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The role of integrated gastro-rheumatological care in IBD-associated Spondyloarthritis in achieving joint–gut remission: Four-year outcomes from the real-world SPIB cohort

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ABSTRACT

Background: Spondyloarthritis associated with inflammatory bowel disease (Spa-IBD) often requires a customised multidisciplinary approach. The aim of this study was to evaluate long-term outcomes of a cohort of SpA-IBD patients with a multidisciplinary management.

Methods: Consecutive patients with SpA-IBD were assessed at our multidisciplinary Gastro-Rheumatological Clinic and enrolled in the SPIB (SpA in Inflammatory Bowel Disease) cohort. The primary endpoint was the proportion of patients achieving remission in both intestinal and articular domains at four years. Secondary outcomes included the cohort's baseline clinical features, progressive improvement in disease activity scores, treatment patterns, and predictors of remission.

Results: The cohort includes 159 patients (58% Crohn's disease, 42% ulcerative colitis). At baseline, 56% of patients were diagnosed with axial SpA-IBD, and 44% with peripheral SpA-IBD.

At baseline, 0.6% of patients were in combined intestinal and articular remission, and this proportion gradually increased to 5.7% at six months and 26.3% at four years. Clinical outcomes at 4 years included improvements in TJC (Δ-3.8), SJC (Δ-1.0), LEI score (Δ-0.3), DAPSA remission status (+36.0%), ASDAS inactive disease status (+38.0%), and remission status for CDAI (+19.3%) and pMayo (+26.2%) scores. At 2 years, bDMARD therapy increased by 36%, while corticosteroid use decreased by 35%. In multivariable analysis, male gender predicted remission during follow-up (OR 2.80, 95% CI 1.21–6.76), whereas axial disease (OR 0.41, 0.17–0.96) and enthesitis (OR 0.26, 0.11–0.59) were negative predictors.

Conclusions: The long-term results of the SPIB cohort highlight the value of close collaboration between rheumatologists and gastroenterologists in the application of joint-gut remission strategies.

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Background

Spondyloarthritis associated with inflammatory bowel diseases (SpA-IBD) is a chronic immune-mediated condition characterised by a complex intersection of joint and gut inflammation, from both pathogenetic and clinical perspectives [1–3]. Categorised within the broader spectrum of Spondyloarthritis (SpA), SpA-IBD refers to forms associated with IBD, particularly Crohn's Disease (CD) and Ulcerative Colitis (UC); furthermore, like other forms of SpA, SpA-IBD may present with axial involvement (axSpA-IBD) as well as peripheral involvement (pSpA-IBD) [4,5]. Axial involvement usually manifests as inflammatory back pain, while peripheral involvement may present as arthritis, enthesitis, and dactylitis. The coexistence of joint and gut inflammation considerably affects daily life and overall well-being, posing complex management challenges because it requires addressing both musculoskeletal and gastrointestinal symptoms concurrently. Therefore, a multidisciplinary approach that combines rheumatological and gastroenterological expertise should be adopted in clinical practice [2,6,7].

The management of SpA-IBD is further complicated by a significant research gap. In fact, current treatment guidelines are mainly based on clinical trials focused on either SpA or IBD. This represents a major limitation, as it does not capture the unique interaction between joint and gut inflammation that characterises SpA-IBD and might therefore fail to inform therapeutic strategies when both conditions coexist.

Therefore, large-scale, longitudinal studies that offer insights into the long-term outcomes of SpA-IBD patients are vital for understanding disease course, the efficacy of various management strategies over time, and their overall impact on patients' quality of life.

In this study we performed a comprehensive analysis of the clinical features and long-term treatment patterns for a large group of SpA-IBD patients within a real-life gastro-rheumatological integrated setting.

Methods

Study design and objectives

The study was designed as a monocentric, observational, retrospective, longitudinal study and was carried out at the integrated Gastro-Rheumatological outpatient clinic of the "Azienda Ospedaliero-Universitaria delle Marche" in Ancona, Italy.

The primary aim of the study was to evaluate the long-term clinical outcomes of a group of patients with SpA-IBD who were managed with an integrated Gastro-Rheumatological approach.

