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Clinical characteristics of patients with spondyloarthritis and inflammatory bowel disease versus inflammatory bowel disease-related arthritis

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Abstract

The purpose of this study was to clarify the clinical characteristics of spondyloarthritis (SpA) patients with inflammatory bowel disease (IBD) compared to those without IBD. Furthermore, among patients with SpA and IBD, we aimed to clarify what clinical characteristics lead rheumatologists to diagnose "IBD-related arthritis." Utilizing SpA and psoriatic arthritis (PsA) patients' data from an international, cross-sectional, observational study, we analyzed information on demographics and disease characteristics, dichotomizing patients by IBD status. The presence or absence of IBD was determined based on data collection of treating rheumatologists. Patients with SpA (including PsA) and IBD were also categorized based on treating rheumatologists' definitive diagnosis in regard to SpA type, and compared by whether the patients had IBD-related arthritis or not. Among 4465 SpA patients, 287 (6.4%, 95%CI 5.7–7.2%) were identified with IBD. Compared to SpA patients without IBD, patients with SpA and IBD had a longer diagnostic delay (5.1 vs. 2.9 years, $p < 0.001$). In patients with SpA and IBD, 111 (38.7%, 95%CI 33.0–44.6%) were diagnosed with IBD-related arthritis. Multivariable analyses showed that HLA-B27 positivity [OR = 0.35, (95%CI 0.15–0.80)], psoriasis [OR = 0.14, (95%CI 0.04–0.50)], IBD as first symptom of SpA [OR = 3.32, (95%CI 1.84–6.01)], and need for IBD-specific treatment [OR = 5.41, (95%CI 2.02–14.50)] were independently associated with the definitive diagnosis of IBD-related arthritis. Collaboration with gastroenterologists is needed to shorten the diagnostic delay in patients with SpA and IBD. The recognition of the factors for the diagnosis of "IBD-related arthritis" may lead to the elucidation of the pathogenesis.

Keywords Spondyloarthritis · Inflammatory bowel disease · Inflammatory bowel disease-related arthritis · Psoriatic arthritis

Introduction

Inflammatory bowel disease (IBD) is observed in 5–10% of spondyloarthritis (SpA) patients [1, 2]. Since the prevalence of IBD in the general population is estimated to be 0.2–0.5% [3], SpA patients demonstrate a substantially higher prevalence of IBD; 46.2% of SpA patients are reported to have microscopic gut inflammation [4]. Musculoskeletal manifestations are the most common extra-intestinal manifestations, affecting 6–48% of IBD patients [5, 6], and SpA occurs in up to 13% of patients with IBD [7].

It has been reported that gut inflammation is linked to degree of bone marrow edema in sacroiliac joints in patients with axial SpA [8]. SpA patients with concomitant IBD may have more severe disease requiring intensified treatment [9]. However, the clinical characteristics of patients with SpA and IBD have not been investigated in a large cohort. Clarifying the clinical characteristics of patients with SpA and IBD would provide rheumatologists with a better

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understanding of SpA with concomitant IBD and potentially help identify these patients earlier. To this end, it may also be useful for rheumatologists to compare the management of patients with SpA and IBD, as it is performed internationally, against their own current practice.

Rheumatologists face many challenges in the management of IBD-related arthritis, including diagnosis, differential diagnosis, and selection of appropriate treatment. Though the definitive diagnosis of SpA and its subtypes are largely rheumatologist-driven, there are no sufficiently detailed descriptions regarding what constellation of clinical symptoms would prompt a rheumatologist to diagnose IBD-related arthritis among those patients with SpA who also have a concurrent or past history of IBD. In patients with SpA and IBD, IBD-related arthritis and other SpA subtypes may be different aspects of a single disease versus two distinct disease entities; this can only be explored and clarified in a large international cohort in which the definitive diagnosis of treating rheumatologists is known. If there are some shared characteristics of patients diagnosed with IBD-related arthritis by their treating rheumatologists, the recognition of these characteristics may lead to the elucidation of the pathogenesis, as in the case of the similarly close but differentiated axial spondyloarthritis (axSpA) versus axial psoriatic arthritis (axial PsA) [10, 11]. For example, differences in demographics, clinical presentations, imaging findings, genetic background, and treatment response have been reported for axial PsA in comparison to axSpA; and understanding of these differences has led to evidence that, in contrast to axial SpA, the interleukin (IL)-23/17 pathway is an important driver of inflammation in axial PsA [11]. Similarly, the purpose of this study is first to clarify the clinical characteristics of SpA patients with versus without IBD, and then to explore what clinical characteristics lead rheumatologists to apply the diagnostic label of IBD-related arthritis.

Methods

Study population and design

We utilized data from the Assessment in SpondyloArthritis international Society—Peripheral involvement in SpondyloArthritis (ASAS-PerSpA) study, an international, multicenter, cross-sectional, observational study involving 24 countries including Africa, America, Asia, and Europe [12]. Patients were recruited consecutively from July 2018 to February 2020 based on a rheumatologist's diagnosis of SpA. The initial aim of ASAS-PerSpA study was to characterize peripheral musculoskeletal involvement in patients with SpA across the world. To ensure appropriate international patient representation, the ASAS-PerSpA Scientific Committee selected national principal investigators from collaborating countries, each of whom invited rheumatologists in their country to participate in the study.

As a predefined inclusion criteria, patients aged ≥ 18 years, with a diagnosis of axSpA, peripheral SpA (pSpA), or psoriatic arthritis (PsA) per clinical diagnosis of treating rheumatologists, and able to give written consent and complete the study questionnaire, were enrolled. Although PsA is a heterogeneous disease, we included any patients with a clinical diagnosis of PsA to best capture the full range of clinical characteristics associated with SpA (including PsA) concomitant with IBD; for this purpose, it was considered appropriate to include all subtypes of PsA in the study. ASAS-PerSpA study was conducted according to the guidelines for Good Clinical Practice and was approved by the ethical committees in all participating countries. Written informed consent was obtained from all subjects before enrollment.

Data collection

A specific case report form was used to collect data. Patient information was collected by a study investigator or research nurse during a face-to-face patient interview at each study site. Medical records were also examined for further information.

Demographic data included country, age, sex, smoking, alcohol intake, and the highest level of education completed. Regarding disease characteristics, we collected the type of SpA per local investigator's diagnosis: radiographic axial SpA (r-axSpA, ankylosing spondylitis: AS); non-radiographic axial SpA (nr-axSpA); pSpA; PsA; reactive arthritis (ReA); IBD-related arthritis; juvenile SpA; or other type of SpA. Additional collected data included date of SpA diagnosis; date of first symptom of SpA; first degree or second degree relative with r-axSpA/AS, psoriasis, uveitis, ReA or IBD; elevated C-reactive protein (CRP) in presence of back pain; Human Leukocyte Antigen-B27 (HLA-B27) status; inflammatory back pain; and sacroiliitis on radiographs or magnetic resonance imaging (MRI).

