RHEUMATOLOGY

Rheumatology 2014;53:1864–1871
doi:10.1093/rheumatology/keu214
Advance Access publication 4 June 2014

Concise report

# Is the risk of tumour necrosis factor inhibitor-induced lupus or lupus-like syndrome the same with monoclonal antibodies and soluble receptor? A case/non-case study in a nationwide pharmacovigilance database

**Guillaume Moulis[1,2,3,4], Agnès Sommet[2,3,4], Maryse Lapeyre-Mestre[2,3,4] and Jean-Louis Montastruc[2,3,4], on behalf of the Association Française des Centres Régionaux de PharmacoVigilance**

## Abstract

**Objective.** Each TNF-α inhibitor (TNFi) can induce lupus or lupus-like syndrome. Nevertheless, the risk may differ between drugs because of different apoptosis induction properties. The aim of this study was to assess the putative association of each TNFi with lupus or lupus-like-syndrome.

**Methods.** All spontaneous reports of TNFi-related lupus recorded in the French pharmacovigilance database between January 2000 and December 2012 were described. We conducted disproportionality analyses (case/non-case method) to assess the link between TNFi and lupus, calculating reporting odds ratios (RORs). We used isoniazid as positive control and acetaminophen as negative control. We performed sensitivity analyses to test for event-related and drug-related competition biases.

**Results.** Among 309 671 spontaneous reports, 5213 involved TNFi. Among these, 39 were lupus or lupus-like syndromes: 25 involved infliximab, 9 adalimumab and 5 etanercept. The male:female sex ratio was 0.1 and the mean age was 44.9 years. Among the 39 cases, 28% fulfilled at least four ACR criteria for SLE. Median time to lupus onset was 11 months. Cutaneous and rheumatological involvement were the most frequent. Antinuclear autoantibodies were present in all patients, with anti-DNA specificity in 77.8%. Improvement was observed after TNFi withdrawal. There was a significant association between TNFi and lupus (ROR = 7.72, 95% CI 5.50, 10.83). The ROR was similar for infliximab (10.97, 95% CI 7.27, 16.56) and adalimumab (9.03, 95% CI 4.64, 17.58) and was 4.02 (95% CI 1.66, 9.75) for etanercept. Sensitivity analyses led to similar results.

**Conclusion.** Although CIs overlap, there is a clear trend towards a decreased risk with etanercept compared with monoclonal TNFis.

**Key words:** TNF-α antagonists, drug-induced lupus, disproportionality analysis.

CLINICAL SCIENCE

## Introduction

TNF inhibitors (TNFis) can trigger lupus. Although these drugs frequently induce ANAs and anti-dsDNA autoantibodies, clinical TNFi-induced lupus is a rare adverse drug reaction (ADR) with an estimated incidence of <0.2% in post-marketing surveys [1]. This ADR has been reported with each TNFi. Lupus-like syndrome, defined by three or fewer ACR criteria, seems to be as frequent as SLE (at least 4 of 11 ACR criteria) [1]. The link between TNFi

[1]Service de Médecine Interne, Centre Hospitalier Universitaire de Toulouse, [2]INSERM U1027, Toulouse, [3]Service de Pharmacologie Médicale et Clinique, Centre Midi-Pyrénées de PharmacoVigilance, de Pharmacoépidémiologie et d'Informations sur le Médicament, Centre Hospitalier Universitaire de Toulouse, Toulouse and [4]UMR 1027, Université de Toulouse III, Toulouse, France

Submitted 15 October 2013; revised version accepted 25 March 2014.

Correspondence to: Guillaume Moulis, Service de Pharmacologie Médicale et Clinique, Faculté de Médecine, 37 Allées Jules Guesde, 31000 Toulouse, France. E-mail: guillaume.moulis@univ-tlse3.fr

exposure and scLE occurrence has been confirmed by one pharmacoepidemiological study [2]. No study has compared the risk with each TNFi.

However, the risk of drug-induced lupus may differ between TNFis because of different structural properties, leading to variable apoptosis induction [3] and therefore variable nuclear antigen exposure to the immune system. In a cohort of SpA patients, 62% had developed new ANAs with infliximab *vs* 15% with etanercept. Similarly, induction of anti-dsDNA antibodies was detected in 71% *vs* 10%, respectively [4]. Furthermore, etanercept seems useful for the treatment of arthritis and serositis in SLE [5]. In addition, several patients with infliximab or adalimumab-induced lupus have been rechallenged with etanercept without recurrence of lupus [6–9]. The aim of this study was to assess the risk of TNFi-induced lupus (full-blown SLE or lupus-like syndromes) with monoclonal antibody TNFis in comparison with other TNFis.

