Rates of new-onset psoriasis in patients with rheumatoid arthritis receiving anti-tumour necrosis factor α therapy: results from the British Society for Rheumatology Biologics Register

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The members of the BSRBR Control Centre Consortium are detailed in the Appendix

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ABSTRACT

Background: Anti-tumour necrosis factor (TNF)α treatments improve outcome in severe rheumatoid arthritis (RA) and are efficacious in psoriasis and psoriatic arthritis. However recent case reports describe psoriasis occurring as an adverse event in patients with RA receiving anti-TNFα therapy.

Objectives: We aimed to determine whether the incidence rate of psoriasis was higher in patients with RA treated with anti-TNFα therapy compared to those treated with traditional disease-modifying antirheumatic drugs (DMARDs). We also compared the incidence rates of psoriasis between the three anti-TNFα drugs licensed for RA.

Methods: We studied 9826 anti-TNF-treated and 2880 DMARD-treated patients with severe RA from The British Society for Rheumatology Biologics Register (BSRBR). All patients reported with new onset psoriasis as an adverse event were included in the analysis. Incidence rates of psoriasis were calculated as events/1000 person years and compared using incidence rate ratios (IRR).

Results: In all, 25 incident cases of psoriasis in patients receiving anti-TNFα therapy and none in the comparison cohort were reported between January 2001 and July 2007. The absence of any cases in the comparison cohort precluded a direct comparison; however the crude incidence rate of psoriasis in those treated with anti-TNFα therapy was elevated at 1.04 (95% CI 0.67 to 1.54) per 1000 person years compared to the rate of 0 (upper 97.5% CI 0.71) per 1000 person years in the patients treated with DMARDs. Patients treated with adalimumab had a significantly higher rate of incident psoriasis compared to patients treated with etanercept (IRR 4.6, 95% CI 1.7 to 12.1) and infliximab (IRR 3.5, 95% CI 1.3 to 9.3).

Conclusions: Results from this study suggest that the incidence of psoriasis is increased in patients treated with anti-TNFα therapy. Our findings also suggest that the incidence may be higher in patients treated with adalimumab.

The cytokine tumour necrosis factor α (TNFα) is known to play a key role in the pathogenesis of rheumatoid arthritis (RA),[1] and is also thought to have a key pathophysiological role in psoriasis.[2] Psoriasis and inflammatory arthritis can coexist as psoriatic arthritis.[3] In approximately 66% of patients with psoriatic arthritis, psoriasis precedes joint disease, while in equal proportions of the remaining cases arthritis precedes the onset of psoriasis, or both occur within 1 year of each other.[3] Treatments that inhibit the action of TNFα have dramatically improved outcome in severe RA.[4–6] Anti-TNFα therapies have also been shown to be efficacious in psoriasis[2 7 8] and psoriatic arthritis.[9] The three anti-TNFα therapies currently licensed for RA in the UK are etanercept, infliximab and adalimumab.

Despite the evident efficacy of anti-TNFα therapies for RA and psoriasis, several recently published case reports describe psoriasis occurring as an adverse event in patients with RA receiving anti-TNFα therapy. We identified 15 studies, which detail 41 cases of psoriasis-like adverse events[10–24] (table 1) through a Medline search combining the terms ''anti-TNF'', ''rheumatoid arthritis'' and ''psoriasis'' and searching the reference lists of relevant articles. The median age of these 41 patients was 51.5 (interquartile range (IQR) 43.5 to 63) and the female to male ratio was 6.6:1. Many of these report incident cases of psoriasis occurred within 9 months of starting anti-TNFα therapy (median 6 months, IQR 2 to 17).[10–16 18 20 21 23] This temporal association points towards possible causality. Adalimumab is cited as frequently as infliximab and etanercept as the anti-TNFα drug involved with these adverse events, despite being the most recent of these three drugs to be launched. However, published case reports cannot determine the incidence of psoriasis as an adverse event because the denominator is not known. Further, they cannot determine whether the incidence is increased by the drug beyond that seen without anti-TNFα treatment, or whether the incidence differs between drugs.

