Acute anterior uveitis in spondyloarthritis: a monocentric study of 301 patients

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Abstract

Objective

To assess the cumulative incidence of uveitis in spondyloarthritis (SpA) and its associated factors and to evaluate the effect of DMARD treatment on uveitis in a real-life setting.

Methods

A cross-sectional monocentric observational study (COSPA) was conducted. Patients with definite SpA underwent a face-to-face interview. General data and specific data concerning uveitis were collected. Cumulative incidence of uveitis flares was estimated by Kaplan-Meier survival curves. Factors associated with uveitis were determined by Cox analysis. Treatment effectiveness was evaluated by comparing the number of uveitis flares before/after treatment using Wilcoxon test.

Results

In total, 301 patients were included, 186 (61.8%) were men, with mean age and disease duration of 44.8 (±13.6) and 16.8 (±11.9) years, respectively. Among them, 82 (27.2%) had at least one uveitis flare. Prevalence of uveitis at the time of SpA diagnosis was 11.5 % (±1.9%) and increased over time to reach 39.3% (±4.1%) 20 years after diagnosis. HLA B27 positivity and heel pain were independently associated with uveitis (HR [IC 95%] = 4.5 [1.3-15.2] and 1.8 [1.1-2.9], respectively). A significant reduction in the number of uveitis before/after treatment was observed in patients treated with anti TNF monoclonal antibodies (n=27), (1.83 (±4.03) vs. 0.41 (±1.22), p=0.002), whereas it was not with etanercept (n=19), (0.44 (±0.70) and 0.79 (±1.36), p=NS).

Conclusion

Prevalence of uveitis in SpA seems to increase with disease duration and seems more likely to appear with HLA B27 positivity and heel pain. Anti-TNF monoclonal antibodies seemed to be more effective in the reduction of uveitis flares.

Key words

spondyloarthritis, uveitis

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Introduction

Acute anterior uveitis (AAU) is the most frequent extra-articular manifestation of spondyloarthritis (SpA), and one of the SpA features included in the classification criteria currently available for SpA (1).

AAU has been described as a prominent feature of SpA, and has even been reported to be the first clinical manifestation (2). Indeed, delay before diagnosis remains a huge challenge in spondyloarthritis and some have reported that approximately 40% of patients with AAU might have undiagnosed SpA (3). Moreover, the presence of AAU in SpA patients seems to be associated with higher disease activity, advanced physical impairment (4, 5) and has a potentially economic impact in terms of health care costs (6).

Furthermore, AAU in SpA may influence treatments decisions: all anti-TNF agents have been proven effective in refractory uveitis in clinical trials (7, 8) but etanercept has been reported to be less effective in preventing uveitis flares compared to other anti-TNF agents (9, 10). Nevertheless, only sparse data on real life are available.

The main objective of this study was a) to describe the prevalence and incidence of uveitis in a SpA population; b) to estimate uveitis incidence over time in this population, and the factors associated with such event; and c) to describe the management/treatment strategies for uveitis flares in real life and the effectiveness of such treatments.

Methods

Study design

A cross sectional observational study, COchin SPondylArthritis (COSPA), was conducted between November 2009 and February 2016, in one tertiary-care university hospital (11, 12). The study was made in accordance with ethical standards in France; oral informed consent was obtained from each patient.

Patients

Patients were selected from the department clinical medical record database through the keywords "spondylarthrite", "spondylarthropathie" or "rhumatisme psoriasique". All patients living in Paris or in the suburb of Paris and seen in our department in the last 4 years were selected, if they fulfilled Amor's criteria for SpA (13). In all, 1237 patients were selected; a random sample of 616 was contacted.

