The Incidence and Predictors of Infection in Psoriasis and Psoriatic Arthritis: Results from Longitudinal Observational Cohorts

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ABSTRACT. ***Objective.*** To investigate the rate, type, characteristics, and predictors of infection in a cohort of patients with psoriatic arthritis (PsA) and a cohort of patients with psoriasis without arthritis (PsC).

Methods. A cohort of patients with PsA and a cohort of patients with PsC were followed according to a standard protocol and information on the occurrence of infections was recorded. The rate of infection was estimated by fitting an exponential model. A Weibull regression model was fitted to estimate the relative risk of first infection associated with a number of covariates. Risk factors for recurrent infections were investigated using generalized estimating equations.

Results. There were 498 and 74 infections reported among 695 and 509 patients with PsA and PsC, respectively, with an incidence rate of 19.6 per 100 person-years in the PsA cohort compared with 12.2 in the PsC cohort. The HR of the time to the first infection in PsA versus PsC was 1.6 (p = 0.002), and higher in patients treated with biologics versus nonbiologics at 1.56 (95% CI 1.22–2.00) in PsA and 1.50 (95% CI 0.64–3.54) in the PsC cohorts. Female sex and treatment with biologics were associated with infection in the PsA cohort, whereas a lower Psoriasis Area and Severity Index score and a higher Functional Comorbidity Index were associated with infection in the PsC cohort. Ultraviolet treatment was protective against infection in both cohorts. No difference in rates of hospitalization was found (p = 0.66). There were no infection-related deaths in either cohort.

Conclusion. The incidence rate of infection was higher in the PsA than the PsC cohort and higher among patients treated with biologics. The data confirm the association between infection and biologic treatment in psoriatic disease. (First Release January 15 2016; J Rheumatol 2016;43:362–6; doi:10.3899/jrheum.140067)

Key Indexing Terms:
PSORIATIC ARTHRITIS PSORIASIS INFECTION

Psoriasis and psoriatic arthritis (PsA) affect women and men equally with a prevalence of 3% and 0.25%, respectively[1,2]. Patients with psoriasis and PsA may be at high risk for infection because of the loss of the integrity of skin barrier, intrinsic cellular immunity alterations, or as a result of immunosuppressive therapy with disease-modifying agents or biologics.

Methotrexate (MTX) is one of the commonly used drugs in clinical practice for the treatment of psoriasis and PsA. It interferes with purine/pyrimidine synthesis, inhibiting T cell activation and granulocyte function[3]. Several studies have demonstrated an increased risk of infection in patients receiving MTX. However, these were conducted on patients with rheumatoid arthritis (RA)[4,5,6]. Other patients are treated with leflunomide, which may potentially interfere with the T cell immune-mediated physiologic response, and it was

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confirmed by Wolfe, *et al* as an independent risk factor for hospitalization for pneumonia in RA (HR 1.2, 95% CI 1.0–1.5)[7].

Since the introduction of tumor necrosis factor-α inhibitors (TNFi), data collected from a metaanalysis of randomized clinical trials suggested that TNFi use is associated with an increased risk of serious infections[8]. However, these studies were conducted primarily on patients with RA, and to date, data have been extrapolated to patients with other rheumatic diseases that are obviously not identical in the innate or adaptive immune system responses. Therefore, it is important to determine the incidence of infection in patients with psoriasis and PsA with and without anti-TNF therapy.

Our goal was to investigate the incidence rate and type of infection in patients with psoriasis and PsA, to describe the types of infections, and to identify factors associated with infection in these patients.

MATERIALS AND METHODS

Patient selection. Patients with PsA from the University of Toronto prospective observational PsA cohort were included in our study if they had a clinical evaluation since January 1, 2006. The vast majority (97%) fulfilled the CASPAR (ClASsification for Psoriatic ARthritis) criteria[9]. Patients in this cohort were assessed at clinic entry and every 6–12 months according to a standard protocol that included a detailed history, physical examination, and laboratory evaluation. Since 2004, the protocol included questions regarding the presence of infection, type of infection, and treatment of infection.