Diagnostic delay was defined as the difference between the date of SpA diagnosis and the date of first symptom. The date of first symptom of SpA was recorded on the standardized case reporting form in the medical chart, recorded by each treating rheumatologists involved in the study. Radiographs and MRIs were performed in patients if clinically indicated as determined by the treating rheumatologist. Each patient was assessed by their treating rheumatologist to determine if they met the Assessment in SpondyloArthritis international Society (ASAS) axial criteria [13], the ASAS peripheral criteria [14], or the ClASsification criteria for Psoriatic ARthritis (CASPAR) criteria [15]. History or presence of axial involvement, "root joint"

(i.e., hip and shoulder) involvement, and peripheral manifestations (including arthritis, enthesitis, or dactylitis) were also collected. In addition, extra-musculoskeletal manifestations including psoriasis, IBD or uveitis, and the presence of fibromyalgia were collected as well. The presence or absence of IBD was determined based on the following yes/no questions on the case report form: "History of Crohn's disease or ulcerative colitis diagnosed by a Doctor" in the diagnosis section, and "IBD" in the extra-musculoskeletal manifestations section. The answers to these questions were provided by treating rheumatologists based on their chart reviews and medical histories, taken from their own patients during actual clinical practice. In addition, the case report form included the question "Has this IBD been confirmed by endoscopy?" Information on specific treatments for IBD was also collected. Gastroenterologists and other specialists were not directly involved in completing or confirming case report forms.

Clinimetric information included Patient Global Assessment [scored according to the following question, expressed as 0 (best) to 10 (worst): "Considering all the ways in which spondyloarthritis has affected you in the last week, please circle the number that best describes your condition"]; the Ankylosing Spondylitis Disease Activity Score-C-reactive protein (ASDAS-CRP: an index to assess disease activity in ankylosing spondylitis patients) [16]; the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI: an index to assess disease activity in ankylosing spondylitis) [17]; the Bath Ankylosing Spondylitis Functional Index (BASFI: an index to assess the degree of functional limitation in patients with ankylosing spondylitis) [18]; and the Assessment of SpondyloArthritis international Society Health Index (ASAS-HI: an index to assess the impact of SpA and its treatment on functioning and health in SpA patients) [19]. Regarding treatments, current treatment with non-steroidal anti-inflammatory drugs (NSAIDs) and corticosteroids, and any history or current treatment with conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs: methotrexate, leflunomide, salazopyrine, hydroxychloroquine, gold salts, azathioprine, sulfasalazine, cyclosporine), biologic disease-modifying anti-rheumatic drugs (bDMARDs: adalimumab, etanercept, infliximab, certolizumab, golimumab, abatacept, rituximab, tocilizumab, bimekizumab, secukinumab, ixekizumab, ustekinumab, vedolizumab), and targeted synthetic disease-modifying anti-rheumatic drugs (tsDMARDs: apremilast, baricitinib, tofacitinib, upadacitinib and filgotinib) were collected.

Patient group definition

Flow diagram of patient categorization is shown in Fig. 1. SpA (including PsA) patients with and without IBD were divided per treating rheumatologist assessment. The definitive diagnosis of IBD-related arthritis in regard to SpA type was made by the treating rheumatologists and reported on the standardized case reporting form. At the beginning of the case reporting form, rheumatologists provided the most applicable clinical diagnosis, choosing between axSpA, pSpA, or PsA. This was followed by a question asking for definitive diagnosis ("In your opinion, which disease better describes your patient?") with answer options including r-axSpA; nr-axSpA; pSpA; PsA; ReA; IBD-related arthritis; juvenile SpA; or other type of SpA. For the purposes of this study, SpA type was categorized per the answer to this question. All SpA types, excluding IBD-related arthritis, were then categorized as "other SpA with IBD." We further grouped patients based on their region as follows: Latin America (Argentina, Chile, Colombia and Mexico), Asia (China, India, Japan, South Korea, and Taiwan), Europe and North America (Canada, France, Germany, Hungary, Italy, the Netherlands, Portugal, Romania, Spain, the UK, and the US), and Middle East and North Africa (Egypt, Lebanon, Morocco and Turkey).

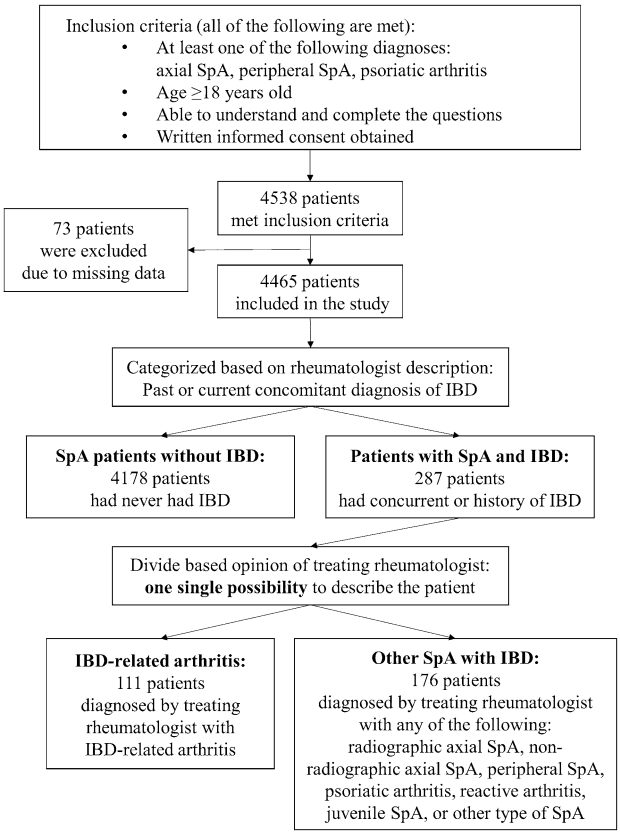

Fig. 1 A flow diagram: method of grouping patients. *SpA* spondyloarthritis, *IBD* inflammatory bowel disease

Statistical analyses

Statistical information on patient demographics, disease characteristics, diagnosis, and treatment was compared between SpA (including PsA) patients with and without IBD. Patients with SpA (including PsA) and IBD were also compared by dividing them into two groups; those specifically carrying a diagnosis of IBD-related arthritis versus other SpA patients with IBD. IBD-related arthritis patients were further compared by region.

In descriptive statistics, categorical variables were presented as number (with percentage) and continuous variables as median (with interquartile range [IQR]) considering non-normal distribution. Chi-square or Fisher's exact test was used to compare categorical variables as appropriate. To analyze differences in continuous variables, Wilcoxon rank-sum test and Kruskal–Wallis test were used as appropriate.

Additionally, associations between clinical features and the definitive diagnosis of SpA (IBD-related arthritis patients versus other SpA patients with IBD) were analyzed using univariable and multivariable logistic regression models. We searched previous studies to determine variables for inclusion in the multivariate analysis, but as far as we could find, no previous studies had compared IBD-related arthritis to other SpA with IBD. As such, after discussion between authors, clinical characteristics that a practicing rheumatologist might typically consider when determining a definitive diagnosis were included in the multivariate logistic regression models. Variables included age at SpA diagnosis; male gender; HLA-B27 positivity ("positive" versus "negative or not available"); presence of axial involvement, root joint involvement, peripheral arthritis, enthesitis, dactylitis, psoriasis, and uveitis; IBD as first symptom of Spa; and need for IBD-specific treatment.

For all analyses, a p value < 0.05 was considered statistically significant. All analyses were performed using R (version 4.0.2), using the tableone package for tables [20] and Easy R (version 1.52), a graphical user interface for R [21].