General data collection

General data collected were: age, age at diagnosis, sex, disease duration, subtype (AS, reactive arthritis, chronic inflammatory bowel disease with arthropathy, psoriatic arthritis, undifferentiated spondyloarthritis or juvenile spondyloarthritis), predominant manifestations, HLA B27 status, family history of SpA, BASDAI (Bath Ankylosing Spondylitis Disease Activity Index), BASFI (Bath Ankylosing Spondylitis Functional Index), presence of an abnormal C-reactive protein in the absence of other causes, radiographic sacroiliitis according to New York modified criteria (14) and treatments.

Uveitis: data collection and interpretation

Data were collected in a face-to-face interview completed with medical records. All patients visited an ophthalmologist who confirmed the diagnosis of uveitis.

Manifestations of uveitis: localisation (unilateral, alternative, and bilateral), duration of the longest uveitis event, sequelae of uveitis (lowered visual acuity, cataract) recurrence of uveitis (if yes: total number of flares since disease onset). Investigations during uveitis flares: visit to the ophthalmologist, ophthalmologic diagnosis (anterior uveitis or anterior and posterior uveitis).

Treatments, date of administration and reason for prescription (*i.e.* articular symptoms *vs.* ophtalmological symptoms) were collected: corticosteroid treatment (systemic: oral; local: drops, injection), non-steroidal anti-inflammatory drusg (NSAIDs), sulfasalazine, anti-TNF treatment.

Statistical analysis

Uveitis prevalence was defined as the number of patients with at least one uveitis over the total number of patients. An estimated cumulative incidence of uveitis over 20 years after SpA

diagnosis, was estimated by Kaplan-Meier survival curves.

Factors associated with uveitis flares were estimated by Cox univariable then by Cox multivariable analysis (only factors with a $p<0.10$ in the univariable analysis were included in the multivariable analysis).

The number of uveitis flares before/during treatment were compared (for the global population and for each treatment) by defining a "treatment period" (= time on treatment) and "control period" (= time before treatment, with identical duration as the treatment period), by Wilcoxon test for paired data. Analyses were performed using SAS v. 9.4.

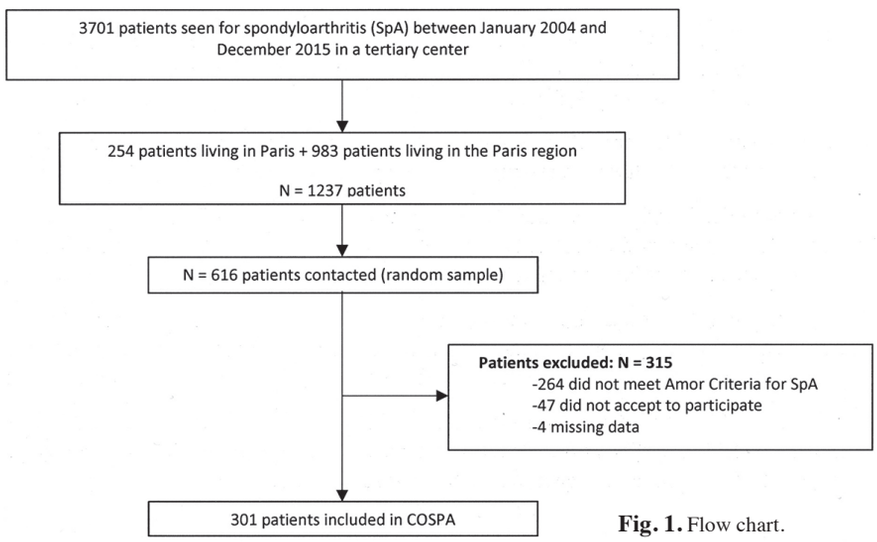

Fig. 1. Flow chart.

Results

Patients' characteristics

In all, 301 patients were included in COSPA (Fig. 1 and Table I). Mean age was 44.8 (±13.6) years, with a mean disease duration of 16.8 (±11.9) years; 186 (61.8%) were men, 215/276 (77.9%) were HLA B27 positive, 205/280 (73.2%) had radiographic sacroiliitis. In all, 179 (59.5%) patients received at least one anti-TNF agent.

