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Concise report

Malignancy and mortality rates in patients with severe psoriatic arthritis requiring tumour-necrosis factor alpha inhibition: results from the British Society for Rheumatology Biologics Register

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Abstract

Objective. The aim of this study was to compare the incidence of cancer and all-cause and cause-specific mortality rates among a cohort of patients with severe PsA receiving TNF inhibitor (TNFi) with those of the general UK population.
Methods. Cancers and deaths were identified from the national cancer and the national death registers in patients with PsA included in the British Society for Rheumatology Biologics Register from start of TNFi until 31 December 2012. Standardized incidence ratios (SIRs) and standardized mortality ratios (SMRs) were calculated using published cancer and death rates for the general population. SIRs were calculated for both overall cancer risk and non-melanoma skin cancer. SMRs were calculated for (1) all-cause mortality, (2) death from malignancy and (3) death from circulatory disease. Gender-specific analyses were also performed.
Results. Thirty-four cancers and 41 deaths among 709 patients were observed. The risk of malignancy overall was not increased (SIR 0.94; 95% CI: 0.65, 1.34). However, there was a significantly increased incidence of non-melanoma skin cancer (SIR 2.12; 95% CI: 1.19, 3.50). The all-cause mortality rate in our cohort was increased (SMR 1.56; CI: 1.12, 2.11). Death from malignancy was not increased, but death from coronary heart disease was increased (SMR 2.42; 95% CI: 1.11, 4.59).
Conclusion. In our cohort of patients with severe PsA, the overall incidence of malignancy was similar to that of the general population, although the incidence of non-melanoma skin cancer was increased. All-cause mortality was significantly increased, in part due to excess of deaths attributed to coronary heart disease.

Key words: PsA, TNF inhibitors, malignancy, mortality, cardiovascular disease

CLINICAL SCIENCE

Rheumatology key messages

- Patients with severe psoriatic arthritis had similar incidence of overall malignancy to the general population
- The incidence of non-melanoma skin cancer was increased in patients with severe psoriatic arthritis
- Mortality, particularly from coronary heart disease, was increased in patients with severe psoriatic arthritis

Introduction

It is not generally possible to study rare and later-occurring adverse events associated with pharmacological treatments within a clinical trial setting. Register-based and other longitudinal observational studies have provided important insights into the long-term safety of TNF-α inhibitors (TNFi) use. However, the amount of long-term safety data regarding the use of TNFi is much lower in patients with PsA than in patients with RA.

There are concerns that the risk of malignancy in patients with PsA may be raised, not only by the primary disease, but also as a consequence of the treatments

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given including conventional DMARD treatments (especially ciclosporin), TNFi and phototherapy. In addition, skin psoriasis itself is associated with an increased risk of non-melanoma skin cancer (NMSC) [1]. Recently, two large observational studies have examined cancer risk in PsA. A Swedish–Danish collaboration reporting reassuringly similar rates of malignancy in TNFi-treated PsA patients compared with non-TNFi-treated patients as well as compared with population controls [2]. A large study of UK data from general practice did, however, identify an increased risk of haematological malignancies in the PsA population overall, and patients receiving DMARD treatment for PsA had higher rates of solid, haematological malignancies and NMSC compared with patients who received no DMARD treatment [3].

Conflicting results have also been reported regarding mortality risk associated with PsA. Excess mortality has been reported in a 2007 paper [4], but a more recent study using UK primary care data did not find a significantly increased rate of mortality associated with PsA, although skin psoriasis was associated with increased risk of death [5, 6]. An increased risk of cardiovascular events in patients with PsA has been reported, but no significant excess cardiovascular mortality [7, 8].

Give the heterogeneity in available results and populations studied, further information on the risks of malignancy and mortality in PsA could contribute to better understanding of long-term outcomes in the disease. The specific aim of this study was to compare incidence of cancer as well as all-cause and cause-specific mortality rates among a cohort of patients with severe PsA receiving TNFi with those of the general population.