Patients with psoriasis without arthritis (PsC) were recruited from the University of Toronto Psoriasis Cohort that was initiated in 2006[10]. Patients were diagnosed with psoriasis by a dermatologist and were assessed by a rheumatologist to exclude the presence of inflammatory arthritis. The same protocol was used as for the PsA clinic cohort. Patients were scheduled to be assessed at clinic entry and at yearly intervals thereafter.

Infections. At each clinic visit, patients were asked about the occurrence of any infection since their last visit. Only infections reported after the first visit in 2006 were included. Data were thus collected prospectively and tracked on a computerized database between 2006 and 2011, and included the type of infection (bacterial/viral/other), the site of infection (sinus, lung, genitourinary tract, meninges, skin, gastrointestinal tract, upper respiratory tract infection, other), whether the patients were treated with antibiotics (oral/parenteral/both), or if they were hospitalized because of infection. The primary goal was to estimate the incidence of all infections in patients with PsC and PsA. Serious infections were defined as infections that required hospitalization or intravenous antibiotics.

Prognostic variables for infection. Demographic and disease characteristics from each protocol visit were used to study factors associated with the infection in PsA and PsC. These included sex and age, family history of psoriasis and/or arthritis, the development of skin lesions before joint manifestations, the presence of nail lesions, functional class, smoking, alcohol use, the number of actively inflamed (tender or swollen) and damaged joints, the modified Steinbrocker score[11], the Psoriasis Area Severity Index (PASI) score, the Functional Comorbidity Index (FCI)[12], and treatment with nonsteroidal antiinflammatory drugs (NSAID), disease-modifying antirheumatic drugs (DMARD), biologics, and phototherapy.

Statistical analysis. Descriptive analyses were used to characterize the demographic and disease features of the patients in both the PsC and PsA cohorts at their first visit since 2006. Infections were summarized in terms of frequency, type of infection, the site, and the type of treatment.

Without accounting for the use of biologics, the incidence rates of infection in the 2 cohorts were estimated by an exponential model with interval censoring. A Weibull model was applied to formally estimate the HR of infection attributable to a trend in the hazard. Accounting for the use of biologics by including it as a time-dependent covariate, a Weibull regression model was used in the analysis of time to first infection to estimate the HR of infection for taking versus not taking biologics in the 2 cohorts. Further, a generalized estimating equation (GEE) Poisson model was used to estimate the relative rate of infection for biologics versus nonbiologics based on infections occurring over the entire followup period.

To examine the effect of biologic use while controlling for other covariates, a multivariate analysis using GEE was carried out to account for the within-subject correlation in the repeated measurements of infection status over the followup period. Since the outcome was the occurrence of an infection (yes/no), a binary outcome was used with the following covariates: duration of disease, sex, PASI, FCI, actively inflamed joint count, and treatment with NSAID, DMARD, biologics, and phototherapy. In addition, a Weibull model adjusting for these covariates at the baseline visit was used to model the time to the first infection.

RESULTS

Demographics and clinical characteristics. Between January 1, 2006, and May 11, 2011, 695 patients with PsA and 509 patients with PsC were followed in the respective cohorts. Table 1 presents the demographics and disease characteristics of these patients at the first visit since 2006. The mean age of patients in the PsA group was 49.5 ± 13.3 years compared with 46.5 ± 13.1 years in the PsC group, with a mean PsA duration of 12.5 ± 11.1 years.

Among the patients with PsA, there were more whites (86% vs 77%) and they were younger at diagnosis of psoriasis (28.1 vs 30.3 yrs). They had a higher body mass index (BMI; 29.3 vs 27.9 kg/m^2), more nail disease (62% vs 49%), worse Health Assessment Questionnaire, poorer Medical Outcomes Study Short Form-36 physical and mental component summaries, and they received more treatment with NSAID and DMARD compared with patients with PsC. However, BMI at baseline was not statistically different in patients with infection compared with the entire cohort.

Patients with PsC consumed more alcohol (71% vs 59%), more were smokers (25% vs 13%), and more were treated with phototherapy (78% vs 16%) than patients with PsA.

Both cohorts shared similar comorbidities at their baseline visit and there were no differences between the 2 cohorts with respect to the duration of psoriasis, the PASI score, treatment with biologics, and the presence of diabetes, congestive heart failure, chronic obstructive pulmonary disease, liver disease, or cancer.