Table I. Patients' characteristics: main characteristics of all the patients, patients with and without uveitis.

	Total n=301	Patients with uveitis** n=82	Patients without uveitis n=219
Age, years*	44.8 (13.6)	48.5 (12.5)	43.4 (13.8)
Age at diagnosis	33.0 (13.1)	31.4 (13.1)	33.7 (13.0)
Duration of disease, years	16.8 (11.9)	23.4 (12.1)	14.3 (10.8)
Sex (males)	186 (61.8%)	58 (70.7%)	128 (58.5%)
HLA B27 + (n=276)	215 (77.9%)	75 (96.2%)	140 (70.7%)
Family history of SpA (n=295)	127 (43.1%)	41 (51.9%)	86 (39.8%)
Radiological sacroiliitis (n=280)	205 (73.2%)	69 (89.6%)	136 (67.0%)
BASDAI (n=281)***	31.9 (22.6)	32.3 (23.9)	31.7 (22.1)
BASFI (n=282)***	27.6 (25.6)	29.9 (26.8)	26.8 (25.1)
Psoriasis****	96 (31.9%)	18 (21.9%)	78 (35.6%)
Heel pain****	137 (45.5%)	46 (56.1%)	91 (41.5%)
Anterior chest pain****	110 (36.5%)	38 (46.3%)	72 (32.8%)
Coxitis****	52 (17.3%)	16 (19.5%)	36 (16.4%)
Peripheral arthritis****	134 (44.5%)	35 (42.7%)	99 (45.2%)
IBD****	50 (16.6%)	17 (20.7%)	33 (15.1%)
Diagnosis of Axial SpA	211 (70.1%)	67 (81.7%)	144 (65.8%)
Diagnosis of PsA	54 (17.9%)	5 (6.1%)	49 (22.4%)

*Numerical variables are presented as mean (standard deviation) and categorical variables are presented as number (% of available data). **A patient was considered as "uveitis positive" in case of at least one episode of uveitis in her/his history confirmed by an ophthalmologist. ***Data collected during the study visit. ****Past history or current symptoms.

SpA: Spondyloarthritis; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; BASFI: Bath Ankylosing Spondylitis Functional Index; IBD: Inflammatory Bowel disease; PsA: Psoriatic Arthritis; ReA: Reactive arthritis.

Prevalence of uveitis

Among the 301 patients, 82 (27.2%) patients presented at least one uveitis flare, with a mean number of uveitis flares of 6.5±5.2 per patient.

The estimated prevalence of uveitis at the time of SpA diagnosis was 11.5 % (±1.9%). This prevalence increased over time and was 19.6% (±2.5%) and 39.3 % (±4.1%), respectively 5 and 20 years after diagnosis of SpA (Fig. 2). Sixty-two patients (75.6%) presented at least one recurrence episode.

Clinical characteristics of uveitis

All patients visited an ophthalmologist during the acute phase of the uveitis who confirmed the diagnosis of non-granulomatous uveitis. Uveitis was unilateral, bilateral and simultaneously-bilateral in 59.7%, 28.1% and 12.2 % of cases, respectively. Mean duration of flares was 21.3 (±24.3) days.The localisation of uveitis was available for 40 (48.7%) patients. Among them, 85% had anterior uveitis and 15% had anterior and posterior uveitis.

Regarding *sequelae*, 19 (23.2%) and 8 (9.8%) patients reported a lowered visual acuity (self-reported) and a cataract, respectively.