## Patients and methods

All the cases of TNFi-induced lupus reported in the French pharmacovigilance database (FPVD) from 1 January 2000 until 31 December 2012 were included in the study. Briefly, this database colligates spontaneous reports of unexpected or serious ADRs from French health practitioners [10]. Unexpected ADRs are ADRs not described in the drug summary of product characteristics. Serious ADRs lead to death, are life-threatening, trigger hospitalization (or prolongation of hospitalization), lead to persistent incapacity or disability or (since 2007) are judged clinically relevant by the physician who reports the case. Each report is then validated by a college of clinical pharmacologists and specialist physicians in the relevant regional pharmacovigilance centre before being recorded in the FPVD. ADRs are encoded using the Medical Dictionary for Regulatory Activities (MedDRA) classification [10]. Under French law, spontaneous reporting of such ADRs is mandatory for every health practitioner in France, without consent of the patient. The ADR forms recorded in the FPVD are fully anonymous [10]. French law (articles 34 and 38 of the law n°78-17 relative à l'informatique, aux fichiers et aux libertés), authorizes the Centres Régionaux de PharmacoVigilance and the Agence Nationale de Sécurité du Médicament to collect data from spontaneous reporting and to use these data for their pharmacovigilance mission. They ensure patients' data privacy.

We used the case/non-case method (disproportionality analysis) to assess the link between TNFi exposure and lupus occurrence [11]. More information regarding this method is provided in section 1 of the supplementary data, available at *Rheumatology* Online. Cases were all reports encoded with the MedDRA high-level-term systemic lupus (including subtypes) from 1 January 2000 until 31 December 2012. Non-cases were all other reports during the same period. Exposure to TNFi was sought in cases and in non-cases. Reporting odds ratios (RORs) were calculated to assess the link between drug exposure and lupus occurrence. The ROR is the ratio of the odds of TNFi exposure among cases divided by the odds of TNFi exposure among non-cases [11].

We used isoniazid (a well-known lupus inducer) as positive control and acetaminophen as negative control. Sensitivity analyses were carried out to test for event-related and drug-related competition biases [12,13]. Event competition bias is due to a frequently reported ADR of the drug of interest (here, TNFi), increasing the number of non-cases exposed to that drug, and therefore artificially decreasing the ROR of the ADR of interest (here, lupus) [12]. As a result, we carried out sensitivity analyses withdrawing from the FPVD infections (selected with the MedDRA system organ class term infections and infestations), which are frequent, severe ADRs still reported over time. We also successively withdrew two unexpected ADRs that might have been increasingly reported with TNFis these last few years due to safety signals: malignancies [MedDRA system organ class term neoplasm benign, malignant and unspecified (including cysts and polyps)] and demyelinating disorders (MedDRA high-level term demyelinating disorders). On the other hand, drug-related competition bias is due to numerous reports of the ADR of interest (here, lupus) due to other drugs than the drug of interest (here, drugs other than TNFis), increasing the relative exposure to other drugs among the cases, and also underestimating the ROR of the drug of interest [13]. Consequently, we performed sensitivity analyses restricted to the marketing period of each TNFi and withdrew the well-known lupus inducers. These were identified from the Chang and Gershwin list [4], updated through a MEDLINE search until 2012 to detect new signals. We considered signals when the link of causality was ascertained by comparative studies or when it was suggested in at least three reports (see supplementary section S2, available at *Rheumatology* Online).