Results

Clinical characteristics of patients with SpA and IBD

Among 4465 SpA patients included in the study, 287 (6.4% of total SpA patients, 95%CI 5.7–7.2%) were identified with IBD. The overall characteristics of SpA patients with IBD compared to those without IBD are summarized in Table 1. Compared to SpA patients without IBD, those with IBD were less likely to be male (54.0 vs. 61.5%, $p = 0.014$), more likely to experience diagnostic delay (5.1 vs. 2.9 years, $p < 0.001$), and more frequently reported a family history of IBD (14.6 vs. 2.3%, $p < 0.001$). In addition, those with IBD were less likely to be HLA-B27-positive (37.2 vs. 68.0%, $p < 0.001$), and more frequently had inflammatory back pain (79.8 vs. 74.0%, $p = 0.036$). Sacroiliitis on radiograph and MRI was similar in both groups. Regarding the fulfillment of classification criteria for SpA, although there was no difference in total number of axSpA, significantly more patients with SpA and IBD met the imaging arm only of the ASAS axial criteria (46.3 vs. 27.0%, $p < 0.001$), while fewer met the ASAS peripheral criteria (8.0 vs. 12.7%, $p = 0.024$). In addition, fewer patients with SpA and IBD met the CASPAR criteria (7.0 vs. 24.5%, $p < 0.001$).

As for clinical characteristics, axial involvement and root joint involvement were similar in those with or without IBD. Among SpA patients with IBD, there was a higher prevalence of oligoarthritis (33.4 vs. 24.7%, $p = 0.001$) and a lower prevalence of dactylitis (9.1 vs. 15.8%, $p = 0.003$), compared to those without IBD. Psoriasis was less common in SpA patients with IBD (13.2 vs 31.6%, $p \leq 0.001$). Indicators of disease activity and functional impairment were comparable in both groups. Regarding the first symptom of SpA, axial involvement (49.5 vs. 57.9%, $p = 0.006$), peripheral arthritis (13.9 vs. 22.6%, $p = 0.001$) and psoriasis (4.5 vs. 20.4%, $p \leq 0.001$) were less common in patients with SpA and IBD. IBD appeared as the first symptom in 39.7% of SpA patients with IBD and was endoscopically confirmed as IBD in 90.9% of these patients.

Regarding treatments ever used, among SpA patients with IBD, csDMARD (88.5 vs. 65.4%, $p < 0.001$), salazosulfapyridine (43.9 vs. 37.1%, $p = 0.025$), bDMARD (70.4 vs. 53.3%, $p \leq 0.001$) and tumor necrosis factor (TNF) inhibitor (69.3vs. 49.7%, $p < 0.001$) were used more commonly than in those without IBD, while methotrexate (26.5 vs. 34.5%, $p = 0.007$), IL-17 inhibitors (2.8 vs. 8.4%, $p < 0.001$) and tsDMARDs (0.0 vs. 2.4%, $p = 0.003$) were used less frequently. Regarding current treatment, in patients with SpA and IBD, salazosulfapyridine (23.3 vs. 18.2%, $p = 0.036$), bDMARD (59.6 vs. 43.8%, $p \leq 0.001$) and TNF inhibitor (55.4 vs. 36.6%, $p < 0.001$) use was more common, while NSAID (41.5 vs. 69.5%, $p < 0.001$), methotrexate (10.1 vs. 17.9%, $p = 0.001$), IL-17 inhibitor (1.0 vs. 6.3%, $p < 0.001$) and tsDMARD (0.0 vs. 1.7%, $p = 0.014$) use was less common.

Clinical characteristics of IBD-related arthritis patients compared to other SpA patients with IBD

Patients with SpA and IBD ($n = 287$) were categorized by their respective rheumatologist-driven clinical diagnoses; 111 (38.7% of SpA patients with IBD, 95%CI 33.0–44.6%) were given a diagnosis of IBD-related arthritis (Figs. 1 and 2). Other diagnoses conferred included r-axSpA/AS ($n = 98$, 34.1%), nr-axSpA ($n = 38$, 13.2%), pSpA ($n = 27$, 9.4%), PsA ($n = 8$, 2.8%), ReA ($n = 2$, 0.7%), juvenile SpA ($n = 2$, 0.2%), and other type of SpA ($n = 1$, 0.3%).

Table 1 Characteristics of patients with SpA and IBD compared to SpA patients without IBD

	Patients with SpA and IBD	SpA patients without IBD	*p* value
N	287	4178	
Male	155 (54.0)	2569 (61.5)	**0.014**
Age at study visit (years)	45.0 [34.0, 56.0]	44.0 [33.0, 55.0]	0.22
Age at SpA diagnosis (years)	36.0 [26.5, 48.0]	35.0 [26.0, 46.0]	0.12
Age at first symptom (years)	27.0 [19.0, 37.0]	28.0 [20.0, 39.0]	0.36
Diagnostic delay (years)	5.1 [1.3, 12.0]	2.9 [0.6, 9.0]	**<0.001**
University education	117 (40.8)	1698 (40.6)	1
Smoking (Ever)	118 (41.1)	1786 (42.7)	0.63
Alcohol (Ever)	102 (35.5)	1713 (41.0)	0.08
Family history of SpA	97 (33.8)	1435 (34.3)	0.9
Family history of IBD	42 (14.6)	96 (2.3)	**<0.001**
CRP elevation in presence of back pain	191 (66.6)	2766 (66.2)	0.96
HLA-B27 measured	183 (63.8)	2937 (70.3)	**0.023**
HLA-B27-positive among measured	68 (37.2)	1998 (68.0)	**<0.001**
Inflammatory back pain	229 (79.8)	3093 (74.0)	**0.036**
Radiographic sacroiliitis	163 (56.8)	2354 (56.3)	0.93
MRI of sacroiliac joint tested	194 (67.6)	2614 (62.6)	0.10
Sacroiliitis on MRI among tested	130 (67.0)	1687 (64.5)	0.54
ASAS axial criteria			
Total	195 (67.9)	2715 (65.0)	0.34
Clinical arm only	8 (2.8)	186 (4.5)	0.23
Imaging arm only	133 (46.3)	1126 (27.0)	**<0.001**
ASAS peripheral criteria	23 (8.0)	532 (12.7)	**0.024**
CASPAR criteria	20 (7.0)	1023 (24.5)	**<0.001**
Axial involvement			
Ever present	234 (81.5)	3194 (76.4)	0.057
As first symptom	142 (49.5)	2421 (57.9)	**0.006**
Root joint involvement			
Ever present	105 (36.6)	1398 (33.5)	0.31
As first symptom	1 (0.3)	22 (0.5)	1
Peripheral arthritis			
Ever present	169 (58.9)	2382 (57.0)	0.577
As first symptom	41 (14.3)	959 (23.0)	**0.001**
Monoarticular	14 (4.9)	283 (6.8)	0.26
Oligoarticular	96 (33.4)	1030 (24.7)	**0.001**
Polyarticular	59 (20.6)	1058 (25.3)	0.08
Enthesitis			
Ever present	139 (48.4)	2051 (49.1)	0.88
As first symptom	25 (8.7)	462 (11.1)	0.26
Dactylitis			
Ever present	26 (9.1)	659 (15.8)	**0.003**
As first symptom	3 (1.0)	110 (2.6)	0.12
Psoriasis			
Ever present	38 (13.2)	1321 (31.6)	**<0.001**
As first symptom	13 (4.5)	851 (20.4)	**<0.001**
Uveitis			
Ever present	59 (20.6)	703 (16.8)	0.12
As first symptom	10 (3.5)	182 (4.4)	0.65
Concomitant fibromyalgia	27 (9.4)	373 (8.9)	0.87
IBD			
Ever present	287 (100.0)	0 (0.0)	**<0.001**