A total of 498 infections were observed among 264 patients with PsA, and 74 infections were observed among 62 patients with PsC (Figure 1). The mean followup time between 2006 and 2011 was 2.64 years in the PsA cohort and 1.20 years in the PsC cohort.

Infection rate. Without accounting for use of biologics, the crude incidence rate of infection based on the exponential model was 0.196 for the PsA cohort compared with 0.122 in the PsC cohort. The estimated HR of infection for PsA versus

Table 1. Characteristics of all patients with PsA and PsC at first visit since 2006. Values are mean (SD) unless otherwise specified.

Variables	PsA, n = 695	PsC, n = 509
Sex, n (%)		
Female	294 (42)	219 (43)
Male	401 (58)	290 (57)
Race, n (%)		
White	601 (86)	391 (77)
Other	94 (14)	118 (23)
Age at study, yrs	49.5 (13.3)	46.5 (13.1)
Age at diagnosis of psoriasis, yrs	28.1 (14.4)	30.3 (16.2)
Age at diagnosis of PsA, yrs	37 (13.1)	—
Duration of psoriasis, yrs	21.5 (13.6)	16.2 (14)
Duration of PsA, yrs	12.5 (11.1)	—
Alcohol, n (%)		
Daily	52 (8)	56 (11)
None	287 (42)	148 (29)
Social	351 (51)	305 (60)
Smoking status, n (%)		
Current	91 (13)	126 (25)
No	370 (53)	232 (46)
Past	233 (34)	151 (30)
Presence of nail lesions, n (%)	430 (62)	248 (49)
PASI score	4.9 (7.4)	5.6 (5.8)
Active SJC or TJC	6.7 (9.2)	—
SJC	1.2 (2.5)	—
TJC	4.2 (7)	—
Damaged joint count	7 (12.1)	—
Body mass index, kg/m^2	29.3 (6.5)	27.9 (5.7)
Diabetes, n (%)	69 (10)	35 (7)
Congestive heart failure, n (%)	5 (1)	0 (0)
Chronic obstructive lung disease, n (%)	2 (0.003)	0 (0)
Liver disease, n (%)	19 (3)	6 (1)
Cancer, n (%)	27 (4)	23 (5)
Use of NSAID, n (%)	419 (60)	18 (4)
Use of DMARD, n (%)	391 (56)	50 (10)
Use of biologics, n (%)	160 (23)	22 (4)
Ultraviolet light therapy, n (%)	112 (16)	398 (78)
Presence of axial disease, n (%)	385 (55)	—
Steinbrocker score	8.1 (18.6)	—

PsA: psoriatic arthritis; PsC: psoriasis without arthritis; PASI: Psoriasis Area and Severity Index; SJC: swollen joint count; TJC: tender joint count; NSAID: nonsteroidal antiinflammatory drugs; DMARD: disease-modifying antirheumatic drugs.

PsC cohort was 1.56 (95% CI 1.18–2.06, p = 0.002) based on the Weibull regression. Including the use of biologics as a time-dependent covariate in the analysis of time to first infection with the Weibull regression, the HR of infection for biologics versus nonbiologics was 1.56 (95% CI 1.22–2.0) in the PsA cohort, and 1.50 (95% CI 0.64–3.54) in the PsC cohort. In the GEE model including use of biologics, the relative rate of infection per person-year for biologics versus nonbiologics use was estimated to be 0.88 (95% CI 0.70–1.11) in the PsA cohort and 1.13 (95% CI 0.62–2.04) in the PsC cohort. Compared with the results from the GEE models, a sensitivity analysis with nonparametric estimation for the crude relative rates did not change the findings in both cohorts.

