RHEUMATOLOGY

Rheumatology 2017;56:907–911
doi:10.1093/rheumatology/kew502
Advance Access publication 31 January 2017

Concise report

Cause-specific mortality in patients with psoriatic arthritis and rheumatoid arthritis

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Abstract

Objective. The objective of this study was to examine cause-specific mortality in patients with PsA compared with the general population and compared with patients with RA.

Methods. A cohort study was performed using The Health Improvement Network among patients aged 18–89 years with data from 1994 to 2010. PsA and RA were defined by medical codes, and up to 10 unexposed controls were matched on practice and start date within the practice. Cause of death was classified using categories from UK death statistics. Each death was manually reviewed to ensure appropriate classification. Age- and sex-adjusted hazard ratios (HRs) and multivariable adjusted HRs were calculated using competing risks survival regression.

Results. Among patients with PsA (8706), RA (41 752) and unexposed controls (81 573), 470, 7004 and 5269 deaths were observed, respectively. The most common causes of death among all patients were cardiovascular disease, followed by malignancy, respiratory deaths and infection. Cause of death was unknown in ~25%. Among PsA patients, cardiovascular (1.09, 0.91–1.32), respiratory (0.97, 0.79–1.20), malignancy (1.03, 0.86–1.25) and infection deaths (1.05, 0.79–1.39) were not elevated. Among patients with RA, cardiovascular (1.55, 1.44–1.66), respiratory (1.85, 1.72–2.01), malignancy (1.18, 1.08–1.28) and infection deaths (2.21, 2.00–2.44) were significantly elevated compared with population controls. Although less common, suicide deaths were elevated in PsA and RA (HR 3.03 and 2.47, respectively).

Conclusion. Overall mortality and cause-specific mortality risk were not elevated among patients with PsA except for suicide deaths. Patients with RA were at increased risk of deaths from cardiovascular, respiratory, cancer and infectious diseases.

Key words: mortality, psoriatic arthritis, rheumatoid arthritis, epidemiology, suicide

CLINICAL SCIENCE

Rheumatology key messages

- We performed a population-based study of cause-specific mortality in PsA and RA.
- Unlike patients with RA, patients with PsA were not at increased risk for cause-specific mortality.
- Suicide deaths were more common in patients with RA and PsA than controls.

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Submitted 11 August 2016; revised version accepted 20 December 2016

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Introduction

PsA is a chronic inflammatory arthritis associated with psoriasis. PsA can have a substantial impact on patients' quality of life and functional ability. In addition to joint disease, PsA is also associated with a number of metabolic co-morbidities, including cardiovascular disease, diabetes and obesity as well as psychological co-morbidities, including depression and anxiety [1]. Early clinic-based studies suggested an increased risk of mortality, although this risk improved over time [2]. However, recent studies suggest no increased risk of mortality among patients with PsA [3, 4]. On the contrary, studies in RA have found an increased risk for all-cause mortality and cause-specific mortality, including cardiovascular, respiratory, infection and cancer deaths [5]. Additionally, a population-based study in psoriasis (although not specifically PsA) found that patients with severe psoriasis have increased cardiovascular, respiratory, infectious and cancer deaths as well [6].

Although there is not a clear link to increased mortality in PsA, there may be elevated risk of cause-specific mortality, in particular cardiovascular mortality, among patients with PsA compared with the general population. There is a paucity of data on cause-specific mortality in PsA [7]. Furthermore, no studies have examined cause-specific mortality in the general population compared with internal controls as opposed to using clinic- or hospital-based cohorts and comparing with population statistics. Identification of increased cause-specific mortality in PsA could aid in targeting interventions to reduce death from specific causes. The objective of this study was to examine cause-specific mortality in patients with PsA compared with the general population and compared with patients with RA.

Methods

Study design and data source

A longitudinal cohort study was performed within The Health Improvement Network (THIN) in the UK. Participating general practitioners from 514 general practices record data as a part of routine patient care in the electronic medical record; the data are then collected by THIN and anonymized for use in research. Data from 1994 to September 2010 were included.

Study population

All patients with PsA or RA between the ages of 18 and 89 years at the start date were included. PsA was defined by a single diagnosis code (positive predictive value 85%) [8]. Diagnosis codes for RA have also been previously validated [9]. Patients were excluded if they died or transferred out of the practice before the implementation of software in that practice. We did not restrict the population to 'incident' diagnoses. For each patient with PsA, up to 10 unexposed controls from the general population were randomly selected and were matched on practice and start date within the practice. More detail on patient selection, cohort time and covariate definitions are available in previous publications using this same cohort [3, 10].