Table 1 (continued)

	Patients with SpA and IBD	SpA patients without IBD	*p* value
As first symptom	114 (39.7)	0 (0.0)	**<0.001**
Confirmed by endoscopy	261 (90.9)	–	–
Patient Global Assessment	4.0 [2.0, 7.0]	4.0 [2.0, 7.0]	0.84
ASDAS-CRP	2.4 [1.7, 3.2]	2.5 [1.6, 3.3]	0.59
BASDAI	3.6 [1.8, 5.6]	3.6 [1.8, 5.8]	1
BASFI	2.8 [0.8, 5.0]	2.3 [0.6, 4.9]	0.24
ASAS HI	6.4 [3.0, 11.0]	6.0 [3.0, 10.0]	0.2
NSAIDs use			
Current	119 (41.5)	2905 (69.5)	**<0.001**
Corticosteroids use			
Current	43 (15.0)	495 (11.8)	0.14
csDMARDs use			
Ever	254 (88.5)	2733 (65.4)	**<0.001**
Current	104 (36.6)	1545 (37.0)	0.94
Salazosulfapyridine use			
Ever	126 (43.9)	1549 (37.1)	**0.025**
Current	67 (23.3)	760 (18.2)	**0.036**
Methotrexate use			
Ever	76 (26.5)	1441 (34.5)	**0.007**
Current	29 (10.1)	747 (17.9)	**0.001**
bDMARDs use			
Ever	202 (70.4)	2226 (53.3)	**<0.001**
Current	171 (59.6)	1831 (43.8)	**<0.001**
TNF inhibitors use			
Ever	199 (69.3)	2077 (49.7)	**<0.001**
Current	159 (55.4)	1531 (36.6)	**<0.001**
IL-17 inhibitors use			
Ever	8 (2.8)	351 (8.4)	**<0.001**
Current	3 (1.0)	264 (6.3)	**<0.001**
tsDMARDs use			
Ever	0 (0.0)	99 (2.4)	**0.003**
Current	0 (0.0)	71(1.7)	**0.014**

Values are expressed as *n* (%) or median (IQR) unless otherwise indicated

Statistically significant differences are bolded ($p < 0.05$)

SpA spondyloarthritis, *IBD* inflammatory bowel disease, *HLA* human leukocyte antigen, *ASAS* Assessment of SpondyloArthritis international Society, *ASDAS-CRP* Ankylosing spondylitis disease activity score with CRP, *BASDAI* Bath ankylosing spondylitis disease activity index, *BASFI* Bath ankylosing spondylitis functional index, *ASAS-HI* ASAS Health Index, *NSAID* nonsteroidal anti-inflammatory drug, *DMARD* disease-modifying anti-rheumatic drug, *csDMARDs* conventional synthetic DMARDs, *bDMARDs* biological DMARDs

Differences in characteristics of IBD-related arthritis versus other SpA patients with IBD are shown in Table 2. IBD-related arthritis patients were older at both SpA diagnosis (41.0 vs. 34.0 years, $p=0.004$) and at manifestation of first symptom (29.0 vs. 26.0 years, $p=0.008$) compared to those categorized as other SpA with IBD. Family history of SpA (24.3 vs. 39.8%, $p=0.010$), CRP elevation (in presence of back pain) (54.1 vs. 74.4%, $p=0.001$), and HLA-B27 positivity (19.3 vs. 45.2%, $p=0.001$) were less common in IBD-related arthritis patients. Inflammatory back pain (66.7 vs. 88.1%, $p<0.001$), and sacroiliitis on radiograph (45.0 vs. 64.2%, $p=0.002$) and MRI (55.2 vs. 73.2%, $p=0.018$) were also less common in IBD-related arthritis patients. Regarding the fulfillment of ASAS classification criteria for SpA, fewer IBD-related arthritis patients met the ASAS axial criteria (51.4 vs. 78.4%, $p<0.001$), while more met the ASAS peripheral criteria (12.6 vs. 5.1%, $p=0.027$).

As for clinical characteristics, axial involvement (68.5 vs. 89.8%, $p<0.001$) was less common in IBD-related arthritis patients versus other SpA patients with IBD. In

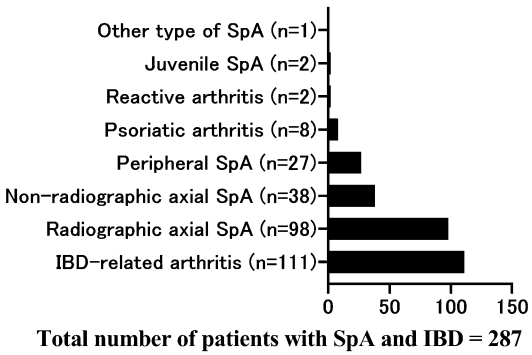

Fig. 2 Definitive diagnosis of patients with SpA and IBD by rheumatologists. *SpA* spondyloarthritis, *IBD* inflammatory bowel disease

contrast, peripheral arthritis was more common (69.4 vs. 52.3%, $p = 0.006$) among IBD-related arthritis patients, especially with regard to oligoarthritis (42.3 vs. 27.8%, $p = 0.016$). Fewer IBD-related arthritis patients had psoriasis (3.6 vs. 19.3%, $p < 0.001$). Receipt of specific treatment for IBD [including steroid enema, 5-aminosalicylic acid (ASA) compounds, or surgery] (94.6 vs. 75.6%, $p < 0.001$) and 5-ASA compound use (83.8 vs. 52.8%, $p < 0.001$) were more common in IBD-related arthritis patients compared to other SpA with IBD patients. IBD-related arthritis patients had a higher rate of endoscopically confirmed IBD (96.4 vs. 87.5%, $p = 0.042$). Indicators of disease activity and ASAS-HI did not differ between the two groups; however, BASFI was lower in IBD-related arthritis patients. For the first symptom of SpA, IBD-related arthritis patients were less likely to have axial involvement (31.5 vs. 61.8%, $p < 0.001$) and psoriasis (0.9 vs. 6.8%, $p = 0.019$), and more likely to have IBD (63.1 vs. 25.0%, $p < 0.001$).

In terms of treatments ever used, among IBD-related arthritis patients, csDMARD (97.3 vs. 83.0%, $p < 0.001$) use was more common, while IL-17 inhibitor (0.0 vs. 4.5%, $p = 0.025$) use was less, compared to other SpA patients with IBD. Regarding current treatments, csDMARD (50.5 vs. 27.3%, $p < 0.001$) and salazosulfapyridine (32.4 vs. 17.6%, $p = 0.006$) use was more common in IBD-related arthritis patients, while bDMARD (50.5 vs. 65.3%, $p = 0.017$) and TNF inhibitor (46.8 vs. 60.8%, $p = 0.028$) use was less frequent.

Table 3 presents the logistic regression analysis comparing IBD-related arthritis patients to other SpA patients with IBD. Multivariable analyses demonstrated that HLA-B27 positivity [odds ratio (OR) = 0.35, (95%CI 0.15–0.80)], psoriasis [OR = 0.14, (95%CI 0.04–0.50)], IBD as first symptom of SpA [OR = 3.32, (95%CI 1.84–6.01)] and need for IBD-specific treatment [OR = 5.41, (95%CI 2.02–14.50)] were independently associated with a definitive diagnosis of IBD-related arthritis.

