# RHEUMATOLOGY

## Original article

# Efficacy and safety of anti-TNF therapies in psoriatic arthritis: an observational study from the British Society for Rheumatology Biologics Register

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## Abstract

**Objectives.** To evaluate the risk–benefit profile of anti-TNF therapies in PsA and to study the predictors of treatment response and disease remission [disease activity score (DAS)-28 < 2.6].

**Methods.** The study included PsA patients ($n = 596$) registered with the British Society for Rheumatology Biologics Register (BSRBR). Response was assessed using the European League against Rheumatism (EULAR) improvement criteria. Univariate and multivariate logistic regression models were developed to examine factors associated with EULAR response and disease remission using a range of covariates. Poisson regression was used to calculate incidence rate ratios (IRRs) for serious adverse events (SAEs) *vs* seronegative RA controls receiving DMARDs, adjusting for age, sex and baseline co-morbidity.

**Results.** At baseline, the mean (S.D.) DAS-28 was 6.4 (5.6). Of the patients, 70.3% were EULAR responders at 12 months. At 6 months, older patients [adjusted odds ratio (OR) 0.97 per year; 95% CI 0.95, 0.99], females (adjusted OR 0.51; 95% CI 0.34, 0.78) and patients on corticosteroids (adjusted OR 0.45; 95% CI 0.28, 0.72) were less likely to achieve a EULAR response. Over 1776.2 person-years of follow-up (median 3.07 per person), the IRR of SAEs compared with controls was not increased (0.9; 95% CI 0.8, 1.3).

**Conclusions.** Anti-TNF therapies have a good response rate in PsA, and have an adverse event profile similar to that seen in a control cohort of patients with seronegative arthritis receiving DMARD therapy.

**Key words:** Psoriatic arthritis, TNF inhibitors, Adalimumab, Etanercept, Infliximab, Efficacy, Risk–benefit, Adverse events.

CLINICAL SCIENCE

## Introduction

The introduction of anti-TNF-α therapies (etanercept, infliximab and adalimumab) has dramatically improved the treatment of PsA. Randomized placebo-controlled trials (RCTs) have shown that these therapies are effective, but observational data are still scarce [1]. A recent meta-analysis has also reported that these agents are superior to conventional DMARDs [2]. Further evidence supports the improvements in symptoms, functional status, quality of life (QoL) and radiographic progression with anti-TNF therapies in PsA patients [3]. RCTs have also demonstrated these therapies to be safe during short-term use (up to 24 weeks) [1].

However, strict inclusion criteria and short duration can limit the external validity of results obtained from RCTs [4, 5]. The effectiveness of a treatment is determined by how well it performs under real-life conditions, outside the context of a randomized trial [6]. In a routine clinical practice, these agents have been shown to be more effective than MTX [7] and result in significant improvements in QoL and functional status in PsA patients [8].

Potential predictors associated with the continuation of anti-TNF therapies have been explored in a number of studies. A Swedish study of 261 PsA patients suggested

that concomitant MTX and high CRP levels were associated with treatment continuation [9]. Whereas a Spanish study reported that drug discontinuation was predicted by older age [10]. A recent British study found that the presence of other co-morbidities was associated with patients' withdrawal due to adverse events [11]. However, there have been minimal data published regarding factors that can identify patients most likely to respond to these therapies or show disease remission. The aim of this study was to evaluate the efficacy–safety profile of anti-TNF therapies in the management of PsA in routine clinical practice, and to study the predictors of treatment response and disease remission.

## Subjects and methods

### Setting

The British Society for Rheumatology Biologics Register (BSRBR) was established in October 2001. Its aim was to examine the long-term safety and efficacy of biologic agents in patients with inflammatory arthropathies in the UK [12]. The study design is a prospective, multicentre, longitudinal, observational study. Although primarily a study of patients with RA, the register has also collected data on patients receiving anti-TNF therapies for other rheumatic conditions, including PsA (2002–06 inclusive).

### Subjects and controls

This analysis was restricted to patients with a physician diagnosis of PsA registered between 2002 and 2006, who had started etanercept ($n = 333$), infliximab ($n = 171$) or adalimumab ($n = 92$) as their first biologic drug within 6 months of registration.