Factors associated with uveitis

Patients with uveitis had longer disease duration (23.4±12.1 *vs*. 14.3±10.8 years, $p<0.0001$), and were more likely to be HLA B27 positive (96.2% *vs*. 70.7%, $p<0.0001$), to present radiological sacroiliitis (89.6% *vs*. 67%, $p<0.0001$) and heel pain (56.1% *vs*. 41.5%, $p=0.02$) (Table I) compared to the other patients. No differences were found in disease activity nor function. Only HLA B27 positivity and heel pain were independently associated with the occurrence of uveitis over time in the multivariable analysis, Hazard Ratio (HR) [Confidence Interval (CI) 95%] = 4.5 [1.3–15.2] and HR [CI 95%] = 1.8 [1.1–2.9], respectively (Table II).

Treatments

Among the 82 patients with uveitis,

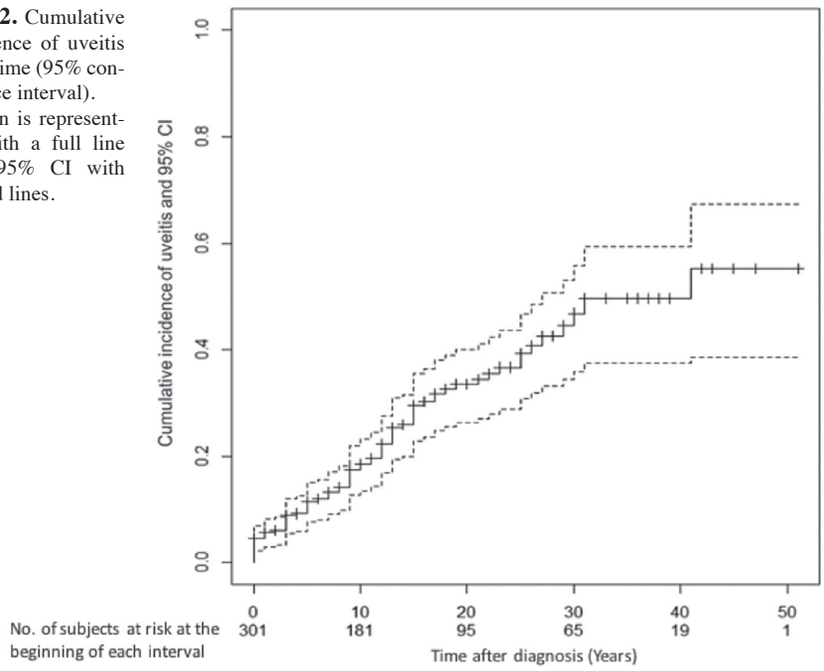

Fig. 2. Cumulative incidence of uveitis over time (95% confidence interval). *Mean is represented with a full line and 95% CI with dotted lines.

Table II. Factors associated with the cumulative incidence of uveitis in 301 SpA patients.

	Univariable HR [95% CI]	*p*-value	Multivariable HR [95% CI]*
Age, years	1.0 [0.9 –1.0]	>0.10	-
Age at diagnosis	1.0 [0.9 – 1.0]	>0.10	-
Duration of disease, years	1.0 [1.0 – 1.0]	0.02	1.0 [0.99-1.0]
Sex (males)	1.3 [0.8 - 2.1]	>0.10	-
HLA B27 + (n=276)	6.4 [2.0 – 20.3]	<0.01	**4.5 [1.4-15.2]**
Family history of SpA (n=295)	1.4 [0.9 – 2.2]	>0.10	-
Radiological sacroiliitis (n=280)	2.6 [1.3 – 5.5]	<0.01	1.5 [0.7-3.4]
BASDAI (n=281)	1.0 [0.9 – 1.0]	>0.10	-
BASFI (n=282)	1.0 [0.9 – 1.0]	>0.10	-
Psoriasis	0.5 [0.3 – 0.9]	<0.01	0.7 [0.4-1.2]
Heel pain	1.6 [1.0 – 2.4]	0.04	**1.8 [1.1-2.9]**
Anterior wall chest pain	1.5 [0.9 – 2.3]	0.06	1.1 [0.7-1.7]
Coxitis	0.9 [0.5 – 1.5]	>0.10	-
Peripheral arthritis	0.8 [0.5 – 1.3]	>0.10	-
IBD	1.5 [0.9 – 2.6]	>0.10	-
Diagnosis of Axial SpA	1.7 [0.9 – 3.0]	0.05	0.7 [0.4-1.3]
Diagnosis of PsA	0.3 [0.1 – 0.7]	<0.01	0.8 [0.3-2.1]

*Factors associated with uveitis flares were assessed by Cox univariable then by Cox multivariable analysis (only factors with a $p<0.10$ in the univariable analysis were included in the multivariable analysis).