Using data on 9826 patients treated with anti-TNFα with RA in the British Society for Rheumatology Biologics Register (BSRBR), we set out to determine whether the incidence rate of psoriasis was higher in patients with RA treated with anti-TNFα therapy compared to those treated with traditional disease-modifying antirheumatic drugs (DMARDs). Additionally we aimed to compare the incidence rates of psoriasis between the three anti-TNFα drugs licensed for RA.

METHODS

The patients included in this study were participants in the BSRBR, a large national prospective

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Table 1 Case reports of new onset psoriasis following treatment for rheumatoid arthritis with anti-tumour necrosis factor (TNF) therapy

Patient	Reference	Age/sex	Affected areas	Diagnosis	Treatment	Latency, months
1	Beuthien *et al*[10]	63F	Injection site (thigh), palms and soles	Papulopustular exanthaema	ADA	3
2	Dereure *et al*[11]	47F	Anterior aspects of legs	Psoriasis	INF	2
3	Dereure *et al*[11]	55F	Palms, soles, umbilicus, ankles wrists and buttocks	Psoriasis	ETA	3
4	Flendrie *et al*[12]	–	Hands and feet	Psoriasis/psoriaform eruption	ADA	9
5	Flendrie *et al*[12]	–	Lower legs	Psoriasis/psoriaform eruption	ADA	48
6	Flendrie *et al*[12]	–	Arms and legs	Psoriasis/psoriaform eruption	ADA	16
7	Grinblat *et al*[13]	37F	Scalp, arms and legs	Psoriasis	INF	<1 week
8	Sfikakis *et al*[14]	65F	Palms, soles, elbows, arms and thighs	Psoriasis	ADA	9
9	Sfikakis *et al*[14]	48F	Soles, elbows, lower legs	Psoriatic plaques	ETA	7
10	Kary *et al*[15]	41F	Palms, soles, legs and arms	Psoriasis vulgaris	ADA	14–15
11	Kary *et al*[15]	65F	Limbs	Psoriasis vulgaris	ADA	4 days
12	Kary *et al*[15]	38M	Limbs and abdomen (Had family sister)	Psoriasis vulgaris	INF	3
13	Kary *et al*[15]	67F	Palms, arms, legs and scalp (Had family brother)	Psoriasis pustulosa	ADA	5
14	Kary *et al*[15]	49F	Legs and soles of feet (pre-existing but asymptomatic)	Psoriasis pustulosa	INF	8
15	Kary *et al*[15]	49F	Legs and arms (pre-existing but asymptomatic for 15 years)	Psoriasis pustulosa	ETA	1
16	Kary *et al*[15]	63F	Extremities and trunk	Psoriasis vulgaris	ETA	2
17	Sari *et al*[16]	30F	Scalp, elbows, abdomen and lower back	Psoriasis	ETA	2
18	Goncalves *et al*[17]	61F	Hands and feet	Plaque psoriasis	INF	14
19	Aslanidis *et al*[18]	64F	Elbows, neck and scalp	Psoriasisiform dermatitis	ADA	3
20	Cohen *et al*[19]	70F	Pubis, umbilicus, legs	Psoriasis	INF	41
21	Cohen *et al*[19]	63F	Legs, arms	Psoriasis	ETA	10
22	de Gannes *et al*[20]	41F	Heel and palm	Palmoplantar psoriasis	ETA	26
23	de Gannes *et al*[20]	53F	Elbows	Plaque psoriasis	ETA	17
24	de Gannes *et al*[20]	66F	Scalp, arms, chest and neck	Plaque and guttate psoriasis	ETA	4
25	de Gannes *et al*[20]	51M	Elbows	Psoriasis	ETA	12
26	de Gannes *et al*[20]	48F	Arms and trunk	Papulosquamous eruption	ETA	3
27	de Gannes *et al*[20]	41F	Scalp, thigh and thumb	Palmoplantar pustular psoriasis	INF	2
28	de Gannes *et al*[20]	52F	Palmoplantar pustular psoriasis	Palmoplantar pustular psoriasis	INF	24
29	de Gannes *et al*[20]	78F	Lesions on shins	Thick surface keratin with focal parakeratosis	INF	2
30	de Gannes *et al*[20]	56M	Palms, soles, legs	Pustular psoriasis	ADA	62
31	de Gannes *et al*[20]	50M	Trunk, shins and arms	Psoriasis	INF	12
32	de Gannes *et al*[20]	55F	Palms, soles and ankles	Plaque and pustular psoriasis	ADA	36
33	de Gannes *et al*[20]	49M	Palms and soles	Pustular psoriasis	ADA	5
34	de Gannes *et al*[20]	37F	Plantar surfaces	Plaque psoriasis with subsequent pustules	ETA	24
35	Ubriani *et al*[21]	65F	Legs, trunk and extremities	Psoriasis	INF	48
36	Ubriani *et al*[21]	45F	Palmoplantar pustulosis	Palmoplantar pustulosis	ADA	1
37	Starmans-Kool *et al*[22]	62F	Hands and feet. Swollen hands, knees	Palmoplantar pustulosis	INF	5th Infusion
38	Michaelsson *et al*[23]	62F	Palmoplantar pustulosis with lesions on legs and arms	Palmoplantar pustulosis & pustular psoriasis	INF	2 weeks
39	Michaelsson *et al*[23]	50F	Palmoplantar pustulosis with lesions on extremities	Palmoplantar pustulosis	INF	1.5
40	Roux *et al*[24]	42F	Psoriatic palmoplantaris pustulosis	Psoriatic palmoplantaris pustulosis	INF	1.5
41	Roux *et al*[24]	32F	Plantaris pustulosis with lesions on legs, arms and trunk	Psoriatic palmoplantaris pustulosis & diffuse erythaematosquamous lesions	INF	7