## Results

During the study period, 309 671 spontaneous reports were collected in the FPVD, of which 5213 (1.68%) involved TNFis. Among these TNFi reports, 39 were lupus (full-blown SLE or lupus-like syndrome) in 37 patients: 25 involved infliximab, 9 adalimumab and 5 etanercept. These cases are described in Table 1. The male:female sex ratio was 0.1 and the mean age was 44.9 years (S.D. 14.4). Seventeen patients were treated for RA, 15 for IBD and 4 for AS. Median time from TNFi introduction to lupus onset was 11 months (range 1–84). Cutaneous (64.9%) and rheumatological (56.8%) involvements were most frequent. Organ involvement was rare (Table 1). When reported ($n = 35$), ANAs were positive in all cases. Anti-dsDNA antibodies were present in 21/27 patients (77.8%). Eleven patients (28.2%) fulfilled at least four ACR criteria for SLE: 10/34 (29.4%) with monoclonal antibodies and 1/5 (20.0%) with etanercept (Fisher's exact test, $P = 0.6$). Improvement was observed after TNFi withdrawal in all cases (data available for half of the reports). HCQ was introduced in five cases and immunosuppressants (corticosteroids or MTX) in seven.

**Table 1** Characteristics of the 37 cases of TNFi-induced lupus reported in the French pharmacovigilance database from 2000 to 2010

| Patient (year) | Age, years, gender | TNFi | Condition | Time to onset, months | Signs | Autoantibodies | Imputation | Treatment/evolution |
|---|---|---|---|---|---|---|---|---|
| 1 (2000) | 54, M | IFX | RA | 6 | Pericarditis, malar rash biopsy-proven | ANA (+) | I1 | n/a |
| 2 (2000) | 75, F | IFX | RA | 4 | n/a | ANA (+)<br>Anti-DNA (+)<br>Anti-histone (+) | I2 | n/a |
| 3 (2002) | 71, F | IFX | RA | 11 | scLE | ANA 1/2560<br>Anti-DNA (+) | I2 | n/a |
| 4 (2002) | 42, F | IFX | RA | 24 | scLE, polyarthralgia | ANA 1/2560<br>Anti-DNA (+) | I1 | IFX withdrawal<br>CS<br>Favourable outcome |
| 5 (2002) | 34, F | IFX | RA | 20 | Polyarthritis, malar rash, lymphopenia | ANA 1/2560<br>Anti-DNA (+)<br>Anti-histone (+)<br>Coombs (+) | I1 | IFX withdrawal<br>CS<br>Favourable outcome |
| 6 (2003) | 62, F | IFX | RA | 16 | Polyarthralgia, rash, mouth ulceration, photosensitivity | ANA (+)<br>Anti-DNA (+) | I1 | n/a |
| 7 (2004) | 44, F | IFX | RA | 8 | Polyarthralgia | ANA 1/1280 (+)<br>Anti-DNA (+) | I1 | IFX withdrawal<br>Evolution n/a |
| 8 (2004) | 49, M | IFX | RA | 23 | Malar rash, scLE biopsy-proven | ANA (+) | I1 | IFX withdrawal<br>Recovery |
| 9 (2005) | 65, F | IFX | RA | 35 | Fever, malar rash, scLE | ANA (+)<br>Anti-DNA (+)<br>Anti-histone (+) | I2 | IFX withdrawal<br>CS<br>Recovery |
| 10 (2005) | 40, F | IFX | CD | 5 | Polyarthritis<br>Pericarditis<br>Pleuritis<br>Malar rash suspected | ANA (+) 1/1280<br>Anti-DNA (−)<br>Anti-nucleosome (+) | I3 | n/a |
| 11 (2006) | 40, F | IFX | AS | 12,9 | Polyarthralgia | ANA (+) | I1 | IFX withdrawal<br>Full recovery |
| | | ETN | | 3 | Pericarditis | ANA (+) | I1 | ETN withdrawal<br>HCQ<br>Full recovery |
| 12 (2006) | n/a, F | IFX | RA | n/a | Polyarthritis | ANA (+) | I1 | IFX withdrawal<br>CS<br>Recovery |
| 13 (2007) | 51, M | IFX | AS | 24 | scLE, pericarditis | ANA 1/5210<br>Anti-DNA (+)<br>Anti-nucleosome (+) | I2 | n/a |

(continued)

