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Prevalence and incidence of uveitis in patients with spondyloarthritis: the impact of the biologics era. Data from the international ASAS-COMOSPA study

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Abstract

Objectives: Uveitis is a common extra-musculoskeletal manifestation in SpA. The aim of this study was to analyze the prevalence of uveitis in SpA patients, and its association with geographical areas, and to determine whether its incidence differed between before and after the biologics era.

Methods: ASAS-COMOSPA is a retrospective study that includes patients fulfilling Assessment in SpondyloArthritis International Society (ASAS) SpA classification criteria from 22 countries. The overall prevalence of uveitis was calculated, and factors associated with the onset of a first episode of uveitis were evaluated using a Cox regression. A Log-Rank test was performed to compare the new onset of uveitis in the non-biologics era (SpA onset before 2000) *vs* biologics era (SpA onset after 2000).

Results: A total of 3984 patients were included. The likelihood of presenting a first uveitis episode increased over time, from a prevalence of 10.5% (95% CI 9.5–11.4%) at the time of the SpA diagnosis to 46.6% (41.6–51.5%) after 30 years since the SpA diagnosis. HLA-B27 positivity, family history of uveitis, peripheral enthesitis, and IBD were associated with higher risk of uveitis. Patients with SpA disease onset after the year 2000 showed a lower prevalence of uveitis compared with those with disease onset before the year 2000 (8.2% *vs* 25.5%, $P < 0.01$), as well as a lower incidence (2.8 per 100 person-years *vs* 6.1 per 100 person-years, respectively).

Conclusion: In our study, the risk of having suffered from at least one episode of uveitis ranged from 10% at the time of the diagnosis of axial SpA to 47% after 30 years of disease duration. Patients with disease onset after biologic therapy introduction showed a significantly lower prevalence and incidence of first episodes of uveitis.

Keywords: spondyloarthritis, uveitis, biological treatment, axial spondyloathritis, prevalence, incidence, extra-musculoskeletal, TNF-α inhibitors.

Rheumatology key messages

- Acute anterior uveitis (AAU) is the most common extra-musculoskeletal manifestation in spondyloarthritis (SpA).
- Biologic therapies, especially monoclonal TNF-inhibitors, have been shown to be effective in uveitis treatment.
- We found a lower frequency of AAU development in SpA patients after the year 2000, the period in which biologics were introduced as SpA treatment.

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Introduction

SpA, a chronic inflammatory disease involving the axial skeleton and peripheral joints, and encompasses several subtypes, including axial SpA [radiographic (r-axSpA) and non-radiographic (nr-axSpA)], PsA, ReA, IBD-related arthritis, juvenile SpA and undifferentiated SpA [1–5]. Acute anterior uveitis (AAU) is the most frequent extra-musculoskeletal manifestation and one of the SpA features included in the classification criteria [6]. The average global prevalence of uveitis in SpA has been reported as 20.3% (ranging from 6% in Italy to 39% in Portugal) [7], and more frequently in HLA-B27–positive patients with r-axSpA [8–10].

In the last decades, control of disease activity in SpA has improved considerably since the introduction of biologic treatments, namely TNF-α inhibitors (TNFis). Some TNFis have been shown to reduce the occurrence of AAU in r-axSpA, while etanercept has been reported to be less effective in preventing uveitis flares [11, 12]. The efficacy of mAbs (adalimumab, infliximab, golimumab) has been well established, with reported changes in AAU ranging from 51.8 to 21.4 attacks per 100 patient-years (PY), 15.6–3.4 per 100 PY and 11.1–2.2 per 100 PY, respectively [13–15]. In a previous review of 2115 uveitis cases in naïve TNFi r-axSpA patients, the longest median time to uveitis development was in patients taking adalimumab (243 days), compared with etanercept (182 days) or infliximab (144 days). In addition, the rate of AAU development at 1 year was lowest in those receiving adalimumab (2.4%) and highest in those receiving etanercept (4.8%) [16].

Thus, the utilization of TNFis for the treatment of SpA in the last decades may have reduced the incidence of AAU. The international COMOSPA study is the first and largest cross-sectional observational study assessing comorbidities and risk factors and their monitoring in a worldwide population of patients with SpA. This study includes patients from all the regions of the world, with a huge variability of disease duration and phenotypes. This study brings the opportunity to evaluate the phenotypes associated with AAU, as well as whether the trend has been towards a reduction in prevalence and incidence of AAU in recent decades.