During this study, etanercept (licensed in 2002) was administered as a subcutaneous injection of 25 mg twice weekly or 50 mg once weekly [13]; and adalimumab (licensed in 2005) was administered as a subcutaneous injection of 40 mg every 2 weeks [14]. In 2004, infliximab was licensed for use in the management of PsA at a recommended dose of 5 mg/kg administered at weeks 0, 2, 6 and 8 and then every 8 weeks thereafter [15,16]. It is also recommended that infliximab be administered in combination with MTX [15].

In order to understand the safety profile of anti-TNF therapies in PsA, it is important to compare the rates of observed adverse events with patients with a similar disease receiving standard DMARDs. As there was no specific PsA control population within the BSRBR, patients with RF-negative RA, who had been recruited to the BSRBR control cohort, were selected as a comparison group. The BSRBR control cohort consisted of patients with active RA [guide 28-joint count disease activity score (DAS-28) $> 4.2$ [17]], receiving therapy with standard non-biologic DMARDs.

### Data collection

At the time of initiation of the anti-TNF therapy, the rheumatologist or rheumatology nurse specialist completed a consultant baseline questionnaire that included details of the patient's age, sex, diagnosis, disease duration and information about current disease activity, including swollen and tender joint counts (based on the 28-joint count), ESR and/or CRP. Details of past and present anti-rheumatic therapies and current co-morbidities were also recorded. Each patient completed a separate patient baseline questionnaire that included details about current work status, ethnicity and smoking.

Rheumatologists were sent a postal follow-up (FUP) questionnaire every 6 months that recorded the current DAS-28 (swollen and tender joint count, ESR/CRP and patient global assessment). Details of all serious adverse events (SAEs), regardless of whether or not the physician believed they were directly related to the anti-TNF therapy, were also recorded. When questionnaires were not returned within 5 weeks, reminders were sent. At each FUP, rheumatologists were also prompted for any missing information from the previous questionnaire.

Any new drugs, hospitalizations, referrals and smoking status during the past 6 months were recorded by the patient on a 6-monthly basis for 3 years. After 2 weeks of non-response, the reminder postcard was sent to the patient. Following a second period of 2 weeks, the patient was then posted another patient FUP questionnaire. All enrolled patients were flagged for death or malignancy with the National Health Service Information Centre (NHS IC) [formerly known as the Office for National Statistics (ONS)] at registration with BSRBR. The NHS IC sends quarterly reports to the BSRBR, including a copy of the death certificate for any patient who has died and the type and site of any malignancies.

### Analysis

Baseline co-morbidity was assessed based on the presence of one or more of a pre-specified list of co-existing conditions: cardiovascular, pulmonary, endocrine, gastrointestinal (GIT), CNS and past malignancies. The prevalence of individual baseline co-morbidities was compared between the PsA cases and RF-negative RA controls adjusting for age, sex and smoking. The presence of co-morbid conditions was compared using logistic regression. Results were presented as adjusted odds ratio (adjusted OR) with 95% CI [18].

Effectiveness at 6, 12 and 18 months was categorized according to the DAS-28 using two approaches. First, based on the European League against Rheumatism (EULAR) response criteria [19], patients were classified into three groups: no response, moderate response and good response. Those patients who discontinued their anti-TNF therapy prior to the end of each 6-month FUP, regardless of reason, were labelled as non-responders within that time period. Secondly, patients achieving remission at each FUP were identified and defined according to the EULAR criteria (DAS-28 $< 2.6$) [20].

Potential predictors of EULAR response at 6 months were modelled using both univariate and multivariate ordinal logistic regression, which models the probability of achieving a higher response category, in the presence of each predictor variable [21]. Univariate and multivariate

logistic regression models were also constructed to identify independent predictors for disease remission [18]. Results were presented as OR with 95% CI. The following covariates were examined in the models: baseline demographic variables [age (years), gender, smoking (yes/no), whether the patient had additional baseline co-morbidities (yes/no)], baseline disease-specific variables {DAS-28 as well as the individual components [high inflammatory markers (CRP > 20 mg/l and/or ESR > 28 mm/h), 28-tender joint count and 28-swollen joint count], HAQ, disease duration (years)} and therapeutic variables [anti-TNF therapy used and concurrent use of MTX, or steroids (yes/no)]. In the multivariate analyses, we used the composite DAS-28 score as a potential predictor rather than its individual components.