Secondarily, the study described the clinical and laboratory features of this cohort, aiming to better characterise the distinctive clinical picture arising from the combination of gut and joint inflammation in a real-world setting.

This observational cohort study was designed, conducted and reported in accordance with the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines.

Study cohort

From October 2016 to June 2023, consecutive adult patients affected by IBD were referred to our Gastro-Rheumatological Clinic and, if diagnosed *As spa*-IBD, enrolled in the SPIB Cohort (SPondyloarthritis in Inflammatory Bowel disease) [8].

The study was designed to include a four-year long-term follow-up, and patients underwent comprehensive gastroenterological and rheumatological assessments at predefined scheduled evaluations.

The primary inclusion criterion was the diagnosis of SpA-IBD, defined as the concurrent presence of both SpA and IBD. The diagnosis of SpA relied on the rheumatologist's expertise, clinical findings, laboratory results, imaging features, and considering the Assessment of Spondyloarthritis International Society (ASAS) Classification Criteria for axial and/or peripheral Spondyloarthritis [9,10]. The diagnosis of axSpA-IBD was confirmed through magnetic resonance imaging (MRI) of the spine and sacroiliac joints (SIJ), identifying active inflammatory and/or structural "post-inflammatory" changes, assessed according to the definitions for a positive MRI endorsed by the ASAS/OMERACT (Outcome Measures in Rheumatology) MRI working group [11–13]. X-ray examination of the SIJ was conducted in all patients diagnosed with axSpA-IBD to detect radiographic sacroiliitis according to the modified New York criteria (mNY) [14]. The diagnosis of IBD (Crohn's disease [CD] or ulcerative colitis [UC]) was based on the gastroenterologist's expertise, combined with clinical, laboratory, and endoscopic evaluations, and in accordance with the accepted criteria of the European Crohn's and Colitis Organisation (ECCO) [15,16].

Other inclusion criteria were defined as follows: i) age at baseline greater than 18 years; ii) presence of both gastroenterological and rheumatological evaluation at baseline and at each time point; iii) presence of at least 1 year of follow-up. Patients were excluded if: (a) diagnosed with rheumatoid arthritis or with a Spondyloarthritis phenotype outside the SpA-IBD spectrum; (b) followed for less than one year. Patients with SpA and incident IBD, referred to the rheumatology clinic from external sources and not eligible for our IBD Unit, were not included due to the impossibility of conducting integrated management.

Study procedures

The study was conducted within an integrated gastro-rheumatology care model, specifically designed for the early identification and longitudinal management of patients with concomitant SpA and IBD.

Firstly, patients affected by IBD were screened through the DETection of Arthritis in Inflammatory boweL diseases (DETAIL) questionnaire, whose validation process has been described elsewhere [8]. Patients who tested positive in the screening were referred to the rheumatologist and, if diagnosed with SpA (IBD-associated), were enrolled in the SPIB cohort. Since enrolment, all patients have been jointly evaluated by a rheumatologist and a gastroenterologist during dedicated combined visits at 3, 6, 12 months, and annually thereafter, during which clinical and laboratory data were collected simultaneously for both disease domains. At follow-up examinations or in the event of new or relapsing symptoms, treatment decisions were made based on the expertise of both specialists and the latest treatment recommendations for both SpA and IBD, with the aim of optimising disease control across all domains of the disease.

For all patients, we collected data on gender, age, smoking habits, IBD disease duration and musculoskeletal symptoms duration. At each timepoint, we recorded both previous and current treatments for SpA and IBD, including non-steroidal anti-inflammatory drugs (NSAIDs) and salicylates, steroids, immunosuppressive agents such as azathioprine and cyclosporine, as well as conventional (cs-) and biologic / targeted synthetic (b-/ts-) disease-modifying anti-rheumatic drugs (DMARDs). Patients' comorbidities were documented at baseline and updated at each evaluation, covering: **a.** cardiovascular diseases, such as hypertension, ischaemic cardiomyopathy, heart failure, cardiac arrhythmias, valvular diseases, stroke, venous thromboembolism, pericardial disease, and other cardiomyopathies; and **b.** metabolic diseases, including obesity, type I and II diabetes, dyslipidaemia, and osteoporosis.