Person-time calculation

Cohort entry was defined as the latest of diagnosis, 6 months after initial registration with the practice, implementation of software in the practice or a practice acceptable mortality reporting. Censoring occurred when the patient died, left the practice, the practice stopped participating in THIN or the study ended in September 2010.

Outcome definition

The primary outcome was cause of death. Death was defined by specific codes noting death and/or codes indicating that the patient was transferred out of the practice because of death [3, 11]. Cause of death was assigned based on an algorithm recommended by Cegedim, the administrators of THIN. We first examined all codes and text comments associated with an administrative or medical code for cause of death and all text comments indicating that a medical code represented the cause of death. For patients without an assigned cause of death after this first step, we then examined medical codes assigned to the patient on the day of their death. Next, we examined the medical codes and text comments within the following time periods sequentially: 180 days after the death date (as some codes may be entered later) and then 10, 30 and finally 60 days before the death date. We continued to look through each period until a patient was assigned a cause of death. If there were not medical codes within the 60 days before or 180 days after the death date, the patient was assigned to the unknown category. We then assigned a cause-of-death category based on the UK causes of death to facilitate comparison with UK death statistics. Two coders (A.O. and S.M.) assigned cause of death. Any discrepancies were resolved through discussion or involvement of a third coder (Y.J.) when necessary. After the first round of coding, the κ statistic for inter-rater agreement between A.O. and S.M. was 0.94.

Statistical analysis

Descriptive statistics were used to examine age, sex, baseline covariates, person-time, covariate distribution and causes of death among the four groups. Competing-risk survival regression models were used to determine the hazard ratio (HR) for each group compared with the unexposed group accounting for the opportunity to die from another cause. Potential confounders, including age, sex, smoking, prior hospitalization in the baseline period, year of cohort entry, socio-economic status (via Townsend deprivation score) and urban *vs* rural living environment, were tested in the models using a purposeful selection approach, and only covariates that were significant in the model were maintained in the final model. As a sensitivity analysis, we instead used Cox proportional hazards models to determine whether there was a difference based on the models used. All statistical analyses were performed using STATA 13.0 (College Station, TX, USA).

Table 1 Baseline characteristics

	Controls (n = 82 590)	PsA (n = 8809)	RA (n = 43 320)
Demographics			
Age, mean (S.D.), years	50.14 (18.37)	50.54 (14.45)	61.53 (15.26)
Male, n (%)	37 340 (45.2)	4502 (51.1)	12 843 (29.7)
Disease duration,[a] mean (S.D.), years	N/A	4.77 (7.46)	7.01 (10.10)
Cohort time, mean (S.D.)	5.23 (3.91)	5.58 (3.96)	5.56 (3.93)
Socio-economic status,[b] mean (S.D.)	2.56 (1.38)	2.52 (1.38)	2.67 (1.39)
Start year in the cohort, median	2004	2004	2002
Visits in baseline period, mean (S.D.)	37.1 (41.0)	44.4 (49.1)	50.3 (54.7)
Co-morbidities			
Diabetes, n (%)	4558 (5.5)	585 (6.6)	3325 (7.7)
Hyperlipidaemia, n (%)	6281 (7.6)	747 (8.5)	4173 (9.6)
Hypertension, n (%)	15 630 (18.9)	1880 (21.3)	12 172 (28.1)
Myocardial infarction, n (%)	2033 (2.5)	199 (2.3)	1921 (4.4)
Stroke, n (%)	1339 (1.6)	109 (1.2)	1220 (2.8)
Chronic kidney disease, n (%)	1531 (1.9)	147 (1.7)	1364 (3.2)
Peripheral vascular disease, n (%)	932 (1.1)	88 (1.0)	717 (1.7)
Atrial fibrillation, n (%)	1771 (2.1)	130 (1.5)	1582 (3.7)
Charlson Index, mean (S.D.)	0.27 (0.8)	0.24 (0.7)	0.41 (0.9)
BMI			
Normal, n (%)	21 595 (26.2)	2294 (26.4)	13 773 (31.8)
Overweight, n (%)	16 945 (20.5)	2431 (27.6)	11 666 (26.9)
Obese, n (%)	9835 (11.9)	1958 (22.2)	7467 (17.2)
Underweight, n (%)	1722 (2.08)	113 (1.28)	1198 (2.77)
Missing, n (%)	32 493 (39.3)	2013 (22.9)	9216 (21.3)
Smoking status			
Non-smoker, n (%)	38 328 (46.4)	4013 (45.6)	18 877 (43.6)
Past smoker, n (%)	15 204 (18.4)	1953 (22.2)	9460 (21.8)
Current smoker, n (%)	18 097 (21.9)	951 (21.5)	9558 (22.1)
Missing, n (%)	10 961 (13.3)	951 (10.8)	5425 (12.5)
Medications			
DMARDs[c]	0	4532 (51)	23 840 (55)
Prescription NSAID	38 775 (47.0)	6649 (75.5)	32 231 (74.4)
Oral CSs	7601 (9.2)	1415 (16.1)	14 089 (32.5)

[a]Disease duration was calculated as time from the diagnosis date to start date. [b]Socio-economic status was measured using the Townsend deprivation score (range 0–5). [c]DMARDs included MTX, SSZ, AZA, LEF, ciclosporin, mycophenolate, HCQ and biologic disease-modifying agents, including adalimumab, etanercept and infliximab.