For the purpose of this analysis, a SAE was defined as 'any adverse event that was (1) fatal, (2) life threatening, (3) resulted in an unplanned hospitalization or prolonged an existing hospitalization, (4) was physically disabling, (5) resulted in a birth defect or (6) required an i.v. antibiotic' [22]. SAEs were classified using the Medical Dictionary for Regulatory Affairs (MedDRA) system organ classification (SOC) [23]. Rates of SAEs were presented as events/1000 person-years with 95% CI. Person-years were calculated from the first day of anti-TNF therapy up to the date of the last FUP completed up to the month and year of drug discontinuation or death, whichever occurred first. The date of drug discontinuation was defined as the date of the first missed dose. Patients in the comparison cohort contributed person-years from their date of registration until the date of the last FUP completed up to month and year of drug discontinuation or death, whichever occurred first. All SAEs occurring during this period were included in the analysis. Incidence rate ratios (IRRs) were calculated relative to controls using Poisson regression and were adjusted for age, sex and baseline co-morbidity using propensity scores [24]. All calculations were conducted using STATA version 9.0 [24].

## Ethical approval

The study was approved by the North West Multicentre Research Ethics Committee and all subjects gave their written consent for participation.

## Results

### Demographic characteristics

Baseline characteristics for all patients are shown in Table 1. At baseline, the PsA patients were significantly younger [mean (s.d.) age was 45.7 (11.1) years vs 59.4 (13.1) years for the control cohort; $P < 0.001$] with a lower proportion of females (53.0 vs 73.5%; $P < 0.001$). The mean (s.d.) disease duration was 12.4 (8.7) and 8.5 (9.7) years and the corresponding mean (s.d.) DAS-28 was 6.4 (5.6) and 5.0 (1.4), respectively, in the anti-TNF and control cohorts. There were no significant statistical differences between the three anti-TNF cohorts in age ($P = 0.325$), sex ($P = 0.581$) or disease duration ($P = 0.384$). There was also no significant statistical difference among patients receiving the three anti-TNF therapies in DAS at baseline, as shown in Table 1. It was noted that 78% of the patients receiving infliximab received the dose recommended for RA (3 mg/kg), the rest receiving the full 5 mg/kg.

### Baseline co-morbidity

The overall prevalence of co-morbidities in the PsA cases and RF-negative RA controls was similar. In the control cohort, 28.6% of the patients had no co-morbid condition, 33.8% had one and 37.6% had more than one. In comparison, 37.0% of the anti-TNF cohort had no co-morbid condition, 30.7% had one and 32.3% had more than one. The most frequent co-morbid condition was hypertension in the anti-TNF (29.2%) and control (33.8%) cohorts, as shown in Table 2. There were no significant differences in the prevalence of any co-morbid diseases between the two cohorts (Table 2) after adjusting for age, sex and smoking status, with the exception of asthma,

TABLE 1 Demographic and disease characteristics of PsA cases and seronegative RA control cohorts at baseline

| Characteristics | Control (n = 1115) | All PsA cohort (n = 596) | Etanercept (n = 333) | Infliximab (n = 171) | Adalimumab (n = 92) | P-value |
|---|---|---|---|---|---|---|
| Demographic characteristics | | | | | | |
| Age | 59.4 (13.1) | 45.7 (11.1) | 45.8 (11.1) | 44.8 (11.0) | 47.0 (11.6) | 0.325 |
| Female, n (%) | 820 (73.5) | 316 (53.0) | 170 (51.1) | 94 (55.0) | 49 (53.3) | 0.581 |
| Disease duration, years | 8.5 (9.7) | 12.4 (8.7) | 12.8 (9.0) | 12.2 (8.0) | 11.4 (8.4) | 0.384 |
| Disease characteristics | | | | | | |
| Tender joint count | 8.7 (7.1) | 13.4 (7.7) | 13.5 (7.6) | 14.1 (8.1) | 12.1 (7.1) | 0.346 |
| Swollen joint count | 6.0 (5.4) | 8.9 (6.1) | 8.8 (6.1) | 8.8 (6.4) | 9.7 (5.7) | 0.293 |
| ESR | 32.1 (23.9) | 40.5 (29.0) | 39.4 (28.1) | 44.2 (31.4) | 37.7 (27.4) | 0.459 |
| CRP | 27.8 (32.4) | 39.3 (47.1) | 35.4 (41.8) | 47.8 (50.0) | 35.0 (56.6) | 0.787 |
| DAS-28 | 5.0 (1.4) | 6.4 (5.6) | 6.1 (1.2) | 7.3 (10.1) | 6.0 (1.0) | 0.464 |
| HAQ, median (interquartile range) | 1.9 (1.4–2.3) | 1.9 (1.4–2.3) | 1.8 (1.4–2.3) | 2.0 (1.4–2.4) | 1.8 (1.1–2.3) | 0.581 |

Values are mean (s.d.) unless otherwise specified; P-value tests for significant differences between the three anti-TNF therapies' cohorts.