Clinical data were collected at baseline, at 6 and 12 months, and then every 12 months for all patients, including tender joint count 68 and swollen joint count 66 (TJC68/SJC66), Leeds Enthesitis Index (LEI), partial Mayo score (pMAYO), and Crohn's Disease Activity Index score (CDAI) for UC and CD patients respectively, Visual Analogue Scale for pain (VAS pain), Patient and Physician Global Assessment (PtGA and PhGA).

The Disease Activity in Psoriatic Arthritis (DAPSA) composite score was utilised to assess peripheral involvement in SpA/IBD, following recent studies demonstrating its good reliability in evaluating pSpA disease activity [17,18], and supported by the latest Italian consensus [2]. Patients with confirmed axial involvement of SpA/IBD were also

clinically evaluated using the Axial Spondyloarthritis Disease Activity Score (ASDAS) based on C-reactive protein (CRP) and the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI).

Laboratory data, including complete blood count, liver and kidney function tests, CRP, and faecal calprotectin, were collected at the same time points. Any adverse event (AE), whether assessed by the physician or reported by the patient, was recorded and classified according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.

Outcomes

The primary outcome of the study was the proportion of patients achieving a combination of remission in both intestinal and articular-related domains, henceforth defined as "*combined remission*" at each time point.

We have coined the term "combined remission" as the simultaneous attainment of the status of: *i.* a DAPSA remission (score $\leq$ 4) in cases with peripheral involvement [19]; *ii.* ASDAS inactive disease status (score $<$ 1.3) in cases with axial involvement [20]; *iii.* CDAI remission (score $<$ 150) in patients with Crohn's disease [21]; *iv.* pMAYO remission (score $<$ 2), in patients with ulcerative colitis [22].

The secondary outcomes included: i) the change from baseline in TJC, SJC, LEI, DAPSA, ASDAS, CDAI, and pMAYO scores, where applicable; ii) the proportion of patients with ulcerative colitis and Crohn's disease, along with the distribution of axial and peripheral involvement at each timepoint; iii) the proportion of patients receiving treatment with b/tsDMARDs, csDMARDs, corticosteroids, and other immunomodulatory drugs at each timepoint; iv) the proportion, type, and severity of recorded AEs.

Data analysis

Study data were collected and managed using the REDCap electronic data capture tool hosted at "Azienda Ospedaliero Universitaria delle Marche" (www.project-redcap.org). REDCap (Research Electronic Data Capture) is a web-based software platform designed to support data collection for research studies [23,24].

All statistical analyses were conducted using the R software (version 4.4.2), and a *p*-value $<$0.05 was regarded as significant. For descriptive analyses, categorical variables were reported as absolute numbers and frequencies, while continuous variables were expressed as mean and standard deviation (SD).

Differences from baseline for continuous variables were analysed with a linear mixed model (LMM) with Bonferroni correction, accounting for repeated measures and inter-subject variability.

Subgroup comparisons were performed using the Mann-Whitney U test for continuous variables and Pearson's chi-square test for categorical variables.

To identify baseline predictors of patients achieving combined remission during follow-up, a bidirectional stepwise logistic regression was used. The model was based on minimising the Akaike Information Criterion (AIC), with each step assessing whether to add or remove variables. Before the stepwise process, potential multicollinearity was checked using the Variance Inflation Factor (VIF), and variables with high multicollinearity were excluded. Results were reported as Odds Ratios (ORs) with 95% confidence intervals (CI).

The figures were generated using the R software, version 4.4.2, and the GraphPad Prism software, version 9.5.1.

Results

Patients' cohort characteristics

Baseline characteristics of the cohort are shown in Table 1 and Fig. 1. A total of 159 patients were enrolled in the SPIB cohort between October 2016 and June 2023, and followed-up until September 2025, consisting of 94 (59.1%) women and 65 (40.9%) men. The mean age was 49.1 $\pm$ 13.7 years, with mean IBD disease duration and musculoskeletal symptoms duration being 11.9 $\pm$ 11.2 and 3.5 $\pm$ 4.5 years, respectively. At the time of SpA-IBD diagnosis, the SPIB cohort comprised 93 (58.5%) patients with CD and 66 (41.5%) with UC.

