Case-control Study on Dactylitis, Enthesitis, and Anterior Uveitis in Spondyloarthritis Associated with Inflammatory Bowel Diseases: Role of Coexistent Psoriasis

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ABSTRACT. ***Objective.*** To evaluate the frequency of dactylitis, enthesitis, and anterior uveitis (AU) in spondyloarthritis (SpA) associated with inflammatory bowel disease (IBD-SpA) compared with other SpA, and to assess the role of associated psoriasis in the occurrence of dactylitis and enthesitis.

Methods. In a 12-month case-control study, the frequency of dactylitis and enthesitis in 29 patients with ulcerative colitis (UC) and 59 with Crohn disease (CD) who satisfied the Spondyloarthritis international Society criteria for axial or peripheral SpA was compared with 176 controls, including 97 (55.1%) with psoriatic arthritis (PsA), 47 (26.7%) with ankylosing spondylitis (AS), and 32 (18.2%) with nonradiographic axial SpA (nr-axSpA). The occurrence of these features in IBD-SpA with and without psoriasis was also evaluated.

Results. Axial, peripheral, or mixed involvement was observed in 46 (52%), 29 (33%), and 13 (15%) patients, respectively; and 14/88 (16%) had psoriasis. Dactylitis was recorded in 4/88 patients (4.5%) with IBD-SpA and in 30 controls (17.4%; p = 0.008), enthesitis in 16 cases (18.1%) and in 78/176 controls (44.3%; p < 0.001), and AU in 3 patients (3.4%) with IBD-SpA and in 26 controls (14.7%; p = 0.01). No significant differences were found between patients with UC-SpA and those with CD-SpA. Dactylitis and enthesitis were significantly more common in patients with IBD-SpA who also had psoriasis compared to those without skin disease (p = 0.009 and 0.003, respectively).

Conclusion. Dactylitis, enthesitis, and AU are significantly less frequent in IBD-SpA compared with other types of SpA. Given the frequent association of psoriasis and IBD, overlooking coexistent skin disease may lead to overestimating the frequency of these features. (J Rheumatol First Release April 15 2017; doi:10.3899/jrheum.161518)

Key Indexing Terms:

DACTYLITIS ENTHESITIS ANTERIOR UVEITIS
IBD-SPA PSORIASIS CROHN DISEASE

The most common forms of the spondyloarthritis (SpA) complex are ankylosing spondylitis (AS), nonradiographic axial spondyloarthritis (nr-axSpA), psoriatic arthritis (PsA), and SpA associated with inflammatory bowel diseases (IBD-SpA). Given the shared clinical manifestations, including axial skeleton involvement, peripheral arthritis, enthesitis, dactylitis, and anterior uveitis (AU), these entities have been included in the same disease group. However, the frequency of these features differs among SpA. Dactylitis, a hallmark of SpA, is observed in about 30% of SpA patients, with some differences among the different entities and with the highest frequency in patients with PsA[1,2].

Similarly, clinical manifestations of enthesitis have been reported with a prevalence of around 40% of the cases both in AS and nr-axSpA[3], and in up to 79% in PsA[4,5].

SpA represents the most frequent extraintestinal manifestation of IBD, with a reported prevalence of at least one-third of the cases[6]. It may occur in 3 clinical patterns including axSpA, peripheral oligoarticular or polyarticular SpA, or mixed, with both axial and peripheral manifestations[7].

To date, a few studies have investigated the clinical characteristics of IBD-SpA, and whether there are differences

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in comparison with other types of SpA in articular and extraarticular manifestations. In particular, the frequency of dactylitis and enthesitis has not been clearly assessed. In published clinical series, dactylitis and enthesitis were reported with a prevalence ranging from 0% to 15.5% and 12.5% to 90%, respectively[8,9,10,11,12,13,14,15,16,17-22].

AU is the most frequent extraarticular manifestation of SpA; it has been reported in at least 30% of the cases with some differences among AS, PsA, and nr-axSpA[23]. A frequency peak of 33.2% has been observed in AS[24], while an estimated prevalence of 2% to 25% has been recorded in PsA, and of 12.4% in nr-axSpA[3]. In a systematic review of the literature, AU occurred in IBD-SpA less often than in other SpA[24], while a frequency rate of 25% of the cases has been reported by other authors[25]. Table 1A and Table 1B summarize the reported prevalence of dactylitis, enthesitis, and AU in patients with IBD-SpA.