Ethics board approval

All data in this study was anonymous to the investigators. This study was approved by the University of Pennsylvania Institutional Review Board and Cegedim's Scientific Review Committee in the UK.

Results

Among patients with PsA (8706), RA (41 752) and unexposed controls (81 573), 470, 7004 and 5269 deaths were observed, respectively. Baseline characteristics of patients in the study population are presented in Table 1. Approximately half of patients with PsA and RA had been prescribed a DMARD in the baseline period. Average follow-up time was similar among the groups (5.02–5.55 years). The average ages at cohort entry and death were older in patients with RA (particularly among patients not on a DMARD), and the average number of causes of death was 1.21 (supplementary Table S1, available at *Rheumatology* Online).

The most common cause of death in all groups was cardiovascular disease (supplementary Table S1, available at *Rheumatology* Online). Cancer, respiratory and infection were also common causes of death. Approximately one-quarter of deaths in the cohort did not have a discernable cause of death. The UK death statistics from 2011 for cause-specific mortality are included in supplementary Table S1, available at *Rheumatology* Online, for reference. The UK statistics do not include unknown cause of death as a category, thus the percentage of deaths is higher for the other groups. However, infectious deaths were more common in our cohort.

Among patients with PsA, there were no significant increases in the age- and sex-adjusted HR for any of the major causes of death compared with unexposed controls (Table 2): cardiovascular (HR = 1.09, 95% CI: 0.91, 1.32), respiratory (HR = 0.97, 95% CI: 0.79, 1.20),

Table 2 Hazard ratios for cause-specific mortality

	Age and sex adjusted		Multivariable adjusted	
	PsA HR (95%CI)	RA HR (95% CI)	PsA HR (95% CI)	RA HR (95% CI)
Cardiovascular	1.09 (0.91, 1.32)	1.55 (1.44, 1.66)	1.04 (0.85, 1.29)	1.42 (1.3, 1.54)
Respiratory	0.97 (0.79, 1.20)	1.85 (1.72, 2.01)	0.95 (0.76, 1.18)	1.45 (1.33, 1.59)
Malignancy	1.03 (0.86, 1.25)	1.18 (1.08, 1.28)	1.04 (0.85, 1.27)	1.07 (0.98, 1.18)
Infection	1.05 (0.79, 1.39)	2.21 (2.00, 2.44)	0.97 (0.72, 1.32)	1.81 (1.62, 2.03)

Note that none of the covariates in the multivariable models changed the point estimates by $\geqslant 10\%$. However, in order to illustrate the relative lack of change accounting for these risk factors for death changed the outcome, we have included the multivariable models. Covariates differed slightly by model but included smoking status, stroke, atrial fibrillation, hypertension, diabetes, hyperlipidaemia, cancer, congestive heart failure, peripheral vascular disease, myocardial infarction, Charlson co-morbidity score, Townsend deprivation score, urban *vs* rural setting and oral glucocorticoid use in the baseline period. HR: hazard ratio.

cancer deaths (HR = 1.03, 95% CI: 0.86, 1.25) and infection (HR = 1.05, 95% CI: 0.79, 1.39). However, patients with RA had increased risk for death from cardiovascular diseases (HR = 1.55, 95% CI: 1.44, 1.66), respiratory diseases (HR = 1.85, 95% CI: 1.72, 2.01) and infectious diseases (HR = 2.21, 95% CI: 2.00, 2.44). Patients with RA also had increased risk of death related to cancer (HR = 1.18, 95% CI: 1.08, 1.28). Adding additional co-morbidities (e.g. Charlson co-morbidity score, obesity/BMI and individual co-morbidities) or risk factors (e.g. smoking) did not significantly change the point estimates for all causes examined. Additionally, restricting the population to only those >60 years of age did not substantially change the results (supplementary Table S2, available at *Rheumatology* Online). Finally, we examined some of the more common individual causes of death (supplementary Table S3, available at *Rheumatology* Online), although these individual outcomes were relatively rare. Among these more rare causes of death, death from suicide was significantly elevated among patients with both PsA (HR = 3.03, 95% CI: 1.56, 5.90) and RA (HR = 2.47, 95% CI: 1.51, 4.04).