Methods

All patients with a rheumatologist's diagnosis of PsA starting a TNFi and registered in the British Society for Rheumatology Biologics Register (BSRBR), which recruited PsA patients between 2002 and 2006, were included. Full details of this study, including data collection, have previously been published [9, 10]. Once included, the patients were flagged with the national cancer and death registers for England and Wales (via the Office for National Statistics and NHS Digital), Scotland (via the NHS Central Register) and Northern Ireland (via the Northern Ireland Cancer Registry and Business Services Organisation), which provide regular reports to the study team at The University of Manchester on all cancers and deaths respectively occurring in study patients. All patients were followed from registration (start of TNFi) until death or 31 December 2012, whichever came first. Population rates are published by the Office for National Statistics annually and the relevant series (MB1 and DR) were accessed from www.ons.gov.uk in July 2014. Although BSRBR patients were recruited from England, Wales, Scotland and Northern Ireland, only English population rates were available for malignancy and were applied to all patients. For mortality the available population rates were for England and Wales combined, and were applied to all patients. Population rates were reported using the International Classification of Diseases version 10 (ICD 10).

Gender-, age- and calendar year-specific population rates were applied to the corresponding patient years in the cohort to calculate the expected numbers of cancers and deaths if study population rates were the same as those in the general population. Standardized incidence ratios and standardized mortality ratios (SMRs) were then calculated based on observed rates [(observed number of events/expected number of events) $\times$ 100].

Overall cancer rates included ICD 10 codes C1–C9; a secondary analysis was performed only for NMSC (C44). In addition, all analyses were repeated for men and women separately. All deaths were included in the primary analyses, with secondary analyses performed for deaths from cancer (ICD 10 codes: C1–C9), deaths from circulatory disease (ICD 10 codes: I00–I99) and deaths from coronary heart disease (ICD 10 codes: I20–I25).

The BSRBR has ethical approval from the North West Multicentre Research Ethics Committee (reference number MREC 00/08/053) and patients gave written informed consent to participate in the BSRBR; no further ethical approvals were required to undertake this analysis.

Results

A total of 709 patients with PsA starting a TNFi were included in this analysis, contributing a total of 5286 patient-years of follow-up. The majority of patients were recruited in England ($n = 579$), but patients from Scotland ($n = 52$), Wales ($n = 33$) and Northern Ireland ($n = 45$) were also included. Baseline characteristics are shown in Table 1. Eleven (1.6%) patients had a cancer registered prior to baseline, none of whom had a further cancer. Nearly all patients had previous or current exposure to methotrexate at start of TNFi and nearly half the patients had previous or current exposure to ciclosporin. Information on baseline psoralen and ultraviolet A (PUVA) photochemotherapy exposure was only available for 23% and was low in these patients (6.7%). The population had a high mean (S.D.) 28-joint DAS [11] (DAS28) of 6.0 (1.2).

Thirty-four cancers in 32 patients were reported. The majority of cancers were NMSC ($n = 15$). Other cancers included malignant melanoma ($n = 4$), genital cancers (male and female, each $n = 3$), lymphatic and haematological cancers ($n = 3$), oropharyngeal cancer ($n = 2$) and other ($n = 4$). The patients with two cancers did both have one NMSC and one solid cancer. While there was no increased risk of overall malignancy observed in this cohort compared with the general population (Table 2), patients had double the risk of NMSC (standardized incidence ratio 2.12; 95% CI: 1.19, 3.50). In the gender specific analysis, incidence of NMSC was significantly higher for women in the PsA cohort compared with the general population, while the difference for men did not reach statistical significance.

There were 41 reported deaths in the cohort (Table 2). Circulatory disease was the most frequent cause of death ($n = 13$, of which nine were from coronary heart disease).