TABLE 2 Baseline co-morbidity in PsA cases and seronegative RA control cohorts at baseline

| Co-morbid disorders | Control (*n* = 1115), *n* (%) | All PsA cohort (*n* = 596) | |
|---|---|---|---|
| | | *n* (%) | Adjusted OR[a] (95% CI) |
| Cardiovascular disorders | | | |
| Hypertension | 377 (34) | 174 (29) | 0.96 (0.87, 1.07) |
| Angina | 93 (8) | 9 (2) | 0.72 (0.47, 1.11) |
| Myocardial infarction | 50 (4) | 6 (1) | 0.64 (0.34, 1.20) |
| Stroke | 38 (3) | 13 (2) | 0.79 (0.56, 1.11) |
| Pulmonary disorders | | | |
| Bronchitis and emphysema | 13 (1) | 6 (1) | 1.07 (0.59, 1.93) |
| Asthma* | 167 (15) | 51 (9) | 0.80 (0.65, 0.98) |
| COPD | 98 (9) | 26 (4) | 0.96 (0.75, 1.22) |
| Endocrine disorders | | | |
| Diabetes | 81 (7) | 32 (5) | 0.97 (0.74, 1.26) |
| Hyperthyroidism | 44 (4) | 8 (1) | 0.82 (0.53, 1.26) |
| GIT disorders | | | |
| Peptic ulcer disease | 75 (7) | 41 (6.88) | 1.19 (0.97, 1.46) |
| Liver disease | 23 (2) | 28 (4.70) | 1.20 (0.91, 1.56) |
| Renal disease | 31 (3) | 12 (2.01) | 0.91 (0.59, 1.40) |
| CNS disorders | | | |
| Demyelination | 7 (1) | 0 (0) | – |
| Epilepsy | 18 (2) | 15 (3) | 1.02 (0.70, 1.49) |
| Depression | 195 (17) | 114 (19) | 1.08 (0.94, 1.23) |
| Past malignancy | 71 (6) | 13 (2) | 0.70 (0.45, 1.06) |

[a]ORs are calculated versus control and adjusted for age, sex and smoking. *$P < 0.05$. COPD: chronic obstructive pulmonary disease.

which was significantly lower in the anti-TNF cohort (adjusted OR = 0.80; 95% CI 0.65, 0.98).

### Treatment response and disease remission

On the basis of EULAR criteria, 37.5% of the anti-TNF cohort reached a good response and 38.3% reached a moderate response at 6 months. The EULAR response appeared to be maintained at 12 and 18 months (Table 3). At 12 and 18 months, respectively, 70.3% and 68.2% of the patients were responders on the basis of EULAR criteria.

There were no significant differences in EULAR response rates at 6 ($P = 0.679$), 12 ($P = 0.904$) and 18 ($P = 0.583$) months between the three anti-TNF therapies. EULAR response rates for the whole anti-TNF cohort were also similar in patients receiving anti-TNF agents in combination with MTX (78.1% at 6 months), another DMARD (73.3%) or anti-TNF monotherapy (79.5%).

Disease remission was achieved by 133 (27.5%), 160 (36.1%) and 131 (35.2%) patients in the anti-TNF cohort at 6, 12 and 18 months, respectively. In the etanercept cohort, 80 (30.9%), 91 (37.3%) and 77 (36.5%) patients; in the infliximab cohort, 28 (19.7%), 37 (28.9%) and 32 (29.6%); and in the adalimumab cohort, 25 (30.1%), 32 (45.1%) and 22 (41.5%) achieved remission at 6, 12 and 18 months, respectively.