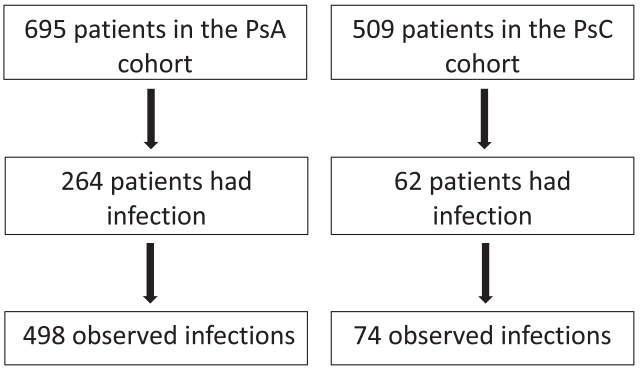

Figure 1. Patient disposition. PsA: psoriatic arthritis; PsC: psoriasis without arthritis.

Characteristics of infections. Among patients with PsC with infection, 52 (83.9%) had only 1 infection and only 3.2% had more than 2 infections, whereas among the 264 patients with PsA with infection, 123 (46.6%) had more than 1 infection and 73 (27.7%) had 3 or more infections during the course of followup.

Among patients with PsA, the most common infections were lung, sinus, skin, and genitourinary, whereas among patients with PsC, skin, genitourinary, and lung were most prevalent. Of the patients in the PsC cohort, 76% had a bacterial etiology for infection compared with 63% of the patients in the PsA cohort. No statistically significant difference was found in the type of infection between the 2 cohorts. Most patients with psoriatic disease (either psoriasis or PsA) required antibiotic treatment. No infection-related deaths occurred in either cohort and there was no statistically significant difference in serious infections in both cohorts (Table 2).

Predictors of infection. Using GEE to account for repeated infections, we conducted a multivariate analysis. In the PsA cohort, female sex and treatment with biologics were predictive of infection, whereas in the PsC cohort, a lower PASI score and a higher FCI were predictors for infection. Ultraviolet light therapy was protective against infection in both cohorts (Table 3).

Based on the Weibull regression model used to fit interval censored infection time, we found that a female sex, a higher FCI, and treatment with biologics were independently associated with a shorter time to infection in the PsA group whereas only a higher FCI score was independently associated with a shorter time to infection in the PsC group (Table 4).

DISCUSSION

Our study compared the incidence rate, characteristics, and predictors for infection in PsC and PsA. The infection rate was higher in the PsA compared with the PsC cohort. The data confirmed the association between infection and

Table 2. Characteristics of infections observed in both cohorts. Values are n (%) unless otherwise specified.

Characteristics	PsA	PsC	p
Total no. infections	498	74	
Infection type			0.057
Bacterial	312 (63)	56 (76)	
Viral	167 (34)	15 (20)	
Other	19 (4)	3 (4)	
Infection site			0.001
Gastrointestinal	11 (2)	4 (6)	
Genitourinary	66 (14)	11 (15)	
Lung	105 (23)	9 (12)	
Sinus	58 (13)	5 (7)	
Skin	72 (16)	14 (19)	
Unknown	21 (5)	4 (6)	
Upper respiratory	47 (10)	0 (0)	
Other	83 (18)	25 (35)	
Treatment of infection with antibiotics	313 (63)	57 (77)	0.019
Type of antibiotics			0.22
Intravenous	24 (8)	1 (2)	
Oral	280 (89)	55 (96)	
Both	9 (3)	1 (2)	
Infection requiring hospitalization	10 (2)	2 (3)	0.66

PsA: psoriatic arthritis; PsC: psoriasis without arthritis.

biologic treatment in PsA. The predictors that were associated with infection in PsA were female sex, biologic treatment, and the FCI, whereas other disease activity indices such as the active joint count, the PASI score, as well as the treatment with DMARD were not associated with infection.

A population-based cohort study by Wakkee, *et al* found that the risk of severe infection requiring hospitalization was significantly higher in patients with psoriasis compared with controls from a randomly selected cohort[13]. In another population-based cohort study in the United Kingdom, patients with severe psoriasis also had an increased risk for mortality from infection compared with the patients without psoriasis (HR 1.65, 95% CI 1.26–2.18)[14]. However, in our study, no infection-related deaths occurred in either cohort. Only a minority of infections required hospitalizations with no difference between the 2 cohorts.