The main objective of this study was to analyze the prevalence and incidence of uveitis in SpA patients included in COMOSPA cohort during recent decades and to evaluate the impact of biologics treatment on this incidence.

Methods

Design and population

This is an observational cross-sectional retrospective study including consecutive adult patients (>18 years old) fulfilling ASAS criteria (either axial or peripheral) included in the COMOSPA registry [7].

COMOSPA is a worldwide registry. Investigators from 22 countries recruited a total of 4028 patients from January 2013 to September 2014. Forty-four patients were excluded because all data in their forms were missing, resulting in 3984 patients being included in the analysis. The COMOSPA study includes a wide set of anthropometric and clinical variables: age, gender, presence of HLA-B27, age at disease onset, disease duration, phenotypic expression of SpA, presence of definite r-axSpA according to radiographic sacroiliitis, NSAID use (determined as the percentage of days of intake since diagnosis of SpA), clinical disease activity (BASDAI index, 0–10 cm) clinical disability (BASFI index, 0–10 cm), inflammatory markers of disease activity (ESR and CRP) and AS DAS (ASDAS).

AAU was defined as the presence of one or more episodes in the past or present. Dates of the first episode of AAU, first SpA symptoms, and diagnosis were collected retrospectively, allowing us to stablish the temporal sequence of events. All patients included signed an informed consent, and the project was approved by the ethical committees of all participant sites.

Statistical analysis

Descriptive data are presented as the mean and S.D. for continuous variables and as absolute frequencies for categorical variables.

In the present study, we calculated the overall prevalence of at least one episode of AAU and evaluated difference across continents and clinical phenotypes. Factors associated with the development of AAU were studied by univariate Cox regressions and thereafter by multivariate Cox regression, including in the model variables selected by the univariate analysis (when $P \leq 0.20$). Interactions, confounding factors and collinearity were tested.

Then, patients were split based on the date of their disease onset (before or after the year 2000, which marks the introduction of TNFis to the market, referred to here as the 'Biologics era'). To determine the incidence of AAU, a Kaplan–Meier survival curve was calculated, and the comparison before and after the biologics era was made using a Log-Rank test. The incidence rate was calculated using the rate of patients-years per group. A P-value of <0.05 was considered statistically significant.

Results

In total, 3984 patients were included in the analysis (Table 1). Sixty-five percent were male, with a mean disease duration of 8.2 ± 9.4 years and mean age at disease onset of 28 ± 13 years. HLA-B27 positivity was found in 72% of the patients. A total of 831 patients (20.9%) from the total population developed at least one episode of AAU, with an incidence rate of 3.3 first episodes per 100 PY. Of the 831 patients with AAU, data on the date of AAU onset was available for 775 patients. At the time of the SpA diagnosis, the mean prevalence of AAU was 10.5%

Table 1. Characteristics of the COMOSPA population

	N (%) or mean (S.D.)
Age (years)	44 (±14)
Gender (male)	2588 (65.0%)
Education level (university)	1683 (42.2%)
Disease duration (years)	8.2 (9.4)
Diagnosis delay (years)	7.3 (9.2)
HLA-B27 positivity	2217/3061 (72.4%)
Axial involvement	3387 (85.4%)
Peripheral joint disease	2379 (60.0%)
Enthesitis ever	1506 (38.0%)
Dactylitis ever	618 (15.6%)
Uveitis ever	831 (20.9%)
Psoriasis ever	894 (22.5%)
IBD ever	228 (5.8%)
BASDAI	3.7 (2.4)
BASFI	3.0 (2.7)

(95% CI 9.5–11.4%). After 10, 20 and 30 years since the diagnosis of SpA, the prevalence of AAU increased to 23.2% (21.4—24.9%), 32.3% (30.2—35.6%) and 46.6% (41.6–51.5%), respectively. Among the total patients who developed AAU at any time, AAU was present at the moment of SpA diagnosis in only 8.5% of patients, while 43.7% and 47.7% patients developed the first episode before and after SpA diagnosis, respectively.

Distribution of AAU across regions

When comparing rheumatology centres from different regions, Europe showed the highest prevalence of AAU (23.3%), while North America exhibited the lowest (15.3%). Asia, Africa and Latin America reported frequencies of 20%, 19.9% and 17%, respectively (Fig. 1). In turn, we found that the frequency of AAU varied according to the HLA-B27 status across continents. While AAU was more prevalent in HLA-B27–positive populations in Europe, Asia, Latin America and North America (ranging from 24.3% in Asia to 31.9% in Europe), Africa showed a higher prevalence of uveitis in HLA-B27–negative patients compared with HLA-B27–positive patients (24.3% *vs* 18.9%) (Fig. 1).