ADA, adalimumab; ETA, etanercept; INF, infliximab.

observational cohort study established in January 2001 primarily to monitor the safety of anti-TNFα therapies in routine clinical practice. The methods of this study have been described in detail previously.[25] Briefly, the first 4000 patients with RA starting each anti-TNFα therapy were required by The National Institute for Health and Clinical Excellence (NICE) to be registered with the BSRBR and followed up for information on drug use, disease activity and adverse events. In the UK, prescription of anti-TNFα drugs is restricted to patients with active disease (28-joint Disease Activity Score (DAS28) >5.1) despite previous therapy with at least two disease-modifying antirheumatic drugs (DMARDS), one of which should be methotrexate.[26] All patients with a doctor diagnosis of RA who were receiving etanercept, infliximab or adalimumab as their first anti-TNFα therapy comprise the anti-TNFα cohort for this study.

A comparison cohort of patients who were biological naive with active RA was recruited in parallel within the BSRBR and followed up with identical methodology. Those patients had doctor-diagnosed RA, active disease (guideline DAS28>4.2), current treatment with a DMARD and no previous exposure to any anti-TNFα drug. Patients registered in the comparison cohort could subsequently receive an anti-TNFα drug if clinically indicated, at which point they would switch to contributing exposure time to the anti-TNFα cohort. The TNF treated cohort and those in the comparison cohort had to have

completed at least 6 months follow-up by 31 July 2007 to be included in this analysis.

Baseline information for the BSRBR is collected from two sources. A rheumatologist or rheumatology specialist nurse completes a standardised form that includes demographic data such as age, sex, diagnosis, disease duration and clinical outcome measures including the DAS28.[27] The patients complete a questionnaire that includes the Stanford Health Assessment Questionnaire adapted for UK use,[28] history of smoking and occupational history.

Follow-up questionnaires are completed by rheumatologists (or specialist nurse) for 5 years (semiannually for the first 3 years and annually for a subsequent 2 years) and patients for 3 years. Rheumatologists are requested to provide details of changes in therapy, current disease activity and development of any adverse events. Adverse events are recorded regardless of whether or not the doctor suspects they are related to anti-TNFα therapy, and are coded using the Medical Dictionary for Regulatory Activities (MedDRA), V. 6.1. Patients were categorised as responders or non-responders based on their 6-month DAS28 scores according to the European League Against Rheumatism (EULAR) definition.[29] Responders were those patients who achieved either a EULAR good or moderate response. Good responders are those patients improving by >1.2 units and achieving an absolute score <3.2 at 6 months, while non-responders are those improving <0.6 and with a 6-month DAS28 score >5.1. Moderate responders were those falling in between these definitions.