### Predictors of treatment response and disease remission at 6 months

Table 4 shows the results from the univariate and multivariate analyses, examining predictors of (i) achieving

a higher EULAR response category and (ii) disease remission. For the EULAR response, both univariate and multivariate analyses suggested that each additional year of age (adjusted OR 0.98, 95% CI 0.96, 0.99 and adjusted OR 0.97, 95% CI 0.95, 0.99, respectively), being female (adjusted OR 0.49, 95% CI 0.35, 0.70 and adjusted OR 0.51, 95% CI 0.34, 0.78, respectively) and receiving corticosteroids (adjusted OR 0.48, 95% CI 0.31, 0.74 and adjusted OR 0.45, 95% CI 0.28, 0.72, respectively) resulted in lower response rates.

For disease remission at 6 months, older patients and females were less likely to achieve disease remission in both the univariate (OR 0.97, 95% CI 0.95, 0.99 and OR 0.37, 95% CI 0.25, 0.55, respectively) and multivariate models (adjusted OR 0.96, 95% CI 0.94, 0.99 and adjusted OR 0.34, 95% CI 0.21, 0.57, respectively). Patients with inflammation were also less likely to achieve disease remission (OR 0.54, 95% CI 0.31, 0.97) in the univariate model. In addition, there was a non-statistically significant trend towards lower remission in patients receiving concomitant steroid therapy and in those with higher HAQ scores in both models (Table 4). The univariate model also showed that patients with elevated baseline laboratory values for inflammation (CRP > 20 mg/l or ESR > 28 mm/h) had lower response rates and disease remission.

### SAEs

For the anti-TNF cohort (*n* = 596) over 1776.2 personyears of FUP (median 3.07 per person), there were 211

TABLE 3 Improvements in disease activity over the FUP period in the PsA cohort

| | All PsA cohort (n = 596) | Etanercept (n = 333) | Infliximab (n = 171) | Adalimumab (n = 92) |
|---|---|---|---|---|
| 6-Month follow-up ($n^a$ = 480) | | | | |
| Baseline DAS-28,[b] mean (S.D.) | 6.2 (1.1) | 6.1 (1.2) | 6.3 (1.1) | 6.0 (1.0) |
| 6-Month DAS-28, mean (S.D.) | 3.5 (1.5) | 3.3 (1.4) | 3.9 (1.6) | 3.32 (1.37) |
| Mean diff. (S.D.) in DAS-28 | 2.6 (1.6) | 2.8 (1.6) | 2.3 (1.7) | 2.66 (1.40) |
| EULAR response | | | | |
| Good, n (%) | 180 (38) | 109 (43) | 35 (24) | 36 (43) |
| Moderate, n (%) | 184 (38) | 92 (37) | 55 (38) | 37 (45) |
| None, n (%) | 116 (24) | 51 (20) | 55 (38) | 10 (12) |
| EULAR response in those remaining on initial therapy | | | | |
| Good, n (%) | 180 (45) | 109 (40) | 35 (338) | 36 (47) |
| Moderate, n (%) | 184 (46) | 92 (42) | 55 (52) | 37 (48) |
| None, n (%) | 35 (9) | 16 (83) | 15 (14) | 4 (5) |
| 12-Month follow-up ($n^a$ = 441) | | | | |
| 12-Month DAS-28, mean (S.D.) | 3.4 (1.5) | 3.2 (1.4) | 3.7 (1.7) | 3.2 (1.5) |
| Mean diff. (S.D.) in DAS-28 | 2.7 (1.7) | 2.9 (1.6) | 2.4 (1.9) | 2.9 (1.6) |
| EULAR response | | | | |
| Good, n (%) | 183 (42) | 112 (48) | 35 (26) | 36 (50) |
| Moderate, n (%) | 127 (29) | 71 (30) | 36 (27) | 20 (28) |
| None, n (%) | 131 (29) | 51 (22) | 64 (47) | 16 (22) |
| EULAR response in those remaining on initial therapy | | | | |
| Good, n (%) | 183 (53) | 112 (55) | 35 (43) | 36 (60) |
| Moderate, n (%) | 127 (37) | 71 (35) | 36 (44) | 20 (33) |
| None, n (%) | 34 (10) | 19 (10) | 11 (13) | 4 (7) |
| 18-Month follow-up ($n^a$ = 384) | | | | |
| 18-Month DAS-28, mean (S.D.) | 3.3 (1.5) | 3.3 (1.4) | 3.5 (1.6) | 3.2 (1.5) |
| Mean diff. (S.D.) in DAS-28 | 2.8 (1.7) | 2.9 (1.7) | 2.7 (1.8) | 2.8 (1.7) |
| EULAR response | | | | |
| Good, n (%) | 150 (39) | 89 (43) | 35 (29) | 26 (48) |
| Moderate, n (%) | 112 (29) | 71 (34) | 28 (23) | 13 (24) |
| None, n (%) | 122 (32) | 48 (23) | 59 (48) | 15 (28) |
| EULAR response in those remaining on initial therapy | | | | |
| Good, n (%) | 150 (53) | 89 (52) | 35 (53) | 26 (58) |
| Moderate, n (%) | 112 (40) | 71 (42) | 28 (42) | 13 (29) |
| None, n (%) | 21 (7) | 12 (7) | 3 (5) | 6 (13) |