Factors associated with the development of AAU

Among the different clinical phenotypes observed in SpA, patients with IBD showed a higher frequency of AAU (33%), followed by patients with peripheral enthesitis (23%), axial disease (22%), peripheral articular disease (19%), dactylitis (19%) and psoriasis (13%) (Fig. 2). It should be mentioned that in this population, 94% of patients with IBD and 89% of patients with enthesitis also presented with axial involvement. A total of 88% of patient with uveitis were HLA-B27 positive, while 17% had a first/second degree relative with uveitis.

Univariate regressions showed no significant differences in the prevalence of AAU between male and female patients (20.8% *vs* 18.7%, $P = 0.68$). We found that HLA-B27 positivity, family history of uveitis, peripheral enthesitis, heel enthesitis, axial involvement and IBD were associated with a higher prevalence of uveitis. On the other hand, peripheral arthritis and psoriasis were associated with a lower prevalence of uveitis (Table 2). HLA-B27 positivity, a family history of uveitis, peripheral enthesitis and IBD were independently associated with higher risk of AAU (Table 3).

Impact of biologics on the development of AAU

Since the probability of having a first episode of uveitis increases over time, we analysed the impact of biologics in the development of uveitis in the first 10 years from the SpA diagnosis. When analysing the frequency of AAU development in SpA patients before and after the year 2000, those patients with disease onset after the year 2000 (i.e. in the 'biologics era') showed lower rates of AAU than those with disease onset before the year 2000 (8.2% *vs* 25.5%, $P < 0.001$), with a hazard ratio of 0.45 (95% CI 0.36–0.56) (Fig. 3). The incidence rate of AAU development was 2.8 per 100 PY in the biologics era, while this rate was 6.1 per 100 PY in the non-biologics era.

Discussion

The COMOSPA study is the largest cross-sectional observational prevalence study assessing comorbidities and risk factors in a worldwide population of patients with SpA. AAU is considered as the most common extra-articular manifestation in SpA, and has even been reported to be the first clinical manifestation in different series. We performed this subanalysis to determine the incidence of uveitis in SpA patients and the influence of biologics treatment on the incidence of this extra-articular manifestation.

In our analysis, the prevalence of uveitis was 20%. This prevalence was significantly lower in patients in which disease onset occurred after the year 2000 compared with those patients with SpA onset before the year 2000 (8.2% *vs* 25.5%). These results are in agreement with previous studies that confirm its prevalence and incidence over time [8, 17, 18]. Of course, disease duration was significantly lower in patients with disease diagnosis after the year 2000, than in those whose diagnosis occurred before the year 2000. Therefore, we limited the analysis to the first 10 years after the diagnosis. Currently, TNFis are widely used in the treatment of rheumatic inflammatory diseases, including SpA, and

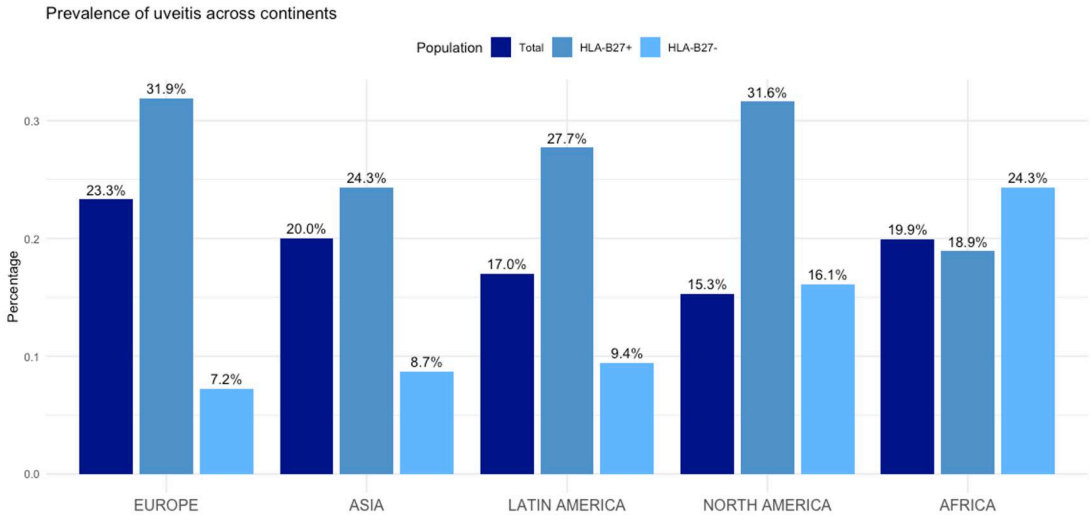

Figure 1. Prevalence of uveitis among different regions and stratified according to the HLA-B27