Patients with new onset psoriasis reported as an adverse event by the rheumatologist were sent a questionnaire for further information. Information collected included whether the patient had prior psoriasis, family history of psoriasis, time from starting anti-TNFα therapy (or date of registration with BSRBR for the comparison cohort) to psoriasis onset, extent and involvement of psoriasis and, if anti-TNFα therapy was stopped due to the psoriasis, whether the psoriasis subsequently improved.

Person years were calculated from the first day of anti-TNFα therapy up to the date of the last follow-up completed up to July 2007, 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 follow-up completed up to July 2007 or death, whichever came first. All psoriasis adverse events occurring during this period were included in the analysis.

All psoriasis adverse events were rheumatologist reported, and inclusion of patients in this study did not require a separate dermatological examination or opinion. Only events occurring while the patient was actively receiving anti-TNF therapy were attributed to the drug. Rates of psoriasis are presented as events/1000 person years and 95% CIs. Incidence rates (IR) of psoriasis within the anti-TNFα treated cohort were compared by calculating incidence rate ratios (IRR), with stepwise adjustment for age and gender, then smoking history and calendar year of registration using Poisson regression with Stata V. 9.2 (Stata, College Station, Texas, USA).[30]

RESULTS

A total of 12 706 patients with RA from the BSRBR were followed prospectively and included in the analysis. In all, 9826 patients with RA had received anti-TNFα therapy and 2880 were from the comparison cohort, treated using traditional DMARDs. The median follow-up time was 2.81 years per person for the anti-TNFα treated cohort and 1.91 years per person for the comparison cohort. Of patients in the anti-TNFα treated cohort, 3910 (40%) received etanercept, 3206 (33%) received infliximab and 2710 (28%) received adalimumab as their first anti-TNFα therapy.

The baseline characteristics of the patients are described in table 2. Patients treated with anti-TNFα therapy were significantly younger, more likely to be female, had longer disease duration, less likely to have ever smoked and had poorer Health Assessment Questionnaire (HAQ) and DAS28 scores. Within the group of patients receiving anti-TNFα therapy, the adalimumab treated group were slightly older ($p = 0.005$) with shorter disease duration ($p = 0.002$), included fewer lifelong non-smokers ($p = 0.036$) and had better HAQ and DAS28 scores ($p<0.001$).

By July 2007 there were 42 cases of consultant-reported psoriasis; 36 (86%) patients returned the questionnaire about their psoriasis. Five of the six patients that did not return a questionnaire were actively receiving anti-TNF treatment at the time of their psoriasis; two patients were receiving etanercept, two adalimumab and one infliximab. The remaining patient developed psoriasis 6 months after cessation of infliximab. Of the 36 patients with reported psoriasis who had returned forms, 9 (25%) were recurrences in patients known to have previous psoriasis; 27 were incident cases in patients who reported no previous psoriasis of which 2 occurred in patients who had discontinued anti-TNFα therapy. The cases of psoriasis reported after the cessation of anti-TNF therapy (both infliximab) occurred at 4 months and 6 months following the end date; the patients had received 15 months and 6 months treatment, respectively. All 25 incident cases occurred in patients receiving anti-TNFα therapy and none in the comparison cohort. The median age of patients with incident psoriasis was 60 (IQR 55 to 63) and the female to male ratio was 5.3:1 (table 3). The median time from the start of anti-TNF therapy to new onset of psoriasis was 6 months (range 1–24). Only one patient reported a positive family history of psoriasis. Of 25 patients, 6 were good EULAR responders, 13 moderate responders and 6 non-responders These 25 cases form the content of this analysis. In order to compare rates of events between the comparison cohort and the anti-TNFα therapies, one patient from the comparison cohort was coded at random with psoriasis and included as a hypothetical reference case.

The crude incidence rate of psoriasis was higher in those treated with anti-TNFα therapy (1.04 per 1000 person years) than in the comparison cohort based on 0 cases (one-sided 97.5% CI 0.71 per 1000 person years) in 5207 person years of follow-up, or a rate calculated using a hypothetical case of psoriasis (0.19 per 1000 person years) (table 4). The unadjusted IRR for new onset psoriasis in the patients treated with anti-TNFα compared to a hypothetical case in the comparison cohort would be 5.4 (95% CI 0.7 to 40.3).