Difference in clinical characteristics of IBD-related arthritis by region

A comparison of IBD-related arthritis patients by region is shown in the Table 4. Although there was no significant difference, diagnostic delay tended to be longer in Asia. Fewer patients in Asia had radiographic sacroiliitis or sacroiliitis on MRI, and fewer met the ASAS axial criteria (both total and imaging arm only). Only patients in Europe and North America received a diagnosis of IBD-related arthritis in the presence of psoriasis. There were regional differences in indicators of disease activity and functional disability, with BASFI being particularly better in Asia. There were also regional differences in the treatment of IBD and SpA, though no significant regional differences in the overall use of csDMARD and bDMARD were identified.

Discussion

In this study, we clarified the clinical characteristics of SpA patients with concomitant IBD. To the best of our knowledge, this is the first worldwide study to characterize rheumatologist-diagnosed IBD-related arthritis in comparison with other SpA patients with IBD. Multivariable analyses showed that the absence of HLA-B27 positivity and psoriasis, the presence of IBD as first symptom of SpA, and need for IBD-specific treatment increased the likelihood that a rheumatologist would apply the diagnostic label of IBD-related arthritis to a patient. Distinguishing IBD-related arthritis patients from other SpA patients with IBD, as well as accumulating knowledge of IBD-related arthritis, may lead to more appropriate diagnoses and treatment.

In a comparison of SpA patients with IBD to those without IBD, proportions of men and women were nearly equal, despite 61% of SpA patients being male in the PerSpA study [12]. In a recent study reporting the incidence of IBD by age group, a gender difference was not seen in the 25–29 year old group, with 48.3 and 44.1% of men having ulcerative colitis and Crohn's disease, respectively [22]. The proportion of men and women among patients with SpA and IBD in our study was similar to those in IBD cohorts.

Diagnostic delay was longer in patients with SpA and IBD compared to those without IBD, and IBD was often the first symptom of SpA in these patients. Although screening tools have been developed to facilitate gastroenterology-driven recognition and diagnosis of SpA [23], more collaboration is needed to optimize timely referral to rheumatology clinics. Diagnostic delay may be mitigated by promoting

Table 2 Characteristics of IBD-related arthritis patients compared to other SpA patients with IBD

	IBD-related arthritis patients	Other SpA patients with IBD	*p* value
N	111	176	
Male	59 (53.2)	96 (54.5)	0.91
Age at study visit (years)	48.0 [34.5, 58.5]	44.0 [34.0, 53.0]	0.13
Age at SpA diagnosis (years)	41.0 [28.5, 52.0]	34.0 [25.0, 44.3]	**0.004**
Age at first symptom (years)	29.0 [23.0, 40.8]	26.0 [18.8, 34.3]	**0.008**
Diagnostic delay (years)	5.9 [1.4, 14.2]	5.1 [1.2, 11.6]	0.39
University education	50 (45.0)	67 (38.1)	0.3
Smoking (Ever)	45 (40.5)	73 (41.5)	0.97
Alcohol (Ever)	42 (37.8)	60 (34.1)	0.6
Family history of SpA	27 (24.3)	70 (39.8)	**0.010**
Family history of IBD	14 (12.6)	28 (15.9)	0.55
CRP elevation in presence of back pain	60 (54.1)	131 (74.4)	**0.001**
HLA-B27 measured	57 (51.4)	126 (71.6)	**0.001**
HLA-B27-positive among measured	11 (19.3)	57 (45.2)	**0.001**
Inflammatory back pain	74 (66.7)	155 (88.1)	**<0.001**
Radiographic sacroiliitis	50 (45.0)	113 (64.2)	**0.002**
MRI of sacroiliac joint tested	67 (60.4)	127 (72.2)	0.051
Sacroiliitis on MRI among tested	37 (55.2)	93 (73.2)	**0.018**
ASAS axial criteria			
Total	57 (51.4)	138 (78.4)	**<0.001**
Clinical arm only	3 (2.7)	5 (2.8)	1
Imaging arm only	49 (44.1)	84 (47.7)	0.64
ASAS peripheral criteria	14 (12.6)	9 (5.1)	**0.027**
Axial involvement			
Ever present	76(68.5)	158 (89.8)	**<0.001**
As first symptom	35 (31.5)	107 (60.8)	**<0.001**
Root involvement			
Ever present	42 (37.8)	63 (35.8)	0.82
As first symptom	0 (0.0)	1 (0.6)	1
Peripheral arthritis			
Ever present	77 (69.4)	92 (52.3)	**0.006**
As first symptom	14 (12.6)	27 (15.3)	0.638
Monoarticular	5 (4.5)	9 (5.1)	1
Oligoarticular	47 (42.3)	49 (27.8)	**0.016**
Polyarticular	25 (22.5)	34 (19.3)	0.61
Enthesitis			
Ever present	56 (50.5)	83 (47.2)	0.67
As first symptom	11 (9.9)	14 (8.0)	0.72
Dactylitis			
Ever present	10 (9.0)	16 (9.1)	1
As first symptom	1 (0.9)	2 (1.1)	1
Psoriasis			
Ever present	4 (3.6)	34 (19.3)	**<0.001**
As first symptom	1 (0.9)	12 (6.8)	**0.019**
Uveitis			
Ever present	18 (16.2)	41 (23.3)	0.2
As first symptom	4 (3.6)	6 (3.4)	1
Concomitant fibromyalgia	7 (6.3)	20 (11.4)	0.21
IBD			
Ever present	111 (100.0)	176 (100.0)	NA

Table 2 (continued)

	IBD-related arthritis patients	Other SpA patients with IBD	*p* value
As first symptom	70 (63.1)	44 (25.0)	**<0.001**
Confirmed by endoscopy	107 (96.4)	154 (87.5)	**0.042**
Specific treatment	105 (94.6)	133 (75.6)	**<0.001**
Steroid enema	26 (23.4)	29 (16.5)	0.19
5-ASA compounds	93 (83.8)	93 (52.8)	**<0.001**
Surgery	20 (18.0)	14 (8.0)	**0.017**
Patient Global Assessment	4.0 [2.0, 6.0]	5.0 [2.0, 7.0]	0.21
ASDAS-CRP	2.3 [1.6, 2.9]	2.5 [1.7, 3.4]	0.11
BASDAI	3.2 [1.7, 5.3]	3.8 [2.2, 6.0]	0.15
BASFI	2.2 [0.3, 4.6]	3.0 [1.1, 5.6]	**0.044**
ASAS HI	6.0 [3.0, 10.1]	7.0 [3.0, 11.3]	0.18
NSAIDs use			
Current	47 (42.3)	72 (40.9)	0.9
Corticosteroids use			
Current	19 (17.1)	24 (13.6)	0.5
csDMARDs use			
Ever	108 (97.3)	146 (83.0)	**<0.001**
Current	56 (50.5)	48 (27.3)	**<0.001**
Salazosulfapyridine use			
Ever	54 (48.6)	72 (40.9)	0.24
Current	36 (32.4)	31 (17.6)	**0.006**
Methotrexate use			
Ever	26 (23.4)	50 (28.4)	0.43
Current	15 (13.5)	14 (8.0)	0.19
bDMARDs use			
Ever	74 (66.7)	137 (77.8)	0.051
Current	56 (50.5)	115 (65.3)	**0.017**
TNF inhibitors use			
Ever	69 (62.2)	130 (73.9)	0.050
IL-17 inhibitors use	52 (46.8)	107 (60.8)	**0.028**
Current			
Ever	0 (0.0)	8 (4.5)	**0.025**
Current	0 (0.0)	3 (1.7)	0.29

