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

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
given including conventional DMARD treatments (espe-
cially 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 reassur-
ingly similar rates of malignancy in TNFi-treated PsA pa-
tients 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 treat-
ment 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 popula-
tions studied, further information on the risks of malig-
nancy 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 receiv-
ing TNFi with those of the general population.

Methods

All patients with a rheumatologist’s diagnosis of PsA start-
ing a TNFi and registered in the British Society for
Rheumatology Biologics Register (BSRBR), which re-
cruited PsA patients between 2002 and 2006, were
included. Full details of this study, including data collec-
tion, 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 occur-
ring in study patients. All patients were followed from
registration (start of TNFi) until death or 31 December
2012, whichever came first. Population rates are pub-
lished 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 avail-
able 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) × 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 circula-
tory disease (ICD 10 codes: I00–I99) and deaths from cor-
ony heart disease (ICD 10 codes: I20–I25).

The BSRBR has ethical approval from the North West
Multicentre Research Ethics Committee (reference num-
ber MREC 00/08/053) and patients gave written in-
formed 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 pa-
tient-years of follow-up. The majority of patients were re-
cruited 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 popu-
lation 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 haematolo-
gical 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 inci-
dence ratio 2.12; 95% CI: 1.19, 3.50). In the gender spe-
cific 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).
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 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 \[ \( n = 163 \) \] | 11 (6.8)    | 7 (8.1)  | 4 (5.3)  |
| Previous ciclosporin exposure \[ \( n = 709 \) \] | 318 (45)    | 165 (44) | 153 (46) |
| Current smoker \[ \( n = 557 \) \] | 118 (21)    | 69 (23)  | 49 (19)  |
| Ever smoker \[ \( n = 557 \) \] | 312 (53)    | 176 (54) | 136 (51) |
| Comorbidity \[ \( n = 709 \) \] | —           | —       | —     |
| 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 \[ \( n = 557 \) \] | 11 (1.6)    | 7 (1.9)  | 4 (1.2)  |
| Co-medications \[ \( n = 709 \) \] | —           | —       | —     |
| None                 | 200 (28)     | 115 (30) | 85 (26)  |
| MTX \[ \( n = 709 \) \] | 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) \[ \( n = 667 \) \] | —       | —       | —     |
| 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.) \[ \( n = 657 \) \] | 6.0 (1.2)   | 6.2 (1.1) | 5.8 (1.3) |
| 28 tender joint count \[ \( n = 664 \) \] | 12 (7–19)   | 14 (8–19) | 11 (6–18) |
| 28 swollen joint count \[ \( n = 667 \) \] | 8 (4–12)    | 8 (4–12)  | 7 (4–12)  |
| ESR, mm/h \[ \( n = 634 \) \] | 34 (18–58)  | 36 (21–58) | 31 (16–56) |
| CRP, mg/l \[ \( n = 295 \) \] | 23 (10–55)  | 23 (9–44) | 26 (11–66) |
| HAQ, 0–3 \[ \( n = 655 \) \] | 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.
Table 2: Standardized ratios of incidence of malignancy and mortality in 709 patients with PsA starting a TNFi

| Total follow-up (person-years) | Overall (n = 709) | Male (n = 331) | Female (n = 378) |
|-------------------------------|-------------------|----------------|------------------|
| Malignancy                    |                   |                |                  |
| All malignancies              | O/E               | SIR (95% CI)  | O/E              | SIR (95% CI)  | O/E              | SIR (95% CI)  |
| NMSC                          | 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) |
| Mortality                     |                   |                 | O/E              | SMR (95% CI)  | O/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        | 9/3.7             | 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] 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) immunomodulatory 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 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.

Acknowledgements

The authors acknowledge the enthusiastic collaboration of all consultant rheumatologists and their specialist nurses in the UK in providing the data (visit www.bsrbr.org for a full list of contributors). The authors would like to gratefully acknowledge the support of the National Institute for Health Research, through the Comprehensive Local Research Networks at participating centres. In addition, the authors acknowledge support from the BSR Executive, the members of the BSRBR Registers Committee and the BSRBR Project Team in London for their active role in enabling the register to undertake its tasks. The authors also acknowledge the seminal role of the BSR Clinical Affairs Committee for establishing national biological guidelines and recommendations for such a register. Finally the authors would like to acknowledge the Arthritis Research UK Centre for Epidemiology who provided the infrastructure support for the study. The BSR commissioned the BSR Biologics Register in RA (BSRBR-RA) as a UK-wide national project to investigate the safety of biologic agents in routine medical practice. K.H. is the principal investigator. BSR receives restricted income from UK pharmaceutical companies, including AbbVie, Celtrion, Hospira, MSD, Pfizer, SOBI, Samsung, UCB and Roche. This income finances a wholly separate contract between the BSR and the University of Manchester. The principal investigator and the BSRBR-RA team at the University of Manchester have full academic freedom and are able to work independently of pharmaceutical industry influence. All decisions concerning analyses, interpretation and publication are made autonomously of any industrial contribution. Members of the BSRBR-RA University of Manchester team, BSR trustees, committee members and staff complete an annual declaration in relation to conflicts of interest. All relevant information regarding serious adverse events outlined in the manuscript have been reported to the appropriate pharmaceutical company as per the contractual agreements/standard operating procedures. K.M.F. was supported through a grant from the South-Eastern Norway Regional Health Authority. Data, infrastructure and statistical analysis support was also provided by the Arthritis Research UK Centre for Excellence Grant (Grant No. 20380).

Funding: No specific funding was received from any bodies in the public, commercial or not-for-profit sectors to carry out the work described in this manuscript.

Disclosure statement: K.L.H. has received honoraria from AbbVie and Pfizer. All other authors have declared no conflicts of interest.

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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. Silt 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.

Funding: No specific funding was received from any bodies in the public, commercial or not-for-profit sectors to carry out the work described in this manuscript.

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

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