In all, 13 patients who developed new onset psoriasis were receiving adalimumab, 6 were receiving infliximab and a further 6 etanercept. Compared to patients in the comparison cohort, the unadjusted IR for psoriasis in adalimumab treated patients was significantly higher at 1.84 per 1000 person years (95% CI 0.98 to 3.15) and elevated but not significant for etanercept (IR 0.59, 95% CI 0.22 to 1.28) and infliximab (IR 0.88, 95% CI 0.32 to 1.93) (table 4). Compared to a hypothetical case in the comparison cohort, the unadjusted IRR for adalimumab would be significantly higher at 9.6 (95% CI 1.2 to 77.8) and elevated for etanercept (3.1, 95% CI 0.4 to 25.5) and infliximab (4.6, 95%

Table 2 Baseline characteristics of the British Society for Rheumatology Biologics Register (BSRBR) patients with rheumatoid arthritis (RA), by treatment group

				Specific anti-TNFα treatment			
	Control (DMARD) (n = 2880)	All anti-TNFα (n = 9826)	p Value	Etanercept (n = 3910)	Infliximab (n = 3206)	Adalimumab (n = 2710)	p Value
Age, mean (SD)	60.0 (12.4)	56.2 (12.2)	<0.001	55.9 (12.2)	55.9 (12.4)	56.8 (11.9)	0.005
Female, %	72%	76%	<0.001	77%	76%	75%	0.055
Disease duration (years), median (IQR)	7 (1 to 15)	11 (6 to 19)	<0.001	12 (6 to 19)	12 (6 to 19)	11 (5 to 19)	0.002
Smoking, %:							
Current	24%	22%	0.002	21%	22%	24%	0.036
Former	40%	38%		38%	38%	38%	
Never	36%	40%		41%	40%	38%	
HAQ, median (IQR)	1.6 (1.0 to 2.1)	2.1 (1.8 to 2.5)	<0.001	2.1 (1.8 to 2.5)	2.1 (1.8 to 2.5)	2.0 (1.6 to 2.4)	<0.001
DAS28, mean (SD)	5.0 (1.3)	6.6 (1.0)	<0.001	6.6 (1.0)	6.6 (1.0)	6.5 (1.0)	<0.001
Calendar year, median (IQR)	2004 (2004 to 2005)	2003 (2003 to 2004)	<0.001	2004 (2003 to 2004)	2003 (2002 to 2003)	2004 (2003 to 2005)	<0.001

IQR, interquartile range.

CI 0.6 to 38.2). Patients treated with adalimumab also had a significantly increased risk of psoriasis compared to those treated with etanercept (IRR 4.6, 95% CI 1.7 to 12.1) and infliximab (IRR 3.5, 95% CI 1.3 to 9.3) adjusted for age, sex, smoking status and calendar year of registration.

Of the 25 patients who developed psoriasis while on anti-TNFα therapy, 8 stopped the drug because of the adverse event. Six of these patients reported an improvement in their psoriasis once anti-TNFα therapy was stopped. A total of 13 patients developed psoriasis within the first 6 months of anti-TNFα therapy and these patients tended to have extensive psoriasis of multiple sites or palmoplantar pustulosis (table 3). Eight of these patients were receiving adalimumab, three infliximab and two etanercept. Of these 13 patients, 4 stopped anti-TNFα therapy due to their psoriasis and 3 reported improvement in their psoriasis after stopping treatment. No information on the course of skin disease in patients who did not stop treatment due to the occurrence of psoriasis was available.