Psoriasis has been recognized as a frequent extraintestinal manifestation of IBD, particularly of Crohn disease (CD). In a controlled study of 136 patients with CD, psoriasis was recorded in 9.6% of the cases, with a significant difference compared with 136 controls[26]. Conversely, in a large epidemiologic study, patients with psoriasis had a relative risk of 4.00 (95% CI 1.72–9.27) of developing CD, while no increased risk was found for ulcerative colitis (UC)[27]. This association may represent a confusing factor for the assessment of clinical features in patients with IBD-SpA and coexistent psoriasis, especially if we consider the

Table 1A. Reported frequency of dactylitis, enthesitis, anterior uveitis, and B27 positivity in patients with IBD-SpA in 7 studies. The reported association with psoriasis is also indicated. Data are n (%) unless otherwise indicated.

Conditions Measured	Orchard[19], 1998 ‡	De Vlam[11], 2000	Salvarani[12], 2001*	Palm[13], 2002	Generini[18], 2004 †	Turkcapar[8], 2006	Pérez Alamino[10], 2011
Overall IBD-SpA, n	107	40	53	88	24	90	45
Dactylitis	NA	1 (2.5)	3 (5.6)	6 (6.8)	NA	0 (0)	7 (15.5)
Enthesitis	NA	7 (17.5)	16 (30.1)	11 (12.5)	16 (66.6)	81 (90)	7 (15.5)
Uveitis	20 (18.6)	NA	NA	7 (7.9)	NA	23(25.5)	NA
B27	NA	7 (17.5)	5 (3.6)	20 (22.7)	NA	47 (52.2)	NA
Psoriasis	NA	4 (10)	NA	4 (4.5)	NA	NA	NA
UC-SpA, n	59	13 (32.5)	NA	54	0	43	NA
Dactylitis, n	NA	0	NA	NA	NA	0 (0)	NA
Enthesitis	NA	2 (15.4)	NA	NA	NA	39 (90.7)	NA
Uveitis	10 (16.9)	NA	NA	NA	NA	8 (18.6)	NA
CD-SpA, n	48	27 (67.5)	NA	34	24	47	NA
Dactylitis	NA	1 (3.7)	NA	NA	NA	0 (0)	NA
Enthesitis	NA	5 (18.5)	NA	NA	16 (66.6)	42 (89.4)	NA
Uveitis	10 (20.8)	NA	NA	NA	NA	15 (31.9)	NA
Followup, mos	120	NA	NA	60	18	20.63 ± 34.3	NA

*IBD group included 3 patients with indeterminate colitis. ‡Data are related to patients with peripheral IBD-SpA. † Enthesitis was assessed both clinically and by ultrasound examination. IBD: inflammatory bowel disease; SpA: spondyloarthritis; UC: ulcerative colitis; CD: Crohn disease; NA: not available.

Table 1B. Reported frequency of dactylitis, enthesitis, anterior uveitis, and B27 positivity in patients with IBD-SpA in 7 more studies. The reported association with psoriasis is also indicated. Data are n (%) unless otherwise indicated.

Conditions Measured	Shivashankar[20,21], 2012, 2013	Al-Jarallah[9], 2013	Zippi[14], 2014	Kamo[15], 2015**	Isene[16], 2015	Subramaniam[17], 2015**	Peluso[22], 2016
Overall IBD-SpA, n	72	45	240	46	99	140	78
Dactylitis	NA	2 (4.4)	NA	7 (15.2)	NA	6 (4.3)	12 (15.4)
Enthesitis	49 (68)	7 (15.5)	NA	15 (32.6)	NA	24 (17.1)	NA
Uveitis	24 (33.3)	NA	26 (10.8)	1 (2.1)	10 (10.1)	8 (5.7)	NA
B27	NA	NA	NA	NA	NA	NA	NA
Psoriasis	23 (31.9)	NA	NA	NA	NA	8 (5.7)	NA
UC-SpA, n	40	27	169	NA	51	44	34
Dactylitis, n	NA	2 (7.4)	NA	NA	NA	3 (6.8)	2 (5.9)
Enthesitis	29 (72.5)	6 (22.2)	NA	NA	NA	6 (13.6)	NA
Uveitis	12 (30)	NA	10 (5.9)	NA	5 (9.8)	1 (2.3)	NA
CD-SpA, n	32	18	71	NA	48	96	44
Dactylitis	NA	0 (0)	NA	NA	NA	3 (3.1)	10 (22.7)
Enthesitis	24 (72)	1 (5.5)	NA	NA	NA	18 (18.8)	NA
Uveitis	12 (37.5)	NA	16 (22.5)	NA	5 (10.4)	7 (7.3)	NA
Followup, mos	480	65 ± 58	NA	NA	120	NA	NA