Discussion

In this population-based study, we found that patients with PsA were not at increased risk of specific causes of death, including cardiovascular, respiratory, infection and cancer deaths. This is consistent with our recent papers reporting that patients with PsA do not have a higher risk of mortality or cardiovascular mortality despite an increased risk of cardiovascular events [3, 10]. On the other hand, previous studies examining mortality in specialty clinics have reported an increased risk of mortality, including cardiovascular mortality. The difference in results may be related to the heterogeneity of PsA. Patients with PsA in the general population may have a range of disease activity from very mild to very severe, whereas patients seen in specialty clinics are more likely to have a more severe or active form of the disease. Finally, one important finding was an increase in the HR of deaths attributable to suicide compared with the general population. This is relevant considering recent reports of suicidal ideation in clinical trials for PsA and, to our knowledge, is the first population-based estimate of the risk for suicide in PsA and RA.

In this study, we found substantially increased risk of cardiovascular, respiratory and infectious deaths and a small increased risk of cancer death in RA. The associations between RA and cardiovascular, infection, cancer and respiratory deaths have been previously reported, but the link to respiratory deaths was surprisingly elevated. Similar to England *et al*. [12] and Sparks *et al*. [13], we also found that ~15% of deaths were related to respiratory diseases. Likewise, these respiratory deaths were most commonly attributed to chronic obstructive lung disease, asthma and interstitial lung disease (data not shown). Although our HR estimates are attenuated from those reported by these two studies, our findings support the increased risk for respiratory death noted among men enrolled in the Veterans Affairs RA registry and women enrolled in the Nurses Health Study.

To our knowledge, this is the largest study with the greatest number of person-years (an average of >5 years per person) to date to examine cause of death in PsA and RA. Additional strengths of this study include validated exposure definitions (PsA and RA), the population-based approach and inclusion of an internal unexposed group. Furthermore, causes of death among controls were similar to UK national statistics after accounting for patients unable to be classified [15]. Limitations of the study include lack of death certificate information and the inferential nature of assigning cause of death. In addition, there may be a lack of statistical power, which may be particularly relevant for patients with PsA. Finally, we do not have information on disease activity. It is possible that patients with more severe disease have increased all-cause and cause-specific mortality, and this may have stronger associations with cardiovascular death as well as other specific causes [14].

In conclusion, this large population-based study confirms increased cause-specific mortality in patients with RA but did not find significantly elevated cause-specific mortality in PsA with the exception of suicide which, although a small number of cases overall, was substantially elevated compared with the general population for both RA and PsA. Despite a lack of other cause-specific mortality in PsA, it is equally important to assess and appropriately manage co-morbidities in patients with PsA because they can have significant impact on quality of life and, potentially, longevity [1].

Acknowledgements

We thank Sean Hennessy, PharmD PhD and Jina Chung for helpful discussions. Contribution statement: A.O. and J.M.G. conceptualized and designed the study. S.M., Y.J. and A.O. reviewed the individual causes of death/performed data analysis. T.L., H.C. and the other authors were integral in interpretation of the results. A.O. performed the programming, statistical analysis, preparation of the data and the first draft of the manuscript. D.S. assisted in programming. All authors were involved in critical review of the data as well as drafting and revision of the manuscript, and all have approved the final version of the paper to be published. Dr A.O. was supported by NIH T32 GM075766-05 and the Rheumatology Research Foundation during the study and is currently supported by K23 AR063764. Dr J.M.G. was supported by K24ARO64310. Dr T.L. was supported by The Icelandic Research Fund, #120433021. Data from The Health Improvement Network is supported by the Clinical and Translational Science Award at the University of Pennsylvania (8UL1TR000003 from the National Center for Research Resources).

Funding: This project was funded by the Rheumatology Research Foundation Investigator Award.

Disclosure statement: A.O. has served as a consultant to Novartis and is a co-investigator on a grant from Pfizer. J.M.G. served as a consultant for Abbvie, Celgene, Coherus, Janssen Biologics (formerly Centocor), Eli Lilly, Merck, Novartis Corp., Valeant and Pfizer Inc., received honoraria and research grants (to the Trustees of the University of Pennsylvania) from Abbvie, Eli Lilly, Janssen, Novartis Corp., Regeneron, Sanofi and Pfizer Inc., received payment for continuing medical education work related to psoriasis that was supported indirectly by Lilly and Abbvie and is a co-patent holder of resiquimod for treatment of cutaneous T cell lymphoma. All other authors have declared no conflicts of interest.

Supplementary data

Supplementary data are available at *Rheumatology* Online.

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