Table 1 Baseline characteristics of 709 patients with PsA starting a TNFi in the BSRBR

	All patients	Females	Males
n	709	378	331
Females [*n* = 709]	378 (53)	—	—
Age, mean (S.D.), years [*n* = 709]	45.7 (11)	46.5 (12)	44.8 (11)
Disease duration, mean (S.D.), years [*n* = 698]	12.7 (8.7)	12.7 (9)	12.6 (8)
Initial TNFi type [*n* = 709]	—	—	—
Etanercept	384 (54)	199 (53)	185 (56)
Infliximab	217 (31)	121 (32)	96 (29)
Adalimumab	108 (15)	58 (15)	50 (15)
First TNFi [*n* = 700]	660 (94)	354 (95)	306 (94)
Number of prior DMARDs [*n* = 709]	3 (2–4)	3 (2–4)	3 (2–4)
Previous MTX exposure [*n* = 709]	693 (98)	371 (98)	322 (97)
PUVA exposure [*n* = 163][a]	11 (6.8)	7 (8.1)	4 (5.3)
Previous ciclosporin exposure [*n* = 709]	318 (45)	165 (44)	153 (46)
Current smoker [*n* = 557][a]	118 (21)	69 (23)	49 (19)
Ever smoker [*n* = 557][a]	312 (53)	176 (54)	136 (51)
Comorbidity[b] [*n* = 709]	—	—	—
0	323 (46)	160 (42)	163 (49)
1	214 (30)	119 (32)	95 (29)
2	114 (16)	67 (18)	47 (14)
3 or more	56 (7.9)	31 (8.2)	25 (7.6)
Hypertension	204 (29)	108 (29)	96 (29)
Angina	15 (2.1)	11 (2.9)	4 (1.2)
Myocardial infarction	9 (1.3)	4 (1.1)	5 (1.5)
Diabetes	42 (6.0)	25 (6.7)	17 (5.2)
Previous cancer[c]	11 (1.6)	7 (1.9)	4 (1.2)
Co-medication [*n* = 709]	—	—	—
None	200 (28)	115 (30)	85 (26)
MTX[d]	427 (60)	227 (60)	200 (60)
Other	82 (12)	36 (10)	46 (14)
Baseline steroid use [*n* = 709]	168 (24)	95 (25)	73 (22)
Patient global assessment of disease activity (0–100) [*n* = 667][a]			
Mean (S.D.)	70.6 (12)	72.1 (21)	68.8 (22)
Median (IQR)	75 (60–85)	75 (63–85)	75 (56–85)
DAS 28, mean (S.D.) [*n* = 657][a]	6.0 (1.2)	6.2 (1.1)	5.8 (1.3)
28 tender joint count [*n* = 664][a]	12 (7–19)	14 (8–19)	11 (6–18)
28 swollen joint count [*n* = 667][a]	8 (4–12)	8 (4–12)	7 (4–12)
ESR, mm/h [*n* = 634][a]	34 (18–58)	36 (21–58)	31 (16–56)
CRP, mg/l [*n* = 295][a]	23 (10–55)	23 (9–44)	26 (11–66)
HAQ, 0–3 [*n* = 655][a]	1.9 (1.4–2.3)	2.0 (1.6–2.4)	1.6 (1.1–2.1)

Results presented as *n* (%) unless otherwise indicated. [a]Over 5% missing data. [b]Includes hypertension, angina, myocardial infarction, stroke, epilepsy, asthma, chronic obstructive airway disease, peptic ulcer disease, liver disease, renal disease, tuberculosis, demyelinating disease, diabetes, cancer and depression as reported by the treating rheumatologist. [c]Reported by the cancer registry. [d]Alone or in combination with other DMARD. BSRBR: British Society for Rheumatology Biologics Register; IQR: interquartile range; PUVA: psoralen and ultraviolet A; TNFi: TNF inhibitor.

Other deaths were attributed to cancer ($n = 7$), respiratory disease ($n = 4$), joint disease [$n = 4$; with secondary causes listed as pneumonia ($n = 3$) and sepsis ($n = 1$)] and other ($n = 10$). Cause of death was missing in three patients. All-cause mortality was significantly higher in the PsA patients compared with the general population (SMR 1.56; 95% CI: 1.12, 2.11). Men had a 75% increased mortality rate (SMR 1.75; 95% CI: 1.11, 2.63), while the difference in women did not reach statistical significance. Standardized mortality rate from malignancy was not significantly different from the general population. Rates for death from circulatory disease (SMR 1.89; 95% CI: 1.01, 3.24), and particularly for coronary heart disease (SMR 2.42; 95% CI: 1.11, 4.59), were significantly higher, although only reaching statistical significance for men in the gender-specific analysis (SMR 2.80; 95% CI: 1.13, 5.78).