78 (95.1%) received local corticosteroid treatment: by eye-drops (78.5%) or by local injection (48.1%). Only 14 (17.1%) patients received an oral corticosteroid; NSAIDs were prescribed as a specific uveitis treatment in 19 patients (23.7%).

Twenty-two (27.2%) patients were treated with sulfasalazine, but only two with a specific ophthalmologic indication.

Fifty-three patients (64.6%) received an anti-TNF treatment: etanercept (41.3%), infliximab (36.9%), and adalimumab (21.7%). Among them, only one patient received an anti-TNF treatment for a specific ophthalmologic indication. None of the patients received golimumab or certolizumab.

Evolution with systemic treatment

The mean number of uveitis flares before/after sulfasalazine treatment was not significantly different (0.84±1.86 *vs*. 2.21±5.75, $p=0.43$) (Table III). Conversely, after anti-TNF treatment (n=46 patients treated with anti-TNF agents and with available data), the mean number of uveitis was twice as low (1.28±3.2 and 0.56±1.28, respectively), even if this difference did not reach statistical significance ($p=0.058$). Among patients treated with etanercept (n=19), the mean number of uveitis flares before/after treatment was not significantly different (0.44±0.70 *vs*. 0.79±1.36, $p=0.734$); conversely, the reduction in the mean number of flares before/after treatment was significantly decreased when patients were treated with a monoclonal antibody (*e.g*. infliximab or adalimumab) (1.83±4.03 *vs*. 0.41±1.22, $p=0.002$).

Discussion

This study confirms that uveitis is a frequent extra-rheumatological feature of SpA present in almost one third of patients. Also, its prevalence increases over time, with a prevalence increasing up to almost 40% after 20 years of disease. These results were comparable to other studies (15-17). Indeed, the prevalence of uveitis in SpA was estimated to 32.7% (0.5%) in a systematic literature review based on 1989 patients (15), and 32.2% in the EXRA survey (16).

In another systematic review and meta-analysis, the pooled prevalence of AAU in SpA patients was estimated at 25.8% and associated with disease duration (17).

The main characteristic of uveitis in SpA was the possibility of recurrence, with 75.6% of patients having had more than one flare.

Patients with uveitis, had longer disease duration, presented more frequently with axial, involvement, x-rays sacroiliitis and heel pain, and were more frequently HLAB27$^+$; conversely, they were less likely to have psoriasis or PsA. Only HLA B27 positivity and heel pain were retained as independently associated with uveitis in the multivariable analysis.

The link between HLA B27 and uveitis has already been widely reported and confirmed in many studies (16-19). Regarding heel pain, similar results were found in other studies (18, 20, 21). In the RESPONDIA American cohort, enthesitis were associated with the presence of AAU ($p=0.004$) (18), but this

Table III. Number of uveitis flares in patients with uveitis according to the treatment.