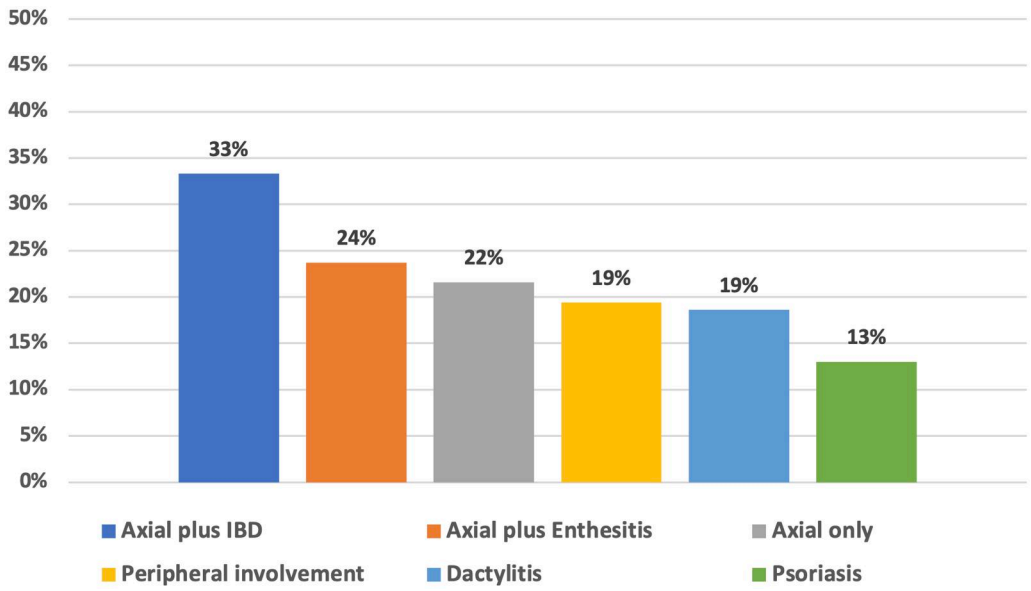

Figure 2. Frequency of uveitis among different SpA clinical phenotypes

Table 2. Cox regression showing the factors associated with uveitis

		Uveitis ever[a] $N = 775$	HR (95% CI)	*P*-value
Number of patient-years	Uveitis ever	9420.5	–	–
	Uveitis never	22098.4		
Sex	Female (1359)	254 (18.7%)	1.03 (0.89–1.2)	0.682
	Male (2509)	521 (20.8%)		
Disease duration (years)	>=5 years (1920)	513 (26.7%)	0.90 (0.76–1.07)	0.217
	<5 years (1944)	258 (13.3%)		
HLA-B27	Positive (2157)	576 (26.7%)	**2.50 (1.98–3.15)**	**<0.001**
	Negative (836)	82 (9.8%)		
Family history of uveitis	Yes (199)	123 (61.8%)	**3.71 (3.06–4.51)**	**<0.001**
	No (3478)	610 (17.5%)		
Peripheral arthritis	Yes (2322)	450 (19.4%)	**0.87 (0.75–0.99)**	**0.048**
	No (1543)	323 (20.9%)		
Peripheral enthesitis	Yes (1476)	347 (23.7%)	**1.33 (1.16–1.54)**	**<0.001**
	No (2396)	426 (17.8%)		
Heel enthesitis	Yes (1321)	313 (23.7%)	**1.33 (1.15–1.54)**	**<0.001**
	No (2513)	452 (18.0%)		
Dactylitis	Yes (597)	111 (18.6%)	0.87 (0.71–1.07)	0.186
	No (3268)	662 (20.3%)		
Axial involvement	Yes (3304)	713 (21.6%)	**1.97 (1.52–2.56)**	**<0.001**
	No (562)	61 (10.9%)		
Psoriasis	Yes (876)	114 (13.0%)	**0.52 (0.42–0.63)**	**<0.001**
	No (2991)	661 (22.1%)		
IBD	Yes (225)	75 (33.3%)	**1.63 (1.29–2.07)**	**<0.001**
	No (3640)	700 (19.2%)		
Continent				
- Africa	331	62 (18.7%)	Reference	
- Asia	1278	245 (19.2%)	0.81 (0.62–1.08)	0.159
- Europe	1671	373 (22.3%)	**0.75 (0.57–0.98)**	**0.035**
- Latin-America	346	58 (16.8%)	**0.66 (0.46–0.95)**	**0.026**
- North-America	242	37 (15.3%)	**0.51 (0.34–0.77)**	**0.001**
ASAS peripheral criteria	Yes (2683)	556 (20.7%)	1.08 (0.92–1.26)	0.345
	No (1185)	219 (18.5%)		