** Questionnaire-based survey. IBD: inflammatory bowel disease; SpA: spondyloarthritis; UC: ulcerative colitis; CD: Crohn disease; NA: not available.

high frequency of dactylitis and enthesitis in PsA[1,2].

The primary endpoint of our study was to evaluate the frequency of dactylitis, enthesitis, and AU in a clinical series of patients with IBD-SpA compared with other SpA including AS, nr-axSpA, and PsA. The co-primary endpoint was to assess the frequency of psoriasis in patients with IBD-SpA and the prevalence of dactylitis, enthesitis, and AU by dividing the case patients into 2 groups: patients with IBD-SpA with and without associated psoriasis.

MATERIALS AND METHODS

A 12-month case-control study was conducted at the Rheumatology Department of the Hospital of Prato in collaboration with the IBD Unit of the Internal Medicine Department of Bologna University, Bologna, Italy.

Case patients. All consecutive patients meeting the Assessment of Spondyloarthritis international Society (ASAS) criteria for both axial and peripheral SpA[28,29], and with a diagnosis of CD or ulcerative colitis (UC) certified by the gastroenterologist, were included. All case patients were also evaluated by a dermatologist for current psoriasis and personal or family history of psoriasis.

Controls. The 2 consecutive patients with other SpA (ASAS criteria) observed after the case patient during the same time interval were the controls.

At baseline, all patients had a standardized diagnostic procedure including history, demographic data recording, symptom duration, date of diagnosis, complete physical examination, articular and extraarticular features evaluation, routine blood examinations including blood cell count with differential count, kidney and liver function tests, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), calcemia, uric acid level, rheumatoid factor, HLA typing, affected joint radiological examination, and pelvis radiographs or magnetic resonance imaging to investigate sacroiliitis. Dactylitis was defined as painful diffuse tenderness and swelling of the entire digit with sausage aspect[2].

Enthesitis was defined as tenderness and swelling at sites of tendon, ligament, and joint capsule insertion into bone, and it was assessed according to the Leeds Enthesitis Index (LEI)[30].

AU diagnosis required certification by an ophthalmologist.

Dactylitis and enthesitis diagnoses were accepted if observed during the study followup visits or if diagnosed in the past by a rheumatologist working in our center and recorded in the patient's chart.

At every visit, patients had a complete physical examination including a complete joint count, and all case patients and controls were evaluated for the presence of dactylitis, enthesitis, and extraarticular manifestations. Patients were followed by the same rheumatologist, and followup visits were scheduled at baseline and every 4 months. All clinical and laboratory data were recorded in a computed clinical chart. The local ethics committee reviewed and approved the study protocol. Before entering the trial, each patient was informed of the nature, duration, and purpose of the study, as well as of all the potential benefits and drawbacks that could be expected. All participants gave written informed consent. According to the policy of our institutions, ethics approval was not required.

The followup duration was calculated from the date of the diagnosis both in cases and controls.

Statistical analysis. All demographic, clinical, and laboratory data were imputed and descriptive statistics and statistical differences were calculated using SPSS statistical package version 11 for Windows (SPSS Inc.). Chi-squared test and Fisher's exact test were used to compare the absence or presence of enthesitis, dactylitis, AU, and HLA-B27 positivity. P values < 0.05 were accepted as significant.

RESULTS

Case patients. There were 88 patients with IBD-SpA [29 (33%) with UC and 59 (67%) with CD], 42 women/46 men, mean age 47.66 ± 15.09 years; 10 (11.3%) were B27-positive. The mean followup duration was 96.23 ± 12.4 months and IBD duration was 127.54 ± 4.4 months.