[a]Number of patients with complete data on DAS-28 at follow-up. [b]Baseline DAS-28 score in only those who had data on disease activity at the corresponding follow-up questionnaire.

SAEs in the anti-TNF cohort including 53 infections, 16 cardiac disorders, 14 GIT disorders, 12 musculoskeletal and CTDs, 14 neoplasms and 13 nervous system disorders, as shown in Table 5. Whereas for the control cohort (n = 1115) and >3409.9 person-years of FUP, there were 624 SAEs. Furthermore, there were no reports of tuberculosis (TB) in any of the two cohorts. When adjusted for age, sex and baseline co-morbidity, there were no significant differences between the anti-TNF and control cohorts in the IRRs for SAEs (Table 5).

There were 10 cases of serious drug hypersensitivity and one of a serious opportunistic infection (cold sore and right facial swelling due to herpes simplex) in the infliximab cohort vs seven cases of serious drug hypersensitivity and three of serious opportunistic infection [lower respiratory tract infections—Aspergillus (1), Pneumocystis jiroveci (2)] in the control cohort. There were also 15, 8, 2 and 49 deaths in the etanercept, infliximab, adalimumab and control cohorts, respectively.

In total, there were 81 malignancies reported in various sites (14 anti-TNF and 67 DMARD control). Of note there were five cases of lymphoma in the control group and no cases in the anti-TNF group. There were 29 reports of skin cancer in total including 17 basal cell cancers (4 in controls, 13 in anti-TNF), 8 non-melanoma skin cancers not otherwise specified (2 anti-TNF, 6 controls) and 4 melanomas (2 in each group). The overall risk of cancer was not increased in the anti-TNF cohort compared with the control group (IRR 1.0; 95% CI, 0.5, 2.2).

## Discussion

The study found that 75.8, 70.3 and 68.2% of the studied PsA cohort were EULAR responders at 6, 12 and 18 months, respectively. Similar findings have been observed in the South Swedish Arthritis Treatment Group register in which 75% of their PsA cohort (n = 261) were EULAR responders at 12 months [9], whereas a previous study

TABLE 4 Predictors of higher EULAR response and disease remission in PsA cohort at 6 months

| Variable | Higher EULAR response, OR (95% CI) | | Disease remission, OR (95% CI) | |
|---|---|---|---|---|
| | Univariate analysis | Multivariate analysis | Univariate analysis | Multivariate analysis |
| Demographic variables | | | | |
| Age at start of therapy | 0.98* (0.96, 0.99) | 0.97* (0.95, 0.99) | 0.97* (0.95, 0.99) | 0.96* (0.94, 0.99) |
| Female | 0.49* (0.35, 0.70) | 0.51* (0.34, 0.78) | 0.37* (0.25, 0.55) | 0.34* (0.21, 0.57) |
| Smoking (yes/no) | 0.96 (0.68, 1.36) | 1.07 (0.71, 1.59) | 0.76 (0.51, 1.14) | 0.74 (0.45, 1.20) |
| Baseline co-morbidity[a] (yes/no) | 0.88 (0.60, 1.29) | 0.83 (0.53, 1.30) | 0.77 (0.51, 1.16) | 0.64 (0.38, 1.06) |
| Disease variables | | | | |
| Baseline DAS-28 | 1.01 (0.99, 1.02) | 0.99 (0.98, 1.02) | 0.99 (0.98, 1.01) | 0.99 (0.96, 1.02) |
| Baseline HAQ | 0.78* (0.62, 0.98) | 0.85 (0.66, 1.08) | 0.78 (0.59, 1.03) | 0.85 (0.63, 1.15) |
| Disease duration (years) | 1.01 (0.99, 1.03) | 1.02 (0.99, 1.04) | 0.99 (0.97, 1.02) | 1.00 (0.97, 1.04) |
| Inflammation[b] | 0.54* (0.30, 0.96) | – | 0.54* (0.31, 0.97) | – |
| TJC | 1.00 (0.98, 1.03) | – | 0.97 (0.95, 1.00) | – |
| SJC | 1.01 (0.99, 1.05) | – | 0.99 (0.95, 1.02) | – |
| Therapeutic variables: concurrent use of | | | | |
| DMARDs | 1.31 (0.42, 4.06) | 0.82 (0.19, 3.55) | 0.42 (0.09, 1.93) | 0.44 (0.05, 4.18) |
| Steroids | 0.48* (0.31, 0.74) | 0.45* (0.28, 0.72) | 0.57 (0.32, 1.01) | 0.55 (0.29, 1.02) |
| Biological therapy: etanercept is the reference category | | | | |
| Infliximab | 0.55 (0.37, 1.82) | 0.60 (0.38, 1.95) | 0.57 (0.35, 1.94) | 0.69 (0.39, 1.22) |
| Adalimumab | 1.01 (0.63, 1.63) | 0.81 (0.44, 1.49) | 1.16 (0.67, 1.99) | 0.97 (0.46, 2.04) |

