and year of entry into study without imputation.
***fully adjusted IPTW model, not including surgery as a time-varying co-variate **with imputation**.
****fully adjusted IPTW model with orthopaedic surgery as a time-varying co-variate **with imputation**.

Supplementary Table 3 - Univariate predictors of VTE in whole cohort.

Univariate predictor	*HR for all patients n=15554*
Age (per year increase)	1.0 [1.0, 1.1]
Sex	0.7 [0.5, 0.9]
Disease duration	1.0 [1.0, 1.0]
Entry year	
2003	0.9 [0.6, 1.3]
2004	0.8 [0.6, 1.2]
2005	0.6 [0.4, 1.0]
2006	0.5 [0.2, 0.8]
2007	0.8 [0.4, 1.5]
2008	0.3 [0.1, 1.1]
DAS28 score	1.0 [0.9, 1.1]
HAQ score	1.4 [1.1, 1.7]
Corticosteroids	1.8 [1.4, 2.3]
Diabetes	1.0 [0.6, 1.8]
Hypertension	1.4 [1.1, 1.8]
Smoking status (current smoker)	0.8 [0.6, 1.1]

Supplementary Table 4 – Risk of VTE in anti-TNF compared to nbDMARD cohort (univariate adjusting).

Univariate predictor	*nbDMARD*	*Anti-TNF*
Unadjusted HR	referent	1.1 [0.8, 1.6]
Age	referent	1.2 [0.9, 1.7]
Sex	referent	1.0 [0.7, 1.4]
Entry year	referent	0.8 [0.6, 1.1]
DAS28 score	referent	0.9 [0.6, 1.4]
HAQ score	referent	0.8 [0.6, 1.2]
Corticosteroids	referent	0.9 [0.6, 1.2]
Diabetes	referent	1.0 [0.7, 1.4]
Hypertension	referent	1.0 [0.7, 1.4]
Smoking status (current smoker)	referent	1.0 [0.7, 1.4]