Discussion

In this population of patients with severe PsA, defined by high disease activity levels at initiation of biologic therapy, the incidence of malignancy overall was similar to that of the general population. However, the incidence of NMSC was significantly increased overall and in women. All-cause mortality was increased as well as mortality from circulatory disease, particularly coronary heart

Table 2 Standardized ratios of incidence of malignancy and mortality in 709 patients with PsA starting a TNFi

	Overall ($n = 709$)		Male ($n = 331$)		Female ($n = 378$)	
Total follow-up (person-years)	**5956.5**		**2745.8**		**3210.7**	
Malignancy						
	O/E	SIR (95% CI)	0/E	SIR (95% CI)	0/E	SIR (95% CI)
All malignancies	34/36.2	0.94 (0.65, 1.34)	16/15.1	1.06 (0.61, 1.72)	18/21.1	0.85 (0.51, 1.35)
NMSC	15/7.1	2.12 (1.19, 3.50)	6/3.3	1.79 (0.66, 3.90)	9/3.7	2.41 (1.10, 4.58)
Mortality						
	O/E	SMR (95% CI)	0/E	SMR (95% CI)	0/E	SMR (95% CI)
All-cause	41/26.4	1.56 (1.12, 2.11)	23/13.1	1.75 (1.11, 2.63)	18/13.2	1.36 (0.81, 2.15)
Cancer	7/11.0	0.64 (0.26, 1.31)	2/4.9	0.41 (0.05, 1.49)	5/6.12	0.82 (0.27, 1.91)
Circulatory disease (all)	13/6.9	1.89 (1.01, 3.24)	9/4.0	2.24 (1.03, 4.27)	4/2.86	1.40 (0.38, 3.58)
Coronary heart disease	9/3.72	2.42 (1.11, 4.59)	7/2.5	2.80 (1.13, 5.78)	2/1.2	1.63 (0.20, 5.90)

E: expected; NMSC: non-melanoma skin cancer; O: observed; SIR: standardized incidence ratio; SMR: standardized mortality ratio; TNFi: TNF inhibitor.

disease in men. Forty-two per cent of the excess deaths were attributed to circulatory disease.

This study complements the available literature on this topic as it includes patients with very high disease activity at baseline. Disease activity may influence risk of malignancy and mortality both directly and through patients having more aggressive treatment. It is likely that previous publications on malignancy and mortality in PsA from larger cohorts have included patients with less severe disease. The Health Improvement Network database is based in general practice with a large proportion of patients receiving no DMARD treatment [5–7] and the Danish DANBIO registry and other Swedish biologics registers have, as reported in other publications, markedly lower disease activity than in our cohort [12, 13].

The increased risk of NMSC is in keeping with previous studies on skin psoriasis [1], and has previously been observed in PsA patients treated with conventional DMARDs and corticosteroids [3]. Unfortunately we do not have any information on the severity of skin disease, which would be important in explaining why this is seen in our cohort. Whether a TNFi is prescribed by a rheumatologist or dermatologist in PsA patients with severe skin disease may vary between countries and hence influence the population included and results from registers such as the BSRBR. In the BSRBR the main indication for TNFi prescription is active joint disease. It is likely that some degree of detection bias of NMSC applies to TNFi-treated populations with PsA compared with the general population due to their increased contact with health care professionals. The degree of this bias may be influenced by geographical differences in approach to patient information, awareness and systematic screening for NMSC. Phototherapy and other (current or previous) immunemodulatory treatment may also influence risk of NMSC, but unfortunately the low number of cases did not allow for further analysis regarding this in our study.