**Table 1** Continued

| Patient (year) | Age, years, gender | TNFi | Condition | Time to onset, months | Signs | Autoantibodies | Imputation | Treatment/evolution |
|---|---|---|---|---|---|---|---|---|
| 14 (2008) | 31, F | IFX | UC | 24 | Malar rash, photosensitivity, scLE, RP | ANA 1/640<br>Anti-DNA (+) | I1 | HCQ<br>Evolution n/a |
| 15 (2008) | 22, F | IFX | CD | 24 | Polyarthralgia | ANA (+)<br>Anti-DNA (+) | I3 | Full recovery after IFX withdrawal<br>Rechallenge positive |
| 16 (2009) | 47, F | IFX | CD | 12 | Malar rash<br>Photosensitivity<br>Polyarthritis | ANA (+) 1/2500<br>Anti-DNA (+)<br>Anti-ENA (−) | I1 | HCQ<br>Recovery |
| 17 (2010) | 56, F | IFX | UC | 7 | Malar rash, photosensitivity, cutaneous biopsy (+), infiltrative lung disease | ANA (+)<br>Anti-DNA (+) | I2 | IFX withdrawal<br>HCQ<br>Full recovery |
| 18 (2010) | 28, F | IFX | CD | 5,1 | Polyarthralgia, scLE (biopsy +), acrocyanosis | ANA 1/1280<br>Anti-DNA (−) | I1 | IFX withdrawal<br>MTX<br>Full recovery at 3 months |
| 19 (2011) | 33, F | IFX | CD | 2 | Polyarthralgia | ANA 1/1280<br>Anti-DNA (+) | I1 | n/a |
| 20 (2011) | 28, F | IFX | Idiopathic scleritis | 12 | n/a | ANA (+) | I1 | n/a |
| 21 (2011) | 33, M | IFX | CD | 84 | Polyarthritis<br>Malar rash | ANA 1/1280 (+)<br>Anti-DNA (+)<br>Anti-SSA/SSB (−) | I2 | IFX withdrawal<br>Recovery |
| 22 (2011) | 47, F | IFX | CD | 3 | Polyarthritis, autoimmune hepatitis biopsy-proven | ANA (+)<br>Anti-DNA (+) | I2 | n/a |
| 23 (2012) | 22, F | IFX | CD | 13 | Polyarthralgia, peripheral sensitive neuropathy | ANA (+)<br>Anti-DNA (+) | I1 | IFX withdrawal<br>Recovery |
| | | ADA | | 1 | Polyarthralgia | ANA (+)<br>Anti-DNA (+) | I2 | ADA withdrawal<br>Recovery |
| 24 (2012) | 41, F | IFX | PsA | 3 | Polyarthritis<br>Lymphopenia | ANA (+)<br>Anti-DNA (−)<br>Anti-nucleosome (+) | I1 | IFX withdrawal<br>CS<br>Evolution n/a |
| 25 (2012) | 34, F | IFX | CD | 12 | Polyarthralgia, myalgia | ANA (+) 1/1600<br>Anti-DNA (+)<br>Anti-RNP (+) | I1 | n/a |
| 26 (2003) | 60, F | ETN | RA | 24 | scLE, alopecia areata | ANA (+)<br>Anti-SSA and anti-SSB (+) | I2 | ETN withdrawal<br>Recovery |
| 27 (2004) | 46, F | ETN | RA | 2 | Malar rash, photosensitivity, scLE biopsy-proven | n/a | I2 | ETN withdrawal<br>Recovery |

(continued)

**Table 1** Continued

| Patient (year) | Age, years, gender | TNFi | Condition | Time to onset, months | Signs | Autoantibodies | Imputation | Treatment/evolution |
|---|---|---|---|---|---|---|---|---|
| 28 (2005) | 35, F | ETN | AS | 18 | Malar rash, photosensitivity, acrocyanosis | ANA (+)<br>Anti-DNA (+) | I1 | ETN withdrawal<br>Incomplete recovery |
| 29 (2007) | 78, F | ETN | RA | 2 | Fever, polyarthralgia | n/a | I2 | n/a |
| 30 (2004) | 38, F | ADA | RA | 1 | scLE | ANA (+)<br>Anti-DNA (+) | I1 | ADA withdrawal<br>Evolution n/a |
| 31 (2004) | 54, F | ADA | RA | 6 | Malar rash, scLE | ANA 1/2560<br>Anti-DNA (+) | I1 | ADA withdrawal<br>Evolution n/a |
| 32 (2005) | 60, F | ADA | RA | 2 | scLE biopsy proven | ANA (+) | I1 | ADA withdrawal<br>HCQ<br>Improvement |
| 33 (2009) | 53, F | ADA | RA | 12 | Chilblain | n/a | I1 | n/a |
| 34 (2009) | 34, F | ADA | CD | 11 | Malar rash, livedo, polyarthritis, acrosyndrome | ANA (+)<br>Anti-DNA (−)<br>Anti-histone (−) | I2 | ADA withdrawal<br>CS<br>Recovery |
| 35 (2009) | 37, F | ADA | CD | 16 | Polyarthritis, RP | ANA 1/1280<br>Anti-DNA (−)<br>Anti-nucleosome (+) | I1 | n/a |
| 36 (2010) | 57, F | ADA | CD | 11 | Polyarthritis | ANA (+)<br>Anti-DNA (−) | I2 | n/a |
| 37 (2010) | 45, F | ADA | Histiocytosis | 2.5 | scLE | n/a | I1 | n/a |