DISCUSSION

We have shown that the incidence rate of new onset psoriasis is elevated in patients with RA treated with anti-TNFα therapy. No cases of new onset psoriasis were reported in over 5000 person years of follow-up in the patients treated with traditional DMARD therapy. A hypothetical case was introduced to allow comparison of rates in patients treated with

Table 3 Anatomical involvement of new-onset psoriasis (and occurring within 6 months of starting anti-tumour necrosis factor (TNF) therapy in patients 1–13)

Patient	Age/sex	Treatment	Affected areas	Time to event, months	Improvement on stopping	EULAR responder
1	60/F	ETA	Elbows and all over body	3	NA	Yes
2	63F	ETA	Not stated	5	NA	–
3	56F	INF	Not stated	5	–	–
4	64/M	INF	Palmoplantar pustulosis	6	NA	Yes
5	30/F	INF	Hairline	6	NA	Yes
6	63/F	ADA	All over, except face	1	Yes	No
7	47/M	ADA	Palmoplantar pustulosis	1	Yes	Yes
8	36/F	ADA	Palmoplantar pustulosis	1	Yes	No
9	62/F	ADA	Back, knees, thighs	1	–*	Yes
10	58/F	ADA	Elbows, ankle	2	NA	Yes
11	63F	ADA	Not stated	3	NA	–
12	66/M	ADA	Right leg and arm	4	NA	Yes
13	70F	ADA	Not stated	4	–	–
14	62M	ETA	Not stated	18	NA	–
15	40F	ETA	Not stated	23	NA	–
16	56F	ETA	Palmoplantar pustulosis	24	Yes	Yes
17	33F	ETA	Body and legs	24	No	Yes
18	66F	INF	Elbows	12	No	Yes
19	54F	INF	Tops of feet and legs	12	NA	Yes
20	58F	INF	Legs, upper arms	18	No	Yes
21	56F	ADA	Palmoplantar pustulosis	10	Yes	Yes
22	60F	ADA	Legs	12	No	Yes
23	57F	ADA	Palmoplantar pustulosis	12	NA	–
24	60F	ADA	Knees	12	NA	Yes
25	61F	ADA	Arms, lower leg, buttocks, face	17	Yes	Yes

*Treatment stopped, response unknown.
ADA, adalimumab; EULAR, European League Against Rheumatism; ETA, etanercept; INF, infliximab; NA, not applicable, treatment was not stopped

Table 4 Comparison of rates of psoriasis by cohort and biological drug compared to disease-modifying antirheumatic drug (DMARD) treatment and within anti-tumour necrosis factor (TNF) treatments compared with etanercept

	Control (DMARD) (n = 2880)	Anti-TNF (n = 9882)	Specific anti-TNF treatment		
			Etanercept (n = 5265)	Infliximab (n = 3569)	Adalimumab (n = 3907)
Person years	5207	23 996	10 167	6782	7047
Follow-up per person, (years) median (IQR)	1.91 (0.96 to 2.45)	2.81 (1.94 to 3.27)	2.95 (2.43 to 3.28)	3.07 (1.99 to 4.04)	1.99 (1.08 to 2.95)
No. of psoriasis	0	25	6	6	13
Rate of psoriasis/1000 person years (95% CI)	0 (0.71†)	1.04 (0.67 to 1.54)	0.59 (0.22 to 1.28)	0.88 (0.32 to 1.93)	1.84 (0.98 to 3.15)
Age-adjusted and sex-adjusted IRR (anti-TNF treatment only)	NA	NA	REF	1.50 (0.48 to 4.64)	3.12 (1.05 to 9.28)
Further adjusted for calendar year and smoking	NA	NA	REF	1.30 (0.42 to 4.03)	4.55 (1.72 to 12.05)
Age-adjusted and sex-adjusted IRR (anti-TNF treatment only)	NA	NA	0.67 (0.22 to 2.07)	REF	2.08 (0.70 to 6.20)
Further adjusted for calendar year and smoking	NA	NA	0.77 (0.25 to 2.40)	REF	3.51 (1.32 to 9.31)

*Hypothetical case of psoriasis for use as comparison; †one-sided 97.5% confidence interval.
IQR, interquartile range; IRR, incidence rate ratio; NA, not applicable; REF, reference value.

anti-TNF therapy compared to RA patients treated with traditional DMARDs. The resulting IRR suggested a fivefold increase that, although not statistically significant, probably represents a considerable underestimate of the increased risk in patients treated with anti-TNF due to the hypothetical "case" in the comparison cohort. Patients with RA treated with adalimumab had a fourfold increased risk compared to patients treated with etanercept and a threefold increased risk compared to patients treated with infliximab. The incidence of psoriasis in patients treated with adalimumab was 1 new case for every 550 patients treated for a 1-year period, compared to less than 1 new case for every 5000 patients treated with DMARDs per year. The temporality and outcome following drug withdrawal point towards a causal relationship; most psoriasis adverse events occurred soon after the onset of anti-TNFα therapy and, in patients whose treatment was subsequently stopped due to psoriasis, an improvement in psoriasis was experienced.