The limitations of our study are that it relied on patient recall and self-report of infections. This limitation is more profound in the PsC cohort because patients were followed on a yearly basis whereas in the PsA cohort, patients were followed every 3–6 months. Moreover, the average patient-year followup was only 1.2 years in the PsC cohort compared with 2.64 years in the PsA cohort. However, patients were asked the same questions at followup visits and were sensitized to record whether they had had an infection in the interim between visits. Another possible limitation is a potential selection bias because the patients were followed in a tertiary referral center and could be potentially different from the total population of patients with PsA. Our cohorts include both severe and mild cases, and thus may be representative of both PsA and PsC. It should also be noted that our study was not designed to differentiate between disease severity or biologic use and the rate of infection.

Despite these limitations, our data showed a similar incidence rate of infection in our cohort compared with the reported rates in RA, which were estimated at 17–19 infections per 100 patient-years[15,16], and the incidence rate is higher than the reported rate in patients without inflammatory arthritis. Still, we find the infection rate high considering that patients in our cohort are not usually treated with steroids, which is a risk factor for infection in patients with rheumatic disease.

Our analyses reveal an association between infection and biologic treatment in PsA, and the data can be extrapolated and used in clinical practice and trials as an estimate for infection risk in PsA and psoriasis. However, not all biologics may predispose patients with psoriatic disease to infection at the same rate. A recent report from the Psoriasis Longitudinal

Table 3. Multivariate analysis of predictors of infection in the PsC and PsA cohorts. OR > 1 indicate higher risk. OR < 1 indicate reduced risk.

Variable	PsA		PsC	
	OR (95% CI)	p	OR (95% CI)	p
Disease duration, yrs	1.00 (0.99–1.01)	0.875	1.01 (0.99–1.03)	0.454
Male vs female	0.47 (0.36–0.61)	< 0.0001	1.03 (0.58–1.82)	0.928
PASI, 1-unit increase	1.00 (0.98–1.02)	0.978	0.92 (0.86–0.98)	0.009
Active joint count, 1-unit increase	1.00 (0.99–1.02)	0.900	NA	NA
Biologics, yes vs no	1.70 (1.33–2.18)	< 0.0001	2.14 (0.88–5.20)	0.09
DMARD, yes vs no	1.15 (0.91–1.47)	0.244	1.28 (0.57–2.86)	0.58
NSAID, yes vs no	1.06 (0.82–1.37)	0.654	1.20 (0.44–3.28)	0.72
Ultraviolet therapy	0.37 (0.18–0.74)	0.005	0.44 (0.23–0.84)	0.01
FCI	1.08 (0.98–1.18)	0.114	1.27 (1.02–1.59)	0.04

PsC: psoriasis without arthritis; PsA: psoriatic arthritis; PASI: Psoriasis Area and Severity Index; DMARD: disease-modifying antirheumatic drugs; NSAID: nonsteroidal antiinflammatory drugs; FCI: Functional Comorbidity Index; NA: not applicable.

Table 4. Predictors of time to first infection since 2006 for the PsC and PsA cohorts. An HR < 1 means that the risk of infection is lower than when the covariate is at the reference level.

Variable	PsA		PsC	
	HR	p	HR	p
Disease duration, yrs	0.99	0.32	0.99	0.51
Active joint count, 1-unit increase	1.01	0.13	NA	NA
Male vs female	0.63	0.0004	0.91	0.71
PASI, 1-unit increase	0.99	0.20	0.99	0.75
FCI	1.18	0.002	1.37	0.02
Biologics, yes vs no	1.61	0.001	1.32	0.73
NSAID, yes vs no	1.19	0.20	1.37	0.67
DMARD, yes vs no	1.05	0.73	0.66	0.44
Ultraviolet therapy	1.25	0.29	0.73	0.33

PsC: psoriasis without arthritis; PsA: psoriatic arthritis; PASI: Psoriasis Area and Severity Index; FCI: Functional Comorbidity Index; NSAID: nonsteroidal antiinflammatory drugs; DMARD: disease-modifying antirheumatic drugs; NA: not applicable.

Assessment and Registry demonstrated a higher risk of infection in patients treated with adalimumab (ADA) and infliximab, and no increase in infection among patients treated with etanercept (ETN) and ustekinumab[17]. The majority of our patients were treated with ETN and ADA.

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