ADA: adalimumab; CD: Crohn's disease; CS: corticosteroids; ETN: etanercept; IFX: infliximab; TNFi: TNF inhibitor; UC: ulcerative colitis; +: positive; −: negative.

TABLE 2 Association of TNF inhibitor exposure with lupus occurrence in the French pharmacovigilance database

| Drug exposure | Lupus reports | All reports | % | Case/non-case study | |
|---|---|---|---|---|---|
| | | | | Reporting odds ratio | 95% CI |
| All drugs | 288 | 309 671 | 0.09 | — | — |
| All TNF inhibitors[a] | 39 | 5213 | 0.75 | 7.72 | 5.50, 10.83 |
| Infliximab | 25 | 2682 | 0.93 | 10.97 | 7.27, 16.56 |
| Adalimumab | 9 | 1110 | 0.81 | 9.03 | 4.64, 17.58 |
| Etanercept | 5 | 1360 | 0.37 | 4.02 | 1.66, 9.75 |
| Isoniazid (positive control) | 5 | 1560 | 0.32 | 3.50 | 1.44, 8.49 |
| Acetaminophen (negative control) | 6 | 21 567 | 0.03 | 0.28 | 0.12, 0.63 |

[a]Infliximab, adalimumab and etanercept. There were no cases of lupus induced by golimumab or certolizumab reported in the French pharmacovigilance database during the study period (2000–12).

Results of disproportionality analyses are presented in Table 2. The association between TNFi exposure and lupus was significant for all the TNFis pooled together and for the positive control isoniazid, but not with the negative control acetaminophen. ROR estimates were 10.97 (95% CI 7.27, 16.56) for infliximab, 9.03 (95% CI 4.64, 17.58) for adalimumab and 4.02 (95% CI 1.66, 9.75) for etanercept. When pooled together, the ROR estimate for monoclonal antibody TNFis was 9.81 (95% CI 6.75, 14.26). Sensitivity analyses led to similar results (see supplementary section S3, available at *Rheumatology* Online).

## Discussion

Our study confirms the link between TNFi exposure and lupus occurrence. We found a 2-fold decrease in the ROR estimate of lupus occurrence for etanercept in comparison with that for infliximab or adalimumab. Although CIs overlap, these results suggest a higher risk of full-blown lupus or lupus-like syndrome with monoclonal antibody TNFis.

The characteristics of the 39 cases reported here are similar to those previously reported. As in our study, cutaneous and rheumatological involvements were the most frequent. ANAs were found in 91% of 89 published case reports and anti-dsDNA in 64% [14]. A favourable evolution after TNFi withdrawal is the rule, although minor immunosuppressive therapy is sometimes prescribed [1,14]. Surprisingly, only one case of TNFi-induced lupus occurred in a patient treated for PsA, and no case concerned psoriasis patients. In the literature, only 2 of 105 cases reported in 2008 were patients treated with TNFi for PsA, and none had psoriasis [14]. Similarly, no patient was found in a systematic retrospective case series [6]. In contrast, psoriasis and lupus share some cytokine pathways, such as increased Th1 and Th17 cytokines and decreased activity of T regulatory cells [15], and psoriasis is also a well-known paradoxical ADR of TNFis [16].

The percentage of cases fulfilling at least four ACR criteria among our patients is lower than in other series, but publication bias may have favoured previous estimates [1]. Another explanation is the concision of the reports in the FPVD, which may have led to underestimation of full-blown SLE. Nevertheless, the fact that a college of specialty physicians and clinical pharmacologists validated each case prior to FPVD registration ensures that the lupus diagnoses are correct [10].