[a] Analysis performed in the 775 patients for whom date of first uveitis episode was available. Bold text indicates variables with significant *P* values. ASAS: Assessment in SpondyloArthritis International Society peripheral criteria; HR: hazard ratio.

several studies have reported the efficacy of TNFis in reducing the incidence of AAU in patients with r-axSpA, especially with mAbs [13, 14, 19, 20]. However, others studies have also suggested that TNFis might actually induce new-onset AAU, especially with etanercept [21–23]. In our study, given the lack of data regarding the type of anti-TNF blocker used, we could not analyse the differential effect of TNFis.

In our study, patients who met ASAS axial classification criteria had a higher frequency of uveitis than those patients who met ASAS peripheral classification criteria. Risk factors

associated with uveitis were family history of uveitis, enthesitis, HLA-B27 positivity and IBD, while the presence of psoriasis was associated with a lower risk of developing uveitis. These results are in line with the findings of Frantz *et al.*, who recently showed that SpA patients with uveitis had longer disease duration and a higher frequency of axial involvement, X-ray-confirmed sacroiliitis, heel pain, and HLA-B27 positivity and were less likely to have psoriasis or PsA [24].

The association between HLA-B27 positivity and uveitis has been well established in previous studies [17, 18, 25, 26], as well as the association between enthesitis and the risk for developing uveitis [25–28]. In our study, HLA-B27 positivity was found to be one of the strongest risk factors for developing uveitis [odds ratio 3.25 (2.41–4.39)].

A striking observation in our study was that IBD and enthesitis were the clinical phenotypes most associated with developing uveitis, even more so than those with axial disease. These contradictory results might be explained by the overlap with axial disease, as most patients with IBD and enthesitis in the registry had also axial involvement, in which the link with AAU is very strong (94% of patients with IBD and 89% who had enthesitis had also axial involvement).

We found that disease duration of >5 years was protective against the development of a first episode of AAU in the Cox model. This finding seemed contradictory to the hypothesis that the prevalence of AAU increases with disease duration. However, this result could be interpreted as patients who do not develop uveitis within the first 5 years having a lower chance of developing it later.

COMOSPA is a worldwide registry including patients with SpA from different sites throughout the world. When comparing rheumatology centres from different regions, European centres showed a significantly higher prevalence of uveitis (23%) compared with centres in Asia (20%), Africa (19,9%), Latin-America (17%) and North-America (15%). This difference may be explained by the higher frequency of HLA-B27 positivity observed in Caucasian SpA patients. The prevalence of HLA-B27 was almost 32% in European patients who developed uveitis. This prevalence was higher than that among Africas, Latin-American, North-American and Asian patients.

Our study has several weaknesses but also some strengths. First, this is an observational cross-sectional study analysing data from a registry, so we can only analyse statistical association between the incidence of uveitis and biologics treatment, not the effect of the treatment on the resolution of the episodes. Second, some patients received multiple biologics treatments at different periods throughout the disease; therefore, it is difficult to establish whether AAU happened before, during or after a certain biologic treatment. In addition, there was no treatment protocol for treating patients with SpA, as their comorbidities or extra-articular manifestations such as uveitis. It should be noted that the disease duration and

Table 3. Factors independently associated with the development of a first episode of uveitis

