CONCISE REPORT

Risk of uveitis and inflammatory bowel disease in people with psoriatic arthritis: a population based cohort study

Rachel Charlton,[1] Amelia Green,[1,2] Gavin Shaddick,[3] Julia Snowball,[1] Alison Nightingale,[1] William Tillett,[1,4] Catherine Smith,[5] and Neil McHugh[1,4] on behalf of the PROMPT study group

[1] Department of Pharmacy and Pharmacology, University of Bath, Bath, UK
[2] Department of Mathematical Sciences, University of Bath, Bath, UK
[3] Department of Mathematics, University of Exeter, Exeter, UK
[4] Royal National Hospital for Rheumatic Diseases, Upper Borough Walls, Bath, UK
[5] St John's Institute of Dermatology, Guy's and St Thomas' NHS Foundation Trust, London, UK

Corresponding author

Dr Rachel Charlton
Department of Pharmacy and Pharmacology
University of Bath
Claverton Down,
Bath
BA2 7AY, UK
r.a.charlton@bath.ac.uk
Tel: +44 (0)1225 383672
Fax: +44 (0)1225 386114

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ABSTRACT (197 words)

Objectives To determine the risk of uveitis and inflammatory bowel disease (IBD) in psoriatic arthritis (PsA) patients compared to the general population and patients with psoriasis.

Methods A cohort study using data from the UK Clinical Practice Research Datalink between 1998 and 2014. Incident PsA patients aged 18-89 years were identified and matched to a cohort of patients with psoriasis and a general population cohort. The incidence of uveitis, all IBD, Crohn's disease and ulcerative colitis was calculated for each study cohort and adjusted relative risks (RR_{adj}) were calculated using conditional Poisson regression.

Results 6,783 incident cases of PsA were identified with a median age of 49 years. The risk of uveitis was significantly higher in the PsA cohort than in the general population and psoriasis cohorts (RR_{adj} 3.55, CI_{95}2.21-5.70 and RR_{adj} 2.13, CI_{95}1.40-3.24 respectively). A significant increase was observed for Crohn's disease (RR_{adj} 2.96 CI_{95}1.46-6.00 and RR_{adj} 3.60 CI_{95}1.83-7.10) but not for ulcerative colitis (RR_{adj} 1.30 CI_{95}0.66-2.56 and RR_{adj} 0.98 CI_{95}0.50-1.92).

Conclusions

In a primary care-based incidence cohort of patients with psoriatic arthritis there were substantial risks of developing uveitis and/or Crohn's disease, but not ulcerative colitis, when compared to the general population and psoriasis controls.

INTRODUCTION

Psoriatic arthritis (PsA) is a chronic inflammatory arthritis which has been reported to affect between 10 and 40% of individuals with psoriasis.[1] In the majority of patients, PsA presents after, or synchronously with, the onset of psoriasis. PsA is well recognised to be progressive and may result in severe disability, reduced quality of life and work disability.[2, 3] Patients with PsA can often suffer from multiple comorbidities, resulting in increased morbidity and mortality.

Uveitis and inflammatory bowel disease (IBD) are known to be associated with spondyloarthritis,[4] however there is limited information on the prevalence and incidence of these conditions in patients with PsA and current estimates and study designs vary. Recent Danish and Taiwanese nationwide cohort studies, using administrative data, have reported an increased risk of uveitis associated with psoriatic disease.[5, 6] The Danish study demonstrated a bidirectional association, with psoriasis and PsA patients having an increased risk of uveitis and patients with uveitis having an increased risk of psoriasis and PsA, suggesting a shared pathogenic pathway.[5] Another study, using the same Danish data source, has reported an increased risk of Crohn's disease and ulcerative colitis amongst patients with psoriasis and PsA,[7] as have two studies using data from US Health Claims databases,[8, 9] and one looking at PsA using data from an Israeli healthcare database.[10] A further study analysing data on 174,476 women participating in a US Nurses' Health Study, however, reported an increased risk of Crohn's disease in patients with psoriasis and/or PsA but not an increased risk of ulcerative colitis.[11]

This study aimed to determine the risks of uveitis and IBD in patients with PsA in the United Kingdom (UK) and compare these with the risks in a matched cohort of psoriasis patients without PsA and a general population cohort.