Values are expressed as *n* (%) or median (IQR) unless otherwise indicated. IBD-specific treatments include steroid enemas, 5-ASA compounds, oral corticosteroids, DMARDs for IBD, or surgery

Statistically significant differences are bolded ($p < 0.05$)

SpA spondyloarthritis, *IBD* inflammatory bowel disease, *HLA* human leukocyte antigen, *ASAS* Assessment of SpondyloArthritis international Society, *ASDAS-CRP* Ankylosing spondylitis disease activity score with CRP, *BASDAI* Bath ankylosing spondylitis disease activity index, *BASFI* Bath ankylosing spondylitis functional index, *ASAS-HI* ASAS Health Index, *NSAID* nonsteroidal anti-inflammatory drug, *DMARD* disease-modifying anti-rheumatic drug, *csDMARDs* conventional synthetic DMARDs, *bDMARDs* biological DMARDs

awareness among gastroenterologists of musculoskeletal manifestations, as well as by strengthening interdepartmental collaboration.

In this study, patients with SpA and IBD had less HLA-B27 positivity compared to SpA patients without IBD. Similarly, previous studies have indicated a higher frequency of IBD in HLA-B27-negative SpA patients compared to SpA patients who were HLA-B27-positive [24–26]. Our results corroborate these previous findings. It has been suggested that this may be due to facilitated classification of SpA in IBD patients with musculoskeletal manifestations via imaging arm only of the ASAS axial criteria, with little consideration of HLA-B27 status.

As for peripheral signs in those with SpA and IBD, oligoarthritis was more common compared to those without IBD, possibly due to the greater prevalence of type I (acute,

Table 3 Logistic regression analysis for the diagnosis of IBD-related arthritis (compared with other SpA with IBD)

Variable	Univariable			Multivariable		
	OR	95% CI	*p* value	OR	95% CI	*p* value
Age at SpA diagnosis	1.03	1.04–1.06	**0.003**	1.01	0.99–1.04	0.20
Male gender	0.95	0.59–1.52	0.82	1.31	0.72–2.37	0.37
HLA-B27 positivity	0.23	0.11–0.46	**<0.001**	0.35	0.15–0.80	**0.012**
Axial involvement	0.247	0.13–0.47	**<0.001**	0.46	0.21–1.00	0.051
Root joint involvement	1.09	0.67–1.79	0.73	0.84	0.46–1.54	0.58
Peripheral arthritis	2.07	1.25–3.41	**0.004**	1.41	0.74–2.70	0.30
Enthesitis	1.14	0.71–1.84	0.59	0.97	0.53–1.79	0.93
Dactylitis	0.99	0.43–2.27	0.98	2.15	0.71–6.53	0.18
Psoriasis	0.16	0.05–0.45	**<0.001**	0.14	0.04–0.50	**<0.001**
Uveitis	0.64	0.35–1.18	0.15	1.01	0.49–1.09	0.98
IBD as first symptom of SpA	5.12	3.06–8.57	**<0.001**	3.32	1.84–6.01	**<0.001**
Need for IBD-specific treatment	5.66	2.32–13.80	**<0.001**	5.41	2.02–14.50	**<0.001**

Statistically significant differences are bolded ($p < 0.05$)

SpA spondyloarthritis, *IBD* inflammatory bowel disease. IBD-specific treatments include steroid enemas, 5-ASA compounds, oral corticosteroids, DMARDs for IBD, or surgery

self-limiting, and oligoarthritis correlated with IBD activity) versus type II (chronic, polyarthritis without correlation to IBD activity) arthropathy [27]. The results of an analysis of 347 patients with SpA and IBD (Crohn's disease or ulcerative colitis) fulfilling axial or peripheral ASAS criteria showed a predominance of type I arthropathy; of 184 patients with pSpA, 57% had type I arthropathy versus 43% with type II arthropathy [28]. In our study, dactylitis was less frequent among patients with SpA and IBD compared to those without IBD. A previous case–control study, in which 88 patients with SpA and IBD who fulfilled axial or peripheral ASAS criteria were compared to 176 SpA patients without IBD, reported a significantly lower prevalence of dactylitis in patients with SpA and IBD (4.5%) than in those SpA patients without IBD (17.4%) ($p = 0.008$) [29]. The same study also reported that a significantly lower prevalence of enthesitis in patients with SpA and IBD (18.1%) compared to those without IBD (44.3%) ($p < 0.001$) [29]. In our study, there was no significant difference in enthesitis, but we noted a tendency for it to be less common in SpA patients with IBD.

In this study, psoriasis was less common in those SpA patients with IBD compared to those without IBD. Psoriasis has been reported to be more common in patients with SpA and IBD compared to the general population [29], and an increased incidence of IBD has also been reported in patients with PsA compared to those with psoriasis [30]. In the present study, the lower prevalence of psoriasis in patients with SpA and IBD may be simply due to the small proportion of PsA (per CASPAR criteria) among SpA patients with IBD.

NSAID use was less common in patients with SpA with IBD compared to those without IBD. This may have been due to fears of NSAID-induced IBD exacerbation precluding their use [31]. Some reports suggest that NSAIDs may exacerbate Crohn's disease, but not ulcerative colitis [32]. It has also been reported that the use of selective cyclooxygenase (COX) -2 inhibitors may not be associated with IBD flares [31]. In patients with SpA and IBD, the use of csDMARDs was higher, especially salazosulfapyridine. This is unsurprising, as salazosulfapyridine is widely used in the treatment of both SpA and IBD patients [33]. In contrast, the use of methotrexate was lower in SpA patients with IBD. Methotrexate has been reported to be useful in patients with Crohn's disease [34]; however, its effectiveness has not been proven in ulcerative colitis [35]; as such, it is likely to be less used in patients with SpA and IBD. Furthermore, the relative infrequency of PsA among SpA patients with IBD in our study population may also have resulted in lower use of methotrexate. In patients with SpA and IBD, bDMARD use was higher than in those without IBD, and TNF inhibitor use was particularly higher. TNF inhibitors are also commonly used to treat both IBD and SpA. In addition, the use of IL-17 inhibitors, which has been reported to exacerbate IBD [36–38], was unsurprisingly less common in patients with SpA and IBD.