Our results represent an interesting paradox as anti-TNFα therapy is now widely used in the management of psoriasis. At present the molecular mechanisms underlying this are unclear as TNFα is clearly proinflammatory in human skin and mice lacking the p75 TNFα receptor have suppressed cutaneous immune responses.[31 32] However, the implication of this observation must be that, in this subset of patients who develop psoriasis, TNFα has an entirely different role than in the majority of patients.

A number of possible explanations for the paradoxical occurrence of psoriasis as an adverse event of anti-TNFα treatment have been explored by other authors. The possibility of misdiagnosis of the primary rheumatological disease exists, and psoriatic arthritis may precede psoriasis in approximately 15% of cases. Alternatively, the patients with psoriasis as an adverse event may have a genetic predisposition to psoriasis, which after all is not uncommon (prevalence 2.5%), in addition to their arthritis.[33] Others have suggested that the adverse event is not psoriasis but either a drug hypersensitivity reaction such as acute generalised exanthaematous pustulosis[14] or a bacterial infection due to the inhibition of TNFα.[15 34] However, neither seems likely. The pattern of the psoriatic adverse events do not match the short time to onset and rapid spontaneous resolution of acute generalised exanthaematous pustulosis[14 35] and biopsies of selected cases have confirmed typical histological features of psoriasis.[12 18 20 21] None of the patients described by Richtlin *et al*[34] or Kary *et al*[15] had experienced a preceding bacterial infection.

If the former explanations are rejected, we must explain why there is a paradoxical true increase in psoriasis following anti-TNFα therapy. One hypothesis surrounds the relationship between TNFα and type 1 interferon (IFN) α, which is a key player in the pathogenesis of psoriasis. Dermal plasmacytoid dendritic cells (PDC) which produce IFNα have recently been shown to have a pivotal role in the early phase of induction of psoriasis[36] and TNFα down regulates the production of PDC cells and their synthesis of IFNα.[37] De Gannes *et al* suggest that TNFα inhibition may induce locally sustained INFα production[20] which in certain patients might lead to an outbreak of psoriasis and demonstrated lesional type 1 IFNα activity was increased in patients who developed psoriasis while on anti-TNFα therapy compared to psoriasis vulgaris. Fiorentino believes this might also explain why monoclonal antibodies primarily cause new psoriasis while etanercept may cause flares of pre-existing disease.[33] Small changes in TNFα such as those associated with etanercept may only be sufficient to induce flares of psoriasis in patients with the disease, while much larger functional reductions associated with the action of monoclonal antibodies might be needed to trigger incident cases of psoriasis.[33]

This large prospective national observational cohort study allows us to investigate the apparent relationship between anti-TNFα therapy and new-onset psoriasis suggested by published case reports. The methodology of the register allows us to calculate rates of psoriasis as an adverse event in anti-TNFα treated patients with RA compared to traditional DMARD therapy and also to compare rates between specific anti-TNFα drugs.

It is important to consider that this analysis represents an early analysis based on 1–2 years of follow-up. This study is also based on low numbers of cases in the patients treated with TNFα, and compared to a hypothetical case of psoriasis in the comparison cohort where no cases of consultant-reported psoriasis were identified. This is reflected by the large confidence intervals around our estimates. Patient follow-up will continue for at least 5 years, and further analysis may allow us to provide more robust estimates. Psoriasis has also been reported as an adverse event in other rheumatological conditions such as spondyloarthropathy[21] including ankylosing spondylitis and enteropathic arthritis,[22] Behçet disease and juvenile idiopathic arthritis.[38] Investigation of the rates of psoriasis adverse events in these groups of patients is precluded by the low numbers of patients within the BSRBR with these conditions.