	HR (95% CI)	*P*-value
Disease duration ≥ 5 years	**0.81 (0.67–0.98)**	**0.034**
HLA-B27 positive	**2.29 (1.78–2.95)**	**<0.001**
Family history of uveitis	**2.93 (2.36–3.64)**	**<0.001**
Peripheral enthesitis	**1.31 (1.12–1.54)**	**0.001**
Heel enthesitis	n.s.	n.s.
Dactylitis	n.s.	n.s.
Axial involvement	n.s.	n.s.
Psoriasis	**0.78 (0.61–0.99)**	**0.046**
IBD	**1.71 (1.31–2.23)**	**<0.001**
ContinentAfrica	n.s.	n.s.
-Asia		
-Europe		
-Latin-America		
-North-America		

Multivariable cox regression using variables with *P*-value of <0.20 from the univariate analysis. Bold text indicates variables with significant *P* values.

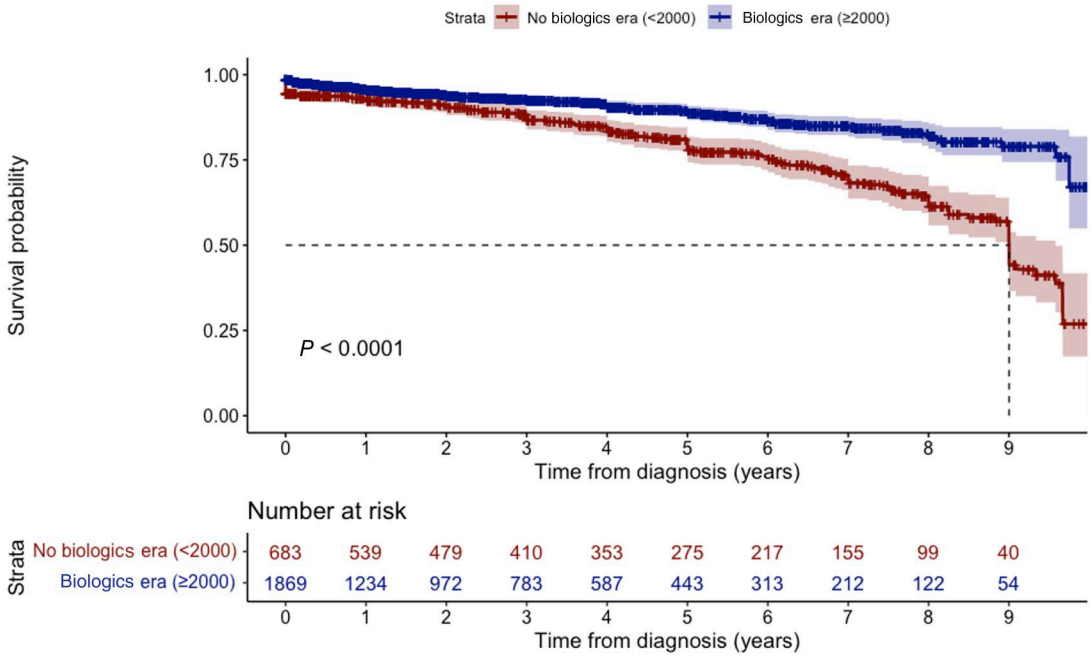

Figure 3. Probability of having at least one episode of uveitis during the first 10 years following the time from diagnosis

follow-up time are shorter for patients from the biologics era. Therefore, we have limited our analysis to the first 10 years since diagnosis to allow for a comparable period across both groups. Finally, patients from the COMOSPA study were recruited in 2013–2014, when IL-17 inhibitors were not available for axSpA. Thus, the 'Biologics era' in this analysis refers to the period when TNFis were available.

On the other hand, one of the strengths of the study is that the COMOSPA registry is a large cross-sectional observational study that included patients from different countries around the world with different ethnicities. In this large registry, we found a lower frequency of AAU development in SpA patients in which disease diagnosis occurred after the year 2000, the period in which the use of biologics therapy was introduced in the management of SpA. This difference may be explained by the impact of the use of this therapy in the comprehensive management of SpA and its extra-articular manifestations.

In conclusion, we found a lower prevalence and incidence of uveitis development in SpA since year 2000 in a large worldwide COMOSPA registry. Prospective studies with longitudinal observations on the development of uveitis and the impact of biologics therapy are needed to confirm our results.

Data availability

Data are available on reasonable request. Researchers willing to use data collected during the study should contact the first author, who will send a study proposal template to be completed by the applicant. Thereafter, the steering committee of the ASAS-COMOSPA study will approve (or not) the proposal and proceed to the data sharing.

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