Regarding comparison of patients carrying a specific diagnosis of IBD-related arthritis versus those patients with other types of SpA and concomitant IBD ("other SpA with IBD"), we were unable to find any previously reports that discussed this distinction, despite the potential for these to be two separate clinical entities. This is the first study to report that the lack of HLA-B27 positivity, the lack of psoriasis, as well as the occurrence of IBD as a first symptom of SpA and need for IBD-specific treatments increases the probability of a diagnosis of IBD-related arthritis. We

Table 4 Regional difference among IBD-related arthritis

	Latin America	Asia	Europe and North America	Middle East and North Africa	*p* value
N	16	28	27	40	
Male	9 (56.2)	14 (50.0)	14 (51.9)	22 (55.0)	0.97
Age at study visit (years)	48.5 [41.0, 54.5]	48.5 [40.0, 59.8]	54.0 [37.5, 61.5]	41.0 [33.3, 55.3]	0.12
Age at SpA diagnosis (years)	44.0 [31.0, 48.3]	47.0 [34.8, 55.0]	40.0 [27.5, 50.0]	34.5 [25.8, 50.3]	0.17
Age at first symptom (years)	35.5 [27.3, 42.8]	29.0 [21.5, 44.5]	27.0 [22.0, 42.0]	29.0 [23.8, 37.3]	0.39
Diagnostic delay (years)	2.84 [0.82, 9.61]	11.09 [2.46, 17.60]	5.00 [2.37, 11.97]	4.84 [1.90, 12.26]	0.25
University education	3 (18.8)	17 (60.7)	16 (59.3)	14 (35.0)	**0.011**
Smoking (Ever)	8 (50.0)	9 (32.1)	16 (59.3)	12 (30.0)	0.07
Alcohol (Ever)	10 (62.5)	16 (57.1)	7 (25.9)	9 (22.5)	**0.003**
Family history of SpA	3 (18.8)	4 (14.3)	10 (37.0)	10 (25.0)	0.27
Family history of IBD	2 (12.5)	4 (14.3)	4 (14.8)	4 (10.0)	0.94
CRP elevation in presence of back pain	5 (31.2)	9 (32.1)	19 (70.4)	27 (67.5)	**0.002**
HLA-B27 measured	13 (81.2)	11 (39.3)	14 (51.9)	19 (47.5)	0.52
HLA-B27-positive among measured	1 (7.7)	3 (27.3)	5 (35.7)	2 (10.5)	0.21
Inflammatory back pain	8 (50.0)	17 (60.7)	19 (70.4)	30 (75.0)	0.28
Radiographic sacroiliitis	7 (43.8)	4 (14.3)	13 (48.1)	26 (65.0)	**<0.001**
MRI of sacroiliac joint tested	10 (62.5)	21 (75.0)	16 (59.3)	20 (50.0)	0.232
Sacroiliitis on MRI among tested	6 (60.0)	6(28.6)	8 (50.0)	17 (85.0)	**0.003**
ASAS axial criteria					
Total	8 (50.0)	7 (25.0)	16 (59.3)	26 (65.0)	**0.009**
Clinical arm only	1 (6.2)	1 (3.6)	1 (3.7)	0 (0.0)	0.32
Imaging arm only	7 (43.8)	6 (21.4)	12 (44.4)	24 (60.0)	**0.017**
ASAS peripheral criteria	2 (12.5)	4 (14.3)	1 (3.7)	7 (17.5)	0.42
Axial involvement					
Ever present	9 (56.2)	17 (60.7)	20 (74.1)	30 (75.0)	0.39
As first symptom	5 (31.2)	8 (28.6)	10 (37.0)	12 (30.0)	0.92
Root joint involvement					
Ever present	8 (50.0)	14 (50.0)	7 (25.9)	13 (32.5)	0.19
As first symptom	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	NA
Peripheral arthritis					
Ever present	12 (75.0)	22 (78.6)	18 (66.7)	25 (62.5)	0.52
As first symptom	1 (6.2)	3 (10.7)	5 (18.5)	5 (12.5)	0.73
Monoarticular	0 (0.0)	0 (0.0)	2 (7.4)	3 (7.5)	0.38
Oligoarticular	9 (56.2)	12 (42.9)	11 (40.7)	15 (37.5)	0.65
Polyarticular	3 (18.8)	10 (35.7)	5 (18.5)	7 (17.5)	0.32
Enthesitis					
Ever present	11 (68.8)	16 (57.1)	13 (48.1)	16 (40.0)	0.23
As first symptom	3 (18.8)	2 (7.1)	3 (11.1)	3 (7.5)	0.62
Dactylitis					
Ever present	2 (12.5)	5 (17.9)	2 (7.4)	2 (5.0)	0.32
As first symptom	0 (0.0)	1 (3.6)	0 (0.0)	0 (0.0)	0.64
Psoriasis					
Ever present	0 (0.0)	0 (0.0)	4 (14.8)	0 (0.0)	**0.008**
As first symptom	0 (0.0)	0 (0.0)	1 (3.7)	0 (0.0)	0.39
Uveitis					
Ever present	5 (31.2)	1 (3.6)	5 (18.5)	7 (17.5)	0.09
As first symptom	0 (0.0)	0 (0.0)	2 (7.4)	2 (5.0)	0.48
Concomitant fibromyalgia	1 (6.2)	0 (0.0)	4 (14.8)	2 (5.0)	0.12

Table 4 (continued)

	Latin America	Asia	Europe and North America	Middle East and North Africa	*p* value
IBD					
Ever present	16 (100.0)	28 (100.0)	27 (100.0)	40 (100.0)	NA
As first symptom	9 (56.2)	21 (75.0)	14 (51.9)	26 (65.0)	0.31
Confirmed by endoscopy	16 (100.0)	25 (89.3)	27 (100.0)	39 (97.5)	0.37
Specific treatment	16 (100.0)	27 (96.4)	26 (96.3)	36 (90.0)	0.64
Steroid enema	3 (18.8)	6 (21.4)	12 (44.4)	5 (12.5)	**0.028**
5-ASA compounds	15 (93.8)	24 (85.7)	21 (77.8)	33 (82.5)	0.59
Surgery	2 (12.5)	7 (25.0)	7 (25.9)	4 (10.0)	0.25
Patient Global Assessment	5.0 [2.8, 8.0]	3.0 [2.0, 5.0]	3.0 [1.0, 4.8]	5.0 [3.0, 7.0]	**0.014**
ASDAS-CRP	2.48 [1.65, 3.64]	1.97 [1.62, 2.70]	1.95 [1.29, 2.42]	2.46 [1.84, 3.07]	0.141
BASDAI	4.25 [2.58, 5.75]	2.80 [1.60, 4.32]	3.20 [1.55, 4.95]	3.60 [1.75, 5.53]	0.293
BASFI	4.85 [1.15, 6.58]	0.30 [0.00, 2.00]	2.50 [0.70, 4.90]	2.90 [1.37, 4.45]	**0.001**
ASAS HI	8.25 [5.05, 11.69]	4.12 [0.00, 9.02]	3.40 [2.12, 10.60]	6.90 [3.85, 10.31]	**0.037**
NSAIDs use					
Current	6 (37.5)	20 (71.4)	6 (22.2)	15 (37.5)	**0.002**
Corticosteroids use					
Current	2 (12.5)	2 (7.1)	6 (22.2)	9 (22.5)	0.32
csDMARDs use					
Ever	10 (62.5)	17 (60.7)	22 (81.5)	25 (62.5)	0.30
Current	10 (62.5)	16 (57.1)	8 (29.6)	22 (55.0)	0.09
Salazosulfapyridine use					
Ever	12 (75.0)	13 (46.4)	6 (22.2)	23 (57.5)	**0.004**
Current	7 (43.8)	10 (35.7)	2 (7.4)	17 (42.5)	**0.007**
Methotrexate use					
Ever	4 (25.0)	10 (35.7)	7 (25.9)	5 (12.5)	0.15
Current	2 (12.5)	8 (28.6)	4 (14.8)	1 (2.5)	**0.014**
bDMARDs use					
Ever	9 (56.2)	15 (53.6)	19 (70.4)	26 (65.0)	0.56
Current	10 (62.5)	16 (57.1)	8 (29.6)	22 (55.0)	0.09
TNF inhibitors use					
Ever	9 (56.2)	15 (53.6)	19 (70.4)	26 (65.0)	0.56
Current	6 (37.5)	11 (39.3)	15 (55.6)	20 (50.0)	0.55
IL-17 inhibitors use					
Ever	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	NA
Current	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	NA