METHODS

A cohort study was conducted using data from the Clinical Practice Research Datalink (CPRD), which is generally representative of the UK population[12] and contains anonymised primary care medical records for ~15 million individuals.

The study period was from 1-Jan-1998 until 31-Dec-2014. A cohort of incident PsA patients were identified in the CPRD who were 18-89 years at diagnosis and had ≥1 year of up-to-standard (UTS) data contribution prior to the diagnosis date. Cases of PsA were matched at a 1:4 ratio to two randomly selected cohorts based on date of PsA diagnosis (their index date), year of birth, sex and general practice: the first matched cohort (general population cohort) included patients with no psoriasis, no PsA and no other inflammatory arthritis diagnoses, and the second cohort (psoriasis cohort) included patients with psoriasis but no diagnosis of PsA or other inflammatory arthritis. Patients in the comparator cohorts were assigned the index date of the matched case and were required to have ≥1 year of UTS data prior to their index date. All patients were followed from the index date until the date they were no longer eligible for the cohort or were diagnosed with the outcome of interest. Patients in the general population and psoriasis cohorts who developed psoriasis or PsA respectively after the index date had their person-time contribution censored the day before the diagnosis date.

The outcomes of interest were uveitis and inflammatory bowel disease (IBD). Diagnoses were identified based on Read codes and IBD was categorised as 'Crohn's disease', 'ulcerative colitis' and 'other/unspecified'. A full description of the methods can be found in the Online Supplement.

Statistical analyses

The incidence of uveitis, all IBD, Crohn's disease and ulcerative colitis was calculated for each of the study cohorts. For each outcome, crude and adjusted relative risks (RR) were calculated using conditional Poisson regression to compare the risk in the PsA cohort with the psoriasis and general population cohorts. The adjusted models accounted for smoking

status, body mass index and psoriasis severity on the index date. Analyses were performed using R 3.3.0 (R Core Team, 2017).

RESULTS

We identified 6,783 eligible incident cases of PsA that were matched to 27,132 psoriasis patients and 27,132 patients from the general population. The median age at PsA diagnosis was 49 years (IQR 39-59). The baseline patient characteristics for each cohort are shown in Table 1. The mean duration of follow-up post index date was similar in all three cohorts at approximately 5.5 years. The baseline prevalence of uveitis was 2.07 times higher in the PsA cohort than the general population (CI_{95}1.63-2.64).

The median age at incident uveitis and ulcerative colitis was lower in the PsA cohort than psoriasis and general population cohorts (Table 2). The incidence and risk of uveitis was significantly higher in the PsA cohort than in the general population and psoriasis cohorts (RR_{adj} 3.55, CI_{95}2.21-5.70 and RR_{adj} 2.13, CI_{95}1.40-3.24) (Table 3). The incidence of all IBD was higher among patients with PsA and when looking at Crohn's disease and ulcerative colitis separately, a significant increase was observed for Crohn's (RR_{adj} 2.96 CI_{95}1.46-6.00 and RR_{adj} 3.60 CI_{95}1.83-7.10 for general population and psoriasis cohorts respectively) but not for ulcerative colitis (RR_{adj} 1.30 CI_{95}0.66-2.56 and RR_{adj} 0.98 CI_{95}0.50-1.92). Of interest, current smokers had a higher incidence of Crohn's disease than ex- or non-smokers but the numbers were too small to be meaningful (data not shown).

DISCUSSION

This UK population-based study identified over a three-fold and two-fold increase in the risk of uveitis in patients with PsA when compared to the general population and patients with psoriasis respectively. A significant increase in risk was also observed for Crohn's disease among patients with PsA but this was not found for ulcerative colitis.