Another classical limitation of studies in pharmacovigilance databases is underreporting [10]. However, there is no reason for major differential underreporting among cases and non-cases. The ROR estimates should therefore not be biased. The small number of reports with adalimumab (marketed later and widely used) suggests an absence of notoriety bias that would have overestimated RORs. Similarly, a differential rate of exposure among TNFis in the general population *per se* does not bias ROR estimates, because cases and non-cases exposed to TNFi vary proportionally to their use. There is very little data regarding TNFi exposure at nationwide levels obtained through claims databases. In France, etanercept was the biopharmaceutical used most (51%) in RA patients during the 2009–10 period, followed by adalimumab (20%) and infliximab (13%) [17]. In a similar study conducted in the USA interested in TNFi exposure in RA, psoriasis, PsA and AS during the 2005–9 period, etanercept was also used most (53%), followed by adalimumab (25%) and infliximab (22%) [18]. This illustrates that prescription rates do not influence RORs. In contrast, *de novo* lupus occurrence in patients treated with TNFis for rheumatic disease is sometimes difficult to differentiate from a flare of the underlying disease [1]. In that case, TNFi-induced lupus might be underdiagnosed, leading to underestimation of RORs. However, there is no reason for differential underreporting among the different types of TNFis. In the end, we did not find any competition bias (drug related or event related).

The ROR of the pooled TNFis in this study (7.72) is similar to the risk of TNFi-induced scLE calculated in a Danish case–control study (OR 8.0) [2]. The pathophysiology of TNFi-induced lupus is complex, including increased apoptosis and impaired clearance of nuclear waste. In some patients, it appears that IFN-$\alpha$ is down-regulated by TNF [19]. As a result, blocking TNF might lead to an increased release of IFN-$\alpha$, whose role in lupus pathophysiology has been clearly demonstrated [4,19]. Additionally, an improved B cell survival favouring autoantibody production has been

suggested [4,19]. Lastly, infectious risk in TNFi-exposed patients can play a role, since infection can trigger autoimmunity and particularly ANA production in TNFi-treated patients [4]. However, etanercept induces less apoptosis *in vitro* than monoclonal antibody TNFi when bound to transmembrane TNF. Transmembrane TNF is expressed on antigen-presenting cells such as macrophages, and consequently this mechanism is evoked to explain the increased rate of infection observed in patients treated with monoclonal antibody TNFis compared with etanercept [3]. As a result, the decreased apoptosis induction and the decreased risk of infection may explain the decreased risk of lupus with the soluble receptor. This pharmacodynamic hypothesis increases the value of the disproportionality analysis [11].

Clinical experience of monoclonal antibody TNFi-induced lupus without recurrence with etanercept, or more recently with certolizumab, is being increasingly reported [8,20]. Nevertheless, the safety of this switch is not a rule set in stone: in our series, one infliximab-induced case relapsed with etanercept (patient 11), and there are few reports in the literature of safe switch from infliximab to adalimumab [7]. Similarly, infliximab has been successfully used to treat lupus in small open series, particularly when there was involvement of arthritis and nephritis. No clinical flare was observed in these series, although an increased rate of anti-dsDNA antibodies was observed [19]. Indeed, TNF seems to play a key role in lupus pathophysiology, and its blockade can be beneficial in some patients [19]. In the previously quoted open trial assessing the efficacy of etanercept in 42 lupus patients, the level of ANA rose in 14% of the patients while no clinical flare was observed with a 2-year follow-up [5]. Nevertheless, a publication bias cannot be excluded and comparative randomized studies in larger cohorts are needed to assess whether some lupus patients can experience flares on TNFis and whether etanercept is more efficient and safer than monoclonal antibody TNFis for the treatment of lupus patients.

Overall, our study confirms the risk of overt lupus with the most commonly used TNFis. It also suggests a higher risk with monoclonal antibodies than with the soluble receptor etanercept. However, this study must be interpreted as a signal detection analysis. Thus case–control studies should refine these results. Prospective follow-up of TNFi-induced lupus patients switched from a given TNFi to another are mandatory to assess the clinical impact of these findings.

**Rheumatology key messages**

- There is a significant association between TNF inhibitor exposure and lupus or lupus-like syndrome occurrence.
- The risk of lupus might be lower with etanercept compared with monoclonal antibody TNF inhibitors.

*Disclosure statement*: The authors have declared no conflicts of interest.

## Supplementary data

Supplementary data are available at *Rheumatology* Online.

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