*$P < 0.05$. [a]Includes any of hypertension, angina, ischemic heart disease, stroke, pulmonary fibrosis, asthma, chronic obstructive pulmonary disease, diabetes, thyroid disease, peptic ulcers, hepatic disease, renal disease, demyelinating disease, epilepsy, depression, TB and cancer. [b]Inflammation (CRP > 20 mg/l or ESR > 28 mm/h). SJC: swollen joint count; TJC: tender joint count.

TABLE 5 SAEs in PsA cases and seronegative RA control cohorts

| SAEs (MedDRA SOC) | Control ($n = 1115$) | All anti-TNF ($n = 596$) |
|---|---|---|
| Total no. of SAEs | 624 | 211 |
| Total person-years of FUP | 3409.9 | 1776.2 |
| Total IRRs[a] (95% CI) | Reference | 0.9 (0.8, 1.3) |
| Infections, *n* | 137 | 53 |
| Rate/1000 person-years (95% CI) | 19.6 (18.7, 20.6) | 11.2 (10.3, 12.1) |
| IRRs[a] (95% CI) | Reference | 0.7 (0.5, 1.1) |
| Neoplasms benign, malignant and unspecified, *n* | 67 | 14 |
| Rate/1000 person-years (95% CI) | 19.1 (18.0, 20.3) | 18.1 (15.9, 20.5) |
| IRRs[a] (95% CI) | Reference | 1.0 (0.5, 2.2) |
| Cardiac disorders, *n* | 56 | 16 |
| Rate/1000 person-years (95% CI) | 4.3 (3.7, 5.0) | 2.6 (1.9, 3.4) |
| IRRs[a] (95% CI) | Reference | 0.6 (0.3, 1.1) |
| GIT disorders, *n* | 31 | 14 |
| Rate/1000 person-years (95% CI) | 10.5 (9.2, 11.9) | 10.5 (8.7, 12.7) |
| IRRs[a] (95% CI) | Reference | 0.9 (0.5, 1.4) |
| Musculoskeletal and CTDs, *n* | 48 | 12 |
| Rate/1000 person-years (95% CI) | 21.6 (20.1, 23.1) | 17.7 (15.3, 20.4) |
| IRRs[a] (95% CI) | Reference | 0.6 (0.2, 1.5) |
| Nervous system disorders, *n* | 43 | 13 |
| Rate/1000 person-years (95% CI) | 29.2 (27.2, 31.3) | 27.8 (24.3, 31.6) |
| IRRs[a] (95% CI) | Reference | 1.0 (0.5, 2.1) |

[a]IRRs were calculated *vs* controls and were adjusted for age, sex and baseline co-morbidity using propensity score.

of RA patients within the BSRBR register that included patients on etanercept and infliximab reported that 68% of these patients were classified as responders at 6 months [25]. The EULAR response rate was similar among the three anti-TNF therapies up to 18 months despite the lower dose used in the infliximab cohort. The use of the lower dose of infliximab (3 mg/kg) may reflect the fact that infliximab did not receive its UK licence for use in PsA until 2004 and national guidelines on use were not issued until 2005, near the end of the recruitment phase for this study. Thus, most physicians may have applied the same dosing regimen as used for RA on these patients. Small numbers precluded an analysis of differential response among those patients receiving the two prescribed doses. The EULAR response rate was also similar in patients receiving anti-TNF agents in combination with MTX, another DMARD or anti-TNF monotherapy at 6 months. Disease remission was achieved by 27.5, 36.1 and 35.2% patients in the whole anti-TNF cohort at 6, 12 and 18 months, respectively.