The increase in risk of uveitis associated with PsA, observed in our study, is in line with Danish and Taiwanese nationwide cohort studies.[5, 6] The incidence rates of uveitis in our study, however, were approximately 50% higher than in the Danish cohorts and lower than the Taiwanese cohorts which may be related to differences in methods of data collection. Genetic factors may also play a role, given the close association between HLA-B27 and acute anterior uveitis,[13] although the background prevalence of HLA-B27 is lower in Taiwan than in the UK.[14] Nonetheless, a three-fold increase in risk of uveitis compared to the general population is clinically meaningful in terms of prospectively managing and informing patients of potential relevant co-morbidities. Furthermore, the risk appears more associated with PsA than with psoriasis, with the latter showing a similar baseline prevalence and incidence of uveitis to the general population. The baseline prevalence in the PsA cohort in our study is in line with an Irish study which included patients with ≤1 year PsA disease duration and reported a prevalence of uveitis of 1.55%[15] but is considerably lower than the 9.09% reported in an Italian study which also included newly diagnosed patients with <1 year disease duration.[16]

The increased risk observed between PsA and Crohn's disease, but not ulcerative colitis, is in line with a study by Li *et al.*, using data from the Nurses' Health study in the United States.[11] The majority of other studies to date, however, have identified an increased risk for both Crohn's and ulcerative colitis, although many do report a higher magnitude of risk for Crohn's than ulcerative colitis.[7, 9]

There are genes in risk loci common to psoriasis, PsA and Crohn's disease such as *IL12B, 5q31, IL23R and IL2/IL21* that may explain our findings.[17] Dysbiosis leading to an upregulated Th17 driven immune response in a genetically susceptible host is another potential common pathogenic pathway.[18] Indeed a recent study reported a specific

dysbiosis in patients with spondylitis and a history of IBD.[19] Lifestyle factors such as smoking may also have an important role, especially considering that smoking is a known risk factor for Crohn's whilst smoking is associated with a lower risk of developing ulcerative colitis.[20] It is likely that an interaction of all these factors is important and worthy of study in larger datasets.

Strengths of our study include its population-based nature, the large number of PsA patients, previous validation of the codes used to identify psoriasis and PsA, inclusion of both a psoriasis and general-population matched comparator group and the length of follow-up after PsA diagnosis. The inclusion of only incident PsA patients was an advantage for looking at the temporal relationship, however one challenge when studying PsA, particularly when looking at comorbidities and risk factors, is disentangling pre-clinical PsA from psoriasis and/or delayed diagnosis.[21] It is therefore possible that some patients within the psoriasis only group may have actually had PsA and this could potentially have elevated the incidence rates in this group. In addition, as PsA is likely to develop some time before a patient visits their GP, it is also possible that some patients identified as having prevalent disease, prior to their PsA diagnosis, may have developed the comorbidity of interest after the initial onset of PsA, but before a formal diagnosis was made, which would result in an underestimate of the incidence rates. Although unlikely for uveitis, assessment/detection bias could also have played a role for mild IBD cases, with PsA patients being likely to visit their healthcare professionals more regularly than those in the comparator groups. Unfortunately, the absence of data on tumour necrosis factor-alpha inhibitor (TNFi) therapy in the CPRD meant it was not possible to explore the effect of PsA therapy on the incidence of uveitis and IBD.

The results of our study demonstrate an increased risk of developing uveitis and Crohn's disease in patients with PsA that in addition to pointing to shared genetic and pathogenic mechanisms has important implications for surveillance and management. More precise information on the estimated risk of these particular comorbidities can be shared with patients, alongside advice on lifestyle factors such as smoking, the latter of which in addition to its association with Crohn's disease[20] has also been shown to have a negative effect on long-term PsA outcome.[22]

Table 1 Baseline characteristics of the PsA, psoriasis and general population cohorts