Values are expressed as *n* (%) or median (IQR) unless otherwise indicated. IBD-specific treatments include steroid enemas, 5-ASA compounds, oral corticosteroids, DMARDs for IBD, or surgery

Statistically significant differences are bolded ($p < 0.05$)

SpA spondyloarthritis, *IBD* inflammatory bowel disease, *HLA* human leukocyte antigen, *ASAS* Assessment of SpondyloArthritis international Society, *ASDAS-CRP* Ankylosing spondylitis disease activity score with CRP, *BASDAI* Bath ankylosing spondylitis disease activity index, *BASFI* Bath ankylosing spondylitis functional index, *ASAS-HI* ASAS Health Index, *NSAID* nonsteroidal anti-inflammatory drug, *DMARD* disease-modifying anti-rheumatic drug, *csDMARDs* conventional synthetic DMARDs, *bDMARDs* biological DMARDs

acknowledge that the need for IBD-specific treatment may quite naturally be an indication of IBD activity. Differences in HLA-B27 positivity may be due to the high prevalence of r-axSpA in our comparator group of other SpA types with IBD [39]. In previous reports of IBD patients, HLA-B27 was associated with an increased likelihood of having axSpA features [39–41]; the presence of axial involvement with HLA-B27 may lead clinicians preferentially to a diagnosis of other SpA, primarily axSpA in our study. The higher use of TNF inhibitors in other SpA patients with IBD may also be explained by the higher prevalence of axial involvement. Among IBD-related arthritis patients, peripheral arthritis was more common, especially oligoarthritis. This may

suggest that rheumatologists consider type I arthropathy to be a more typical feature of IBD-related arthritis.

Regarding regional trends, IBD-related arthritis patients in Asia have significantly less positive imaging evidence of sacroiliitis compared to other countries. We have previously reported regional differences in SpA patients, finding that fewer SpA patients in Asia had sacroiliitis on MRI compared to those in other countries [42, 43]. These results may reflect local strategies of diagnosis and referral. In most Asian countries, rheumatologists receive more patients with mechanical back pain—that is, with a low likelihood of a positive imaging test—compared with specialists in other countries, who may receive more targeted referrals.

This study has several limitations that warrant mention. First, the cross-sectional nature of ASAS-PerSpA study precludes the study of causal links and only allows for examination of associations. Second, information about IBD was collected through descriptions from rheumatologists; first-hand information from gastroenterologists regarding patients' IBD was not available. It is possible, however unlikely, that more complete information regarding IBD (results of colonoscopy, biopsies, etc.) may have been available to some treating rheumatologists. Nonetheless, a documented history of IBD is necessary item for the diagnosis of SpA, and, as such, all rheumatologists practicing in the ASAS-associated centers in each country should certainly collect this information. Therefore, in this study, the presence or absence of IBD was determined based on patients' medical records including medical history and documented results of endoscopy, and subsequently recorded by the treating rheumatologist. This limitation highlights the need for enhanced interprofessional collaboration between gastroenterologists and rheumatologists to better identify and treat these populations. Finally, the definitive diagnosis of IBD-related arthritis is a subjective decision ultimately made by rheumatologists. However, as there are no definite criteria to classify "patients with SpA and IBD" and "IBD-related arthritis;" differences in clinical characteristics can only be revealed via large international cohorts involving specialized centers in which the definitive diagnosis of treating rheumatologists is clearly known and reported.

In conclusion, we clarified the clinical characteristics of SpA patients with and without IBD, as well as clarifying differences in patients with SpA and concomitant IBD versus those carrying a formal diagnosis of IBD-related arthritis. We found diagnostic delay in patients with SpA and IBD. Among this group, since IBD is often the first symptom of SpA, early referral to rheumatologists from gastroenterologists warrants facilitation. The absence of HLA-B27 positivity and psoriasis, the presence of IBD as first symptom of SpA, and need for IBD-specific treatment are factors that may influence rheumatologists to make a formal diagnosis of IBD-related arthritis.

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Declarations

Conflict of interests Mitsumasa Kishimoto received consulting fees and/or speaker fees from AbbVie, Amgen-Astellas BioPharma, Asahi-Kasei Pharma, Astellas, Ayumi Pharma, BMS, Chugai, Daiichi-Sankyo, Eisai, Eli Lilly, Gilead, Janssen, Kyowa Kirin, Novartis, Ono Pharma, Pfizer, Tanabe-Mitsubishi, Teijin Pharma, and UCB Pharma. Minoru Matsuura received consulting and lecture fees from Janssen Pharmaceutical K.K., Takeda Pharmaceutical Co. Ltd., AbbVie GK, Mitsubishi Tanabe Pharma Corporation, Kyorin Pharmaceutical Co. Ltd., Mochida Pharmaceutical Co., Ltd., JIMRO Co., Nippon Kayaku Co. Ltd., Mylan EPD G.K., and Aspen Japan Co. Ltd. Fabian Proft reports grants and personal fees from Novartis, grants and personal fees from Lilly, grants and personal fees from UCB, personal fees from AbbVie, personal fees from AMGEN, personal fees from BMS, personal fees from Hexal, personal fees from MSD, personal fees from Pfizer, personal fees from Roche. Naoto Tamura has received speaker fees and/or consulting fees from AbbVie, Astellas, Bristol-Myers, Squibb, Eisai, Eli Lilly, Janssen, Kyowa Kirin, Mitsubishi-Tanabe and Novartis.Yoshinori Taniguchi has received speaker fees and/or consulting fees from AbbVie, Eli-Lilly, Janssen, Kyowa Kirin, and Novartis. Hideto Kameda has received consulting fees, speaking fees and/or honoraria from AbbVie G.K., Asahi Kasei Pharma Co., Ltd, Bristol-Myers Squibb, Chugai Pharmaceutical Co., Ltd, Eli Lilly Japan K.K., Gilead Sciences Inc., Janssen Pharmaceutical K.K., Mitsubishi Tanabe Pharma, Novartis Pharma K.K., Pfizer Inc., and Sanofi K.K. and has received research grants from AbbVie G.K., Asahi Kasei Pharma Co., Ltd, Astellas Pharma Inc., Chugai Pharmaceutical Co., Ltd, Eisai Co., Ltd, and Mitsubishi Tanabe Pharma. Akimichi Morita has received research grants, consulting fees, and/or speaker's fees from AbbVie, Amgen, Boehringer Ingelheim, Bristol Myers Squibb,Celgene, Eli Lilly, Eisai, Janssen, Kyowa Hakko Kirin, LEO Pharma, Maruho, Mitsubishi Tanabe, Nichi-Iko, Nippon Kayaku, Novartis, Pfizer, Sun

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Compliance with ethical standards The study was conducted according to the guidelines for Good Clinical Practice and was approved by the ethical committees in all countries. Written informed consent was obtained from all subjects before enrolment.

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