There are however a number of methodological issues that should be considered in interpreting these results. The first is the definition of the exposure period-at-risk to anti-TNFα treatment. We have taken a conservative approach, which limits the period-at-risk to the time that the patient was actively

treated using an anti-TNFα drug. It is possible that a patient remains at risk for a lag period after discontinuation of a drug (which may also vary between drugs), and adverse events occurring in this period would be missed. The definition of the period-at-risk being the time "on drug" used in our analysis would underestimate the incidence rate in the anti-TNFα treated cohort and does not explain our finding of an increased risk.

There are also a number of weaknesses in the case ascertainment and definition. This analysis focuses on non-serious adverse events and we must acknowledge that we may not have captured all mild cases of incident psoriasis. Doctors may not detail all non-serious adverse events in their follow-up forms as they consider them "trivial" and/or unrelated despite the questionnaires requesting details of adverse events and not adverse drug reactions. Therefore, our incident rates are likely to be an underestimate. Furthermore, the use of a hypothetical event in the comparison cohort to generate incident rate ratios will lead to an underestimate of the true rate ratios between the cohorts. The use of a hypothetical event in the patients treated with DMARDs also prevented us presenting adjusted incidence rate ratios because it would be inappropriate to adjust results according to the characteristics of an arbitrarily selected patient, therefore the differences between the patients in the anti-TNF treated and comparison cohorts cannot be completely accounted for.

It is also possible that psoriasis was preferentially reported in the anti-TNF treated cohort following the publication of case reports, thus explaining our positive finding. However, psoriasis as an adverse event of anti-TNF therapy was not widely recognised during much of the follow-up period of this study. Because adalimumab was licensed later than the other two drugs, a higher proportion of follow-up for patients treated with adalimumab falls after the initial publications compared with patients treated with infliximab or etanercept. However, adjustment for year of entry into the study did not attenuate our findings. In fact, the point estimate for risk associated with adalimumab rose to 4.5.

It is possible that there may be some misclassification of the psoriasis adverse events. Few events had histological confirmation, and inclusion did not require a dermatological opinion. However, we sought to collect additional detailed information from the patient after initial reports from the doctor. The cases we describe are largely consistent with the case reports of occurrences of psoriasis following initiation of anti-TNFα in the literature.

CONCLUSIONS

Results from this prospective study support the published case reports that, paradoxically, the incidence of psoriasis is increased in patients treated with anti-TNFα therapy. The findings also suggest that the incidence may be higher in patients treated with adalimumab.

Competing interests: None declared.

Ethics approval: Ethics approval was obtained.

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APPENDIX

The members of the British Society for Rheumatology Biologics Register: Musgrave Park Hospital, Belfast (Dr Allister Taggart); Cannock Chase Hospital, Cannock Chase (Dr Tom Price); Christchurch Hospital, Christchurch (Dr Neil Hopkinson); Derbyshire Royal Infirmary, Derby (Dr Sheila O'Reilly); Russells Hall Hospital, Dudley (Dr George Kitas); Gartnavel General Hospital, Glasgow (Dr Duncan Porter); Glasgow Royal Infirmary, Glasgow (Dr Hilary Capell); Leeds General Infirmary, Leeds (Professor Paul Emery); King's College Hospital, London (Dr Ernest Choy); Macclesfield District General Hospital, Macclesfield (Professor Deborah Symmons); Manchester Royal Infirmary, Manchester (Dr Ian Bruce); Freeman Hospital, Newcastle-upon-Tyne (Dr Ian Griffiths); Norfolk and Norwich University Hospital, Norwich (Professor David Scott); Poole General Hospital, Poole (Dr Paul Thompson); Queen Alexandra Hospital, Portsmouth (Dr Fiona McCrae); Hope Hospital, Salford (Dr Romela Benitha); Selly Oak Hospital, Selly Oak (Dr Ronald Jubb); St Helens Hospital, St Helens (Dr Rikki Abernethy); Haywood Hospital, Stoke-on-Trent (Dr Andy Hassell); Kings Mill Centre, Sutton-In Ashfield (Dr David Walsh).

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