Controls. There were 176 patients with SpA: 97 (55.1%) with PsA (51 women/46 men), 47 (26.7%) with AS (38 men/9 women), and 32 (18.2%) with nr-axSpA (20 men/12 women). The control group included 72 women/104 men, with a mean age of 46.35 ± 24.88 years. There were 70 controls who were B27+ (39.8%), and the mean disease duration was 43.21 ± 28.34 months.

In IBD-SpA, axial involvement was observed in 46 patients (52%), peripheral SpA in 29 (33%), and mixed in 13 (15%). Peripheral SpA was oligoarticular (≤ 4 joints involvement) in 26/29 patients (90%) and polyarticular in 3 (10%). SpA onset was preceded by IBD in 76 patients (86.4%), with a mean interval of 38.06 ± 26.14 months. SpA and IBD occurred concurrently in 4 patients (4.5%), and in 8 patients (9%), IBD complicated the SpA course after a mean interval of 21.4 ± 8.21 months.

The demographic and clinical features of 88 case patients and 176 controls are shown in Table 2.

Overall, a significantly lower occurrence of dactylitis was recorded in case patients with 4 episodes (4.5%) in IBD-SpA patients and 30 (17.4%) in controls ($p = 0.008$). The comparison of the frequency of dactylitis between UC and CD showed no differences occurring in 1/29 (3.4%) and in 3/59 (5.08%), respectively ($p = 0.843$). All 3 patients with CD had associated psoriasis.

Enthesitis prevalence was significantly lower in IBD-SpA, occurring in 16/88 patients (18.1%) and in 78/176 controls (44.3%; $p < 0.001$). AU was recorded in 3 patients (3.4%) with IBD-SpA and in 26 controls (14.7%; $p = 0.010$), and B27 positivity was recorded in 10 (11.3%) of IBD-SpA and in 70 (39.8%) of SpA ($p < 0.001$). The followup duration was 96.23 ± 12.4 months in case patients and 101.11 ± 34.22 months in controls ($p = 0.456$).

Psoriasis was recorded in 14 out of 88 patients (16%), 3 cases in the UC group and 11 in the CD group, with no significant difference ($p = 0.490$).

As shown in Table 2, a significantly lower occurrence of dactylitis compared with controls was recorded in IBD-SpA patients without psoriasis (1 case in 74 patients; $p = 0.001$), while dactylitis occurrence was not significantly different in 3 out of 14 patients (21.4%) with coexistent psoriasis ($p = 0.960$).

Enthesitis frequency was significantly higher in 14 IBD-SpA patients with associated psoriasis (50%) compared with the remaining 74 cases (12.1%; $p = 0.003$). Similarly to dactylitis, enthesitis occurrence was not different in patients with UC and those with CD ($p = 0.103$).

DISCUSSION

Dactylitis, or the sausage digit, occurring in around 30% of the patients with SpA[1,2], was described more than 40 years ago[31,32]. The occurrence of this clinical manifestation has

Table 2. Demographic and clinical features in 88 IBD-SpA patients compared with 176 controls.