		PsA		Psoriasis cohort		General population cohort	
		N	%	N	%	N	%
N		6,783		27,132		27,132	
Sex (% male)		3,327	49.05	13,308	49.05	13,308	49.05
Median age*, years (IQR)		49	(39-59)	49	(39-59)	49	(39-59)
Mean follow-up post index, years (SD)		5.8	(4.1)	5.5	(4.1)	5.5	(4.1)
Mean duration of psoriasis,* years (SD)		11.3	(10.9)	11.8	(10.6)	---	---
Uveitis prevalence†, ¥		100	1.47	205	0.76	193	0.71
Inflammatory bowel disease prevalence†		51	0.75	323	1.19	249	0.92
	Crohn's disease†	16	0.24	122	0.45	95	0.35
	Ulcerative colitis†	24	0.35	150	0.55	127	0.47

* on index date

† ≥1 diagnosis recorded in the CPRD on or before the index date

¥ Of all the uveitis records identified, 71.5% were anterior, 1.5% were posterior, 0.3% were panuveitis and for 26.7% the anatomic subtype was unknown. There was one case of posterior uveitis in the PsA cohort and 6 cases in both the psoriasis and general population cohorts.

Table 2 Incidence of uveitis and IBD in the PsA, psoriasis and general population cohorts

	Cases	Median age at diagnosis (IQR)	Person years	Incidence rate per 10,000 person years (CI_{95})
Uveitis				
General population	46[†]	55.0 (41.0-62.0)	146,738	3.13 (2.30-4.18)
Psoriasis	74[‡]	55.0 (48.0-65.0)	145,482	5.09 (3.99-6.39)
PsA	42[¥]	47.0 (40.0-58.0)	38,678	10.86 (7.83-14.68)
Inflammatory bowel disease (All)				
General population	67	55.0 (43.5-67.5)	146,345	4.58 (3.55-5.81)
Psoriasis	67	53.0 (44.0-68.0)	144,793	4.63 (3.59-5.88)
PsA	30	51.5 (42.0-60.0)	39,077	7.68 (5.18-10.96)
Crohn's disease				
General population	25	50.0 (43.0-68.0)	146,345	1.71 (1.11-2.52)
Psoriasis	22	50.5 (44.0-62.0)	144,793	1.52 (0.95-2.30)
PsA	16	49.5 (33.0-56.5)	39,077	4.09 (2.34-6.65)
Ulcerative colitis				
General population	35	57.0 (44.0-66.0)	146,345	2.39 (1.67-3.33)
Psoriasis	38	60.5 (46.0-71.0)	144,793	2.62 (1.86-3.60)
PsA	11	54.0 (46.0-61.0)	39,077	2.81 (1.41-5.04)

[†] 31 anterior, 15 subtype unknown [‡] 50 anterior, 1 panuveitis, 23 subtype unknown [¥] 29 anterior, 1 panuveitis, 12 subtype unknown

Table 3 Risk of uveitis and inflammatory bowel disease in patients with PsA compared with patients in the general population and patients with psoriasis

Comorbidity	PsA compared with a general population cohort (no PsA and no psoriasis)						PsA compared with a psoriasis cohort (psoriasis and no PsA)					
	Unadjusted			Adjusted†			Unadjusted			Adjusted‡		
	RR	CI_{95}	*P*	RR	CI_{95}	*P*	RR	CI_{95}	*P*	RR	CI_{95}	*P*
Uveitis	3.83	2.45-5.99	<0.0001	3.55	2.21-5.70	<0.0001	2.17	1.46-3.22	<0.0001	2.13	1.40-3.24	<0.001
All inflammatory bowel disease	1.95	1.28-2.98	<0.0001	1.90	1.21-3.00	0.0056	1.71	1.13-2.61	<0.01	1.71	1.12-2.61	<0.05
- Crohn's disease	3.08	1.64-5.80	<0.0001	2.96	1.46-6.00	0.0025	3.55	1.83-6.88	<0.0001	3.60	1.83-7.10	<0.001
- Ulcerative colitis	1.30	0.68-2.46	0.43	1.30	0.66-2.56	0.44	1.08	0.58-2.02	0.80	0.98	0.50-1.92	0.96

† adjusted for smoking status and body mass index (in the 3 months prior to the index date) ‡ adjusted for smoking status and body mass index (in the 3 months prior to the index date) and psoriasis disease severity on the index date

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