Patients with uveitis n=82	Patients during control period*		Patients during treatment		*p*-value
	Treatment periods (months) Mean (±SD)	Number of uveitis flares Mean (±SD)	Treatment period (months) Mean (±SD)	Number of uveitis flares Mean (±SD)	
Sulfasalazine (n=19)	33.3 (±28.4)	0.84 (±1.86)	33.3 (±28.4)	2.21 (±5.75)	0.437
1st TNFb (n=46)	54.1 (±35.6)	1.28 (±3.20)	54.1 (±35.6)	0.56 (±1.28)	0.058
1st TNFb=Infliximab or Adalimumab (n=27)		1.83 (±4.03)		0.41 (±1.22)	0.002
1st TNFb=: Etanercept (n=19)		0.44 (±0.70)		0.79 (±1.36)	0.734

*The control period is the period before treatment with identical duration as the treatment period.

relation did not persist with multivariable regression. Regarding psoriasis and PsA, this is consistent with the findings of previous studies: in the RESPONDIA group, Sampaio-Barros *et al*. found a negative association between anterior uveitis and psoriasis in logistic regression (18), in the DESIR cohort, there was no relation between the presence of psoriasis or diagnosis of PsA and the presence of uveitis (21). Patients with uveitis were more frequently presenting with radiographic sacroiliitis, even if this was not retained in the multivariable analysis. Similar results were observed in the EXTRA survey (16): radiologic sacroiliitis was significantly associated with past or current history of uveitis in univariate analysis but not in multivariate analysis.

Regarding anti-TNF therapy, when patients were treated with monoclonal antibodies (*i.e*. infliximab or adalimumab) the number of uveitis after treatment was significantly reduced, whereas this was not observed when the treatment was etanercept. Similar results were found in other studies: In the Swedish biologics register, on 1365 patients, Lie *et al*. found a four-fold increase in the risk for anterior uveitis, during the first 2 years after treatment start, for patients with SpA starting treatment with etanercept compared with adalimumab, and a two-fold increase for etanercept compared with infliximab, but no statistical difference between adalimumab and infliximab, suggesting a clear advantage for adalimumb/infliximab over etanercept (22). This findings are in line with the study based on US claims data (10). In a retrospective study of 46 patients, Guignard *et al*. shown that anti-TNF antibodies decreased the rate of uveitis flares, whereas soluble TNF receptor did not seem to decrease this rate, with a number of uveitis flares per 100 patient-years before and during anti-TNF of, respectively: for soluble TNF receptor 54.6 *vs*. 58.5 (p=0.92); and for anti-TNF antibodies 50.6 *vs*. 6.8 (p=0.001) (9). In a systematic literature review, Braun found that flare of anterior uveitis occurred less frequently with Infliximab than with etanercept (3.4 per 100 patient-years and 7.9 per 100 patient-years, respectively), but the difference was not significant (7). In the RHAPSODY trial, Adalimumab led to clinically relevant reduction of 51% in all 1250 patients with AS (8). Recently, a multicentre, double-masked, randomised, placebo-controlled phase 3 trial (VISUAL II) showed that Adalimumab significantly lowered the risk of uveitic flare or loss of visual acuity in patients with inactive, non-infectious intermediate, posterior, or panuveitic uveitis controlled by systemic corticosteroids (23).

This study has some limitations, but also some strength. First, the information collected in this study was retrospective but collected in a standardised face-to-face interview with a detailed pre-specified checklist of questions. Moreover, the data reported by the patients were confirmed by the information contained in the patient's medical files. Secondly, information on the clinical characteristics of uveitis and the history of uveitis itself was patient-reported but all patients had the diagnosis confirmed by an ophthalmologist at some point in the disease course. Thirdly, a selection bias (*i.e*. patients only included in a tertiary-care university centre) might have occurred, including more severe patients, since 179 patients (59.5%) received anti-TNF agents over the disease course. However, the standardised procedure for SpA follow-up in the centre contributed to reduce missing data in the retrolective assessment of medical files; furthermore, it was a real-life study with a significant number of uveitis events and long-term data.

Awareness of uveitis, among clinicians, is important in view of the high frequency of uveitis events over disease course and should lead to a specific management with collaboration between rheumatologists and ophthalmologists. Prospective studies aiming to evaluate longitudinal outcomes of SpA patients with uveitis should confirm our results.

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