Feature	IBD-SpA	Overall SpA	PsA	AS	Nr-axSpA	p
N (%) of patients						
Overall	88	176	97 (55.1)	47 (26.7)	32 (18.2)	
UC	29 (33)					
CD	59 (67)					
IBD + psoriasis	14 (16)					
UC + psoriasis	3 (13.7)					
CD + psoriasis	11 (18.6)					
Age, yrs, mean ± SD						
Overall	47.66 ± 15.09	46.35 ± 24.88	52 ± 10.42	38 ± 9.21	34 ± 8.43	0.650
UC	51.07 ± 11.46					
CD	45.67 ± 17.05					
B27+, n (%)	10 (11.3)	70 (39.8)	14 (14.4)	43 (91.4)	13 (40.6)	< 0.001
Axial	7 (70)					
Mixed	3 (30)					
AxSpA, n (%)	46 (52)	88 (50)	9 (9.2)	47 (100)	32 (100)	0.828
UC	15 (52)					
CD	31 (52.5)					
Overall peripheral SpA, n (%)	29 (33)	62 (35)	62 (64)	0	0	0.819
Oligoarticular	26 (90)	41 (66)	41 (66)	0	0	
Polyarticular	3 (10)	21 (34)	21 (34)	0	0	
Mixed, n (%)	13 (15)	24 (14)	24 (25)	0	0	0.950
Disease duration, mos						
Overall	60.05 ± 54.66	43.21 ± 28.34	63.25 ± 14.65	67.33 ± 24.16	23.26 ± 4.15	0.001
UC	76.28 ± 49.87					< 0.001
CD	51.98 ± 55.44					0.116
Dactylitis, n (%)						
Overall	4 (4.5)	30 (17.4)	22 (22.6)	4 (8.5)	4 (12.5)	0.008
UC	1/29 (3.4)					
CD	3/59 (5.1)					
IBD/psoriasis+	3/14 (21.4)					0.960
IBD/psoriasis-negative	1/74 (1.3)					0.001
Enthesitis, n (%)						
Overall	16 (18.1)	78 (44.3)	55 (56.7)	11 (23.4)	12 (37.5)	< 0.001
UC	2 (6.9)					< 0.001
CD	14 (23.7)					0.008
IBD/psoriasis+	7 (50)					0.895
IBD/psoriasis-negative	9 (12.1)					< 0.001
Anterior uveitis, n (%)						
Overall	3 (3.4)	26 (14.7)	11 (11.3)	11 (23.4)	4 (11.4)	0.010
B27+	2 (66.6)	19/26 (73)	4/11 (36.3)	9/11 (81.8)	2/4 (50)	0.655
UC	1 (3.4)					0.169
CD	2 (3.3)					0.035
IBD/psoriasis+	0					0.253
IBD/psoriasis-negative	3 (4.0)					0.028
Followup, mos	96.23 ± 12.4	101.11 ± 34.22				0.456

IBD: inflammatory bowel disease; SpA: spondyloarthritis; PsA: psoriatic arthritis; AS: ankylosing spondylitis; axSpA: axial SpA; nr-axSpA: nonradiographic axSpA; UC: ulcerative colitis; CD: Crohn disease.

been evaluated in patients with AS and with PsA, showing some differences between the 2 diseases. One or more episodes of dactylitis occurred in 294 out of 736 patients (39%) with PsA described by Gladman, *et al*[2]. In a large cohort of patients with SpA included in the RESPONDIA database, dactylitis was observed in 42% of psoriatic spondylitis and in 8% of AS cases ($p < 0.05$), while no significant difference was recorded for enthesitis occurrence[10]. Similarly, dactylitis was recorded in 6.3% of 236 patients with AS in the German Spondyloarthritis Inception Cohort[3].

The frequency of dactylitis and enthesitis in patients with IBD-SpA has been poorly investigated and its prevalence has been reported with conflicting results. None of the clinical series published during the 1970s indicated the occurrence of this feature, and in more recent publications, dactylitis prevalence was recorded in only 8 out of 14 studies[8,9,10,11,12,13,15,17]. With the exception of 2 clinical series of 45 and 46 IBD-SpA patients in whom dactylitis occurred in 15.5% and 15.2% of the cases[10,15], respectively, in the remaining reports the frequency was lower than in

Table 3. Frequency of dactylitis, enthesitis, anterior uveitis, and HLA-B27 positivity in patients with IBD-SpA with and without coexistent psoriasis. Data are n (%) unless otherwise indicated.

Clinical Feature	Overall UC-SpA	Overall CD-SpA	p	IBD-SpA with Psoriasis	IBD-SpA without Psoriasis	p
No. patients	29	59		14	74	
Dactylitis	1 (3.4)	3 (5.1)	0.843	3 (21.4)	1 (1.3)	0.009
Enthesitis	2 (6.9)	14 (23.7)	0.103	7 (50)	9 (12.1)	0.003
Anterior uveitis	1 (3.4)	2 (3.3)	0.541	0	3 (4.0)	0.95
HLA-B27+	1 (3.4)	9 (15.2)	0.199	2 (14.2)	8 (10.8)	0.969

UC: ulcerative colitis; CD: Crohn disease; SpA: spondyloarthritis; IBD: inflammatory bowel disease.