Response to therapy was measured using the DAS-28 and the EULAR response criteria. A full set of domains to assess improvements in PsA patients would ideally include outcomes that measure skin involvement, dactylitis, enthesitis, spine involvement and radiological outcome. For feasibility reasons, we used the DAS-28, which was originally developed specifically for RA, but has been shown to perform better than PsARC in RCTs of PsA [26], and to be discriminant and responsive in observational cohorts of PsA [9].

At 6 months, female and older patients achieved lower improvements in their EULAR response and disease remission. Patients with higher baseline HAQ also experienced lower EULAR response and disease remission but this did not reach statistical significance. These results are closely related to the predictors reported for RA patients within the same register where higher baseline HAQ was associated with lower response and females were less likely to achieve remission [25]. It was also reported that concurrent use of MTX and current smokers were associated with higher and lower response rates in RA patients, respectively. These covariates did not reach statistical significance in our PsA cohort, but patients receiving corticosteroids experienced statistically significant lower EULAR response rates. Our results are also similar to those of the South Swedish Arthritis Treatment Group Register where they reported that lower baseline HAQ was associated with better treatment outcomes in a cohort of 1565 RA patients [27]. To our knowledge, no study has explored potential predictors for treatment efficacy in PsA patients.

During the FUP, there were no significant differences between the PsA cohort receiving anti-TNF therapies and RF-negative RA control cohort receiving DMARDs in the IRRs for all SAEs. Likewise, the incidence of malignancy was similar in both the anti-TNF and control cohorts, but these numbers are low and likely to be underpowered to detect any important difference in malignancy if one existed. There is also a selection bias that affects the influence of anti-TNF agents on malignant outcome, as BSR guidelines suggest that all anti-TNF-treated patients had to be free of malignancy for the 10 years prior to commencing treatment. We found a lower but insignificant prevalence of past-malignancy at baseline in the anti-TNF cohort than in the control cohort. The majority of the reported malignancies also occurred within the first year following registration [mean time (S.D.) from registration to the reported tumour date was 265.4 (230.3 days)]. This period of time is likely to be too short for the anti-TNF agents to play a pathogenic role in tumour genesis, raising the potential risk of protopathic bias.

To our knowledge, this is the largest longitudinal observational study of a large unselected population of patients with PsA receiving anti-TNF therapy in routine clinical practice. The present results can be considered as a reflection of the treatment outcomes as they have occurred in the real world of routine clinical practice, as treatments were open-labelled, treatment decisions were not randomized but rather left to rheumatologists, and there were no restrictions to patient participation.

Limitations to this study emerged from the rationale behind the construction of this register. Its aim was initially to establish the long-term safety and efficacy of biologic agents in patients with RA in the UK [12]. As data collection started, a subgroup of PsA patients receiving anti-TNF therapies was constructed over time ($n = 596$). Ideally, a parallel cohort of controls with PsA receiving DMARDs would have been collected with which to compare the rates of SAEs. As this was not available, the most closely related cohort (RF-negative RA patients receiving DMARDs) within the BSRBR control cohort was selected. A second limitation is that the collected data did not include any assessment of the impact on psoriatic skin lesions. Finally, as there is no definition for disease remission in the literature for PsA, we used one that is routinely applied in RA.

In conclusion, anti-TNF therapies were effective in the management of PsA with no added risk to the incidence of SAEs compared with conventional DMARDs; although the anti-TNF-treated patients had probably somewhat better malignancy and respiratory history at baseline. The mean FUP time on the BSRBR is still too short to comment on the safety profile of these agents beyond 3 years. There is still a need to continue FUP of these therapies in PsA for longer periods.

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**Rheumatology key messages**

- Anti-TNF therapies are effective in PsA.
- Increasing age, female sex and concurrent use of corticosteroids predicted poorer treatment response.
- Over 1776.2 person-years, anti-TNF therapies had a comparable safety profile to DMARDs.

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## Acknowledgements

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