Increased mortality rates in PsA patients compared with the general population have been reported previously [4]. However, more recent larger studies based in general practice [5, 6] found no increased mortality. An association between death from cardiovascular disease and prior disease activity in PsA has been reported by Juneblad *et al*. [14], so we may speculate that the increased mortality rates in this cohort are related to the severity of their disease. This is further supported by the increased mortality due to circulatory disease/coronary heart disease observed in our cohort.

This study included patients from start of TNFi between 2002 and 2006, early in the TNFi era, followed until the end of 2012, resulting in a long follow-up period to be analysed (mean (S.D.)): 8.4 (1.5) years). Due to linkage with the mandatory national cancer and death registries, completeness of these data is very high. The cancer registry has an estimated >99% coverage and cause of death is usually only missing if the death occurred outside of the UK [15, 16]. Rates for the general population are published yearly and are gender and age specific, allowing our analysis to take into account differences between men and women, age groups and general fluctuations over the years. Regional differences in risk between countries in the UK were, however, not captured as English and Welsh rates were applied to all patients. However, despite the large sample size and long follow-up, the outcomes under investigation are relatively rare and consequently there are corresponding low numbers of events. This is reflected in the low precision of our estimates and limited the number of specific causes of mortality and malignancy we could explore, particularly with regard to the gender-specific analyses. Consequently, we were unable to explore any relationship between specific patient characteristics and outcomes. A weakness of the study is that due to the lack of a biologic naïve PsA cohort for comparison we cannot conclude on the role of TNFi in the observed outcomes.

In conclusion we found reassuringly similar rates for malignancy in our population with severe PsA compared with the general population adding to data that TNFi are safe treatments in this regard in patients with PsA. However, we observed an increased risk of NMSC,

particularly in women. All-cause mortality in the cohort was increased, most notably mortality from coronary heart disease, supporting the need for increased awareness of management of cardiovascular risk factors in PsA patients.

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Clinical Vignette

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Necrotic erythema nodosum leprosum masquerading as cutaneous vasculitis

A young male in his 30s presented with fever, joint pains, multiple tender nodules and ulcerated skin lesions of 2 months duration. Multiple crusted ulcers with sharply defined borders and surrounding rim of erythema mimicking cutaneous vasculitis were present on the trunk and extremities (Fig. 1A and B). Cutaneous examination revealed madarosis with diffuse infiltration of the skin of face and ears (Fig. 1C). Ulnar, radial cutaneous and common peroneal nerves (right > left) were asymmetrically thickened with glove and stocking anaesthesia. Slit skin smear showed multiple acid-fast bacilli. Histopathological examination from the noduloulcerative lesions confirmed necrotic erythema nodosum leprosum (ENL) (Fig. 1D). A diagnosis of previously undiagnosed lepromatous leprosy presenting with necrotic ENL was rendered.

ENL, an immune complex-mediated type 2 leprosy reaction, is seen most commonly in the lepromatous spectrum of Hansen's disease. It classically presents as crops of tender, evanescent nodules usually involving the extremities, trunk and face, and associated with systemic symptoms like fever, malaise, joint pains and lymphadenopathy. Apart from the classical lesions, other less common but severe morphological variants of ENL include vesicobullous, pustular and necrotic types. Necrotic ENL can often mimic cutaneous vasculitis. Hence, dermatologists and clinicians should be aware of the different presentations of this disease for prompt diagnosis and treatment thereby avoiding debilitating consequences. A high degree of suspicion and close attention to the often subtle ancillary skin findings are imperative, especially in areas where leprosy is still widely prevalent.

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Fig. 1 Necrotic erythema nodosum leprosum in the patient. Multiple crusted ulcers with sharply defined borders and surrounding rim of erythema mimicking cutaneous vasculitis on the face, trunk and upper extremities (**A**–**C**). Histopathology shows ill-formed granulomas with neutrophilic infiltrate and presence of vascultis (**D**) with Ziehl Neelson staining confirms presence of numerous acid-fast bacilli (inset).