other SpA, ranging from 0% to 5.6%[8,9,10,11,12,13,17]. According to the results of studies reporting a low frequency of dactylitis in IBD-SpA, in our case-control study of 88 patients this features was recorded in 4.5% of the cases, with a significant difference in comparison with patients with other types of SpA (p = 0.008). The higher frequency of dactylitis reported in 2 previously cited studies[10,15] may be attributable to the different selection of patients and to the different study design. Indeed, in contrast to our report, in which all clinical patterns of IBD-SpA were considered and dactylitis diagnosis was accepted only if observed by a rheumatologist, in the study by Pérez Alamino, *et al*[10], only patients with IBD-SpA satisfying the modified New York criteria for AS[33] were included, and the questionnaire-based survey of Kamo, *et al*[15] may have overestimated the occurrence of sausage digit. Because dactylitis may occur at diagnosis or complicate the SpA disease course, an adjunctive, confounding item may be related to the different length of disease duration and of followup. Confirming this concept, no episodes of dactylitis were recorded in a clinical series of 90 IBD-SpA with a relatively short followup of 20 months[8], while in other studies with a longer followup duration this feature was observed in 4.4% and 6.8% of the cases[9,13]. Of note, in most reports the followup duration was not indicated[10,11,12,14,15,17]. The mean followup duration of 96 months in our cohort of patients with IBD-SpA seems to be adequate for the assessment of dactylitis frequency and confirms that this feature is significantly less frequent compared with patients with AS, PsA, and nr-axSpA.

Similarly to dactylitis, enthesitis occurrence was reported with largely variable percentages, ranging from 12.5% to 90% of the cases (Table 1A and 1B). However, these results may be biased by the different assessment of enthesitis. In several studies, only Achilles enthesitis and plantar fasciitis were evaluated[9,12,13,20,21]. The assessment method was not specified in 2 studies[8,11], the Maastricht Ankylosing Spondylitis Enthesitis Score[34] was used in 1 study[10], and ultrasonography in another[18], while enthesitis occurrence was evaluated by a questionnaire-based study in 2[15,17]. In our clinical series, enthesitis was assessed using the LEI and it was significantly less frequent among controls (18.1% vs 44.3%; p < 0.001). This frequency is similar to that reported in other studies[10,11,17,19], even if a different assessment method was used.

In accord with other studies[26,27], 14 case patients (16%) in our cohort had associated psoriasis, a frequency higher than the estimated prevalence of 2.1% in the general population in Italy[35]. Of note, 3 out 4 cases of dactylitis and 7 out of 16 (43.7%) of enthesitis were observed in patients with IBD-SpA who also satisfied the ClASsification for Psoriatic ARthritis (CASPAR) criteria for PsA[36]. As shown in Table 3, in this subgroup the frequency of the 2 clinical features was not different compared with controls. In a clinical series of 40 patients with IBD-SpA by de Vlam, *et al*[11], the percentage of patients with coexistent psoriasis was not indicated, but psoriasis was associated in 4 of 103 patients (3.88%) with IBD, and although not precisely reported, other patients had a family history of psoriasis. Similarly, psoriasis was present in 5% of 160 patients with IBD described by Salvarani, *et al*[12], and 4 (4.5%) of patients with IBD-SpA reported by Palm, *et al*[13]. Twenty-three (31.2%) of 72 patients of the 2 studies of Shivashankar, *et al*[20,21] met the classification criteria for PsA. Therefore, in most clinical series the coexistence of psoriasis with no extrapolation of the cases of SpA associated with both IBD and the skin disease may have led to overestimating the frequency of dactylitis and enthesitis in IBD-SpA.

Compared with other reports[8,19,20,21], in our cohort of patients with IBD-SpA, AU was observed in a low percentage of subjects (3.4%). Given the well-known association between AU occurrence and B27 positivity[23], this result may reflect the low prevalence of B27 in our patients (11.3%). Confirming our data, AU frequency was 2.4% in 82 patients described by Palm, *et al*[13], in whom B27 positivity was 9.8%, whereas in the report of Turkcapar, *et al*[8], AU was observed in 33.3% of 90 patients, of whom 47 (52.2%) were B27-positive.

The results of our case-control study show that dactylitis, enthesitis, and AU are significantly less frequent in IBD-SpA compared with other types of SpA. Owing to the frequent association of psoriasis with IBD, and especially with CD, the coexistence of skin disease should be taken into account when evaluating the prevalence of dactylitis and enthesitis in patients with IBD-SpA. As expected, the low occurrence of AU was attributable to the low percentage of B27-positive subjects.

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