About half of patients (70; 44%) had peripheral involvement (pSpA) without axial inflammation, with enthesitis and peripheral arthritis being the most common peripheral domains (51.6% and 79.9% of patients, respectively).

A definite diagnosis of axSpA-IBD was confirmed in 89 (56.0%)

Table 1
Clinical characteristics of the SPIB cohort at baseline. a. Ischemic Cardiomyopathy, Heart Failure, Cardiac Arrhythmias (any), valvular disease (any), Stroke, Venous Thromboembolism, Pericardial Disease, other Cardiomyopathies. b. Diabetes (type I or type II), Obesity, Dyslipidaemia, Osteoporosis. c. csDMARDs include Sulfasalazine, Azathioprine, Ciclosporin, Methotrexate, and Hydroxychloroquine. # Refers to treatment ongoing before baseline prescriptions.

Patients n. (%)	**All patients 159 (100)**
Sex (F/M), n. (%)	94(59.1)/65(40.9)
Age, yrs ± SD	49.1 ± 13.7
Smoke, active, n. (%)	24 (15.1)
IBD disease duration, years ± SD	11.9 ± 11.2
Musculoskeletal symptoms duration, years ± SD	3.5 ± 4.5
IBD type (CD/UC), n. (%)	93(58.5)/66(41.5)
HLA-B27, n. (%)	44 (27.7)
Comorbidities, n. (%)	
CVD[a], n. (%)	40 (25.2)
MTB[b], n. (%)	47 (29.6)
Disease Domains	
r-axSpA, n. (%)	20 (12.6)
nr-axSpA, n. (%)	69 (43.4)
Peripheral involvement, n. (%)	142 (89.3)
Peripheral Arthritis, n. (%)	127 (79.9)
Entesitis, n. (%)	82 (51.6)
Dactylitis (ever), n. (%)	7 (4.4)
Psoriasis (ever), n. (%)	32 (20.1)
Uveitis (ever), n. (%)	14 (8.8)
Hydradenitis suppurativa, n. (%)	3 (1.9)
Erythema Nodosum (ever), n. (%)	9 (5.7)
Disease Activity, baseline	
Tender Joint Count, mean ± SD	5.3 ± 4.1
Swollen Joint Count, mean ± SD	1.1 ± 1.5
DAPSA, mean ± SD	18.1 ± 6.8
LEI, mean ± SD	0.9 ± 1.1
ASDAS, mean ± SD	2.6 ± 0.8
BASDAI, mean ± SD	5.5 ± 1.3
CDAI, mean ± SD	150.0 ± 69.2
pMAYO, mean ± SD	1.8 ± 1.5
CRP (mg/dl), mean ± SD	1.1 ± 1.5
Calprotectin (mg/kg), mean ± SD	235.8 ± 326.5
Treatment, baseline #	
Mesalazine, n. (%)	98 (61.6)
Corticosteroids (oral), n. (%)	70 (44.0)
csDMARDs[c], n. (%)	55 (34.6)
TNFi	42 (26.4)
Anti IL-12/23 or IL-23	1 (0.6)
JAKi	0 (0.0)
Vedolizumab	4 (2.5)
Apremilast	1 (0.6)

Abbreviations: F: females; M: males; IBD: Inflammatory Bowel Diseases; CD: Crohn's Disease; UC: Ulcerative Colitis; HLA-B27: Human Leukocyte Antigen B-27; CVD: cardiovascular diseases; MTB: metabolic diseases; r/nr-axSpA: radiographic/non-radiographic axial spondyloarthritis; DAPSA: Disease Activity in Psoriatic Arthritis; LEI: Leeds Enthesitis Index; ASDAS: Axial Spondyloarthritis Disease Activity Score; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; CDAI: Crohn's Disease Activity Index; pMAYO: partial (without endoscopy) Mayo Clinic score for Ulcerative Colitis; CRP: C-reactive protein; csDMARDs: conventional synthetic disease modifying anti-rheumatic drugs; TNFi: Inhibitors of Tumor Necrosis Factor α; IL-12/23: Interleukin 12/23; JAKi: Janus Kinase Inhibitors; yrs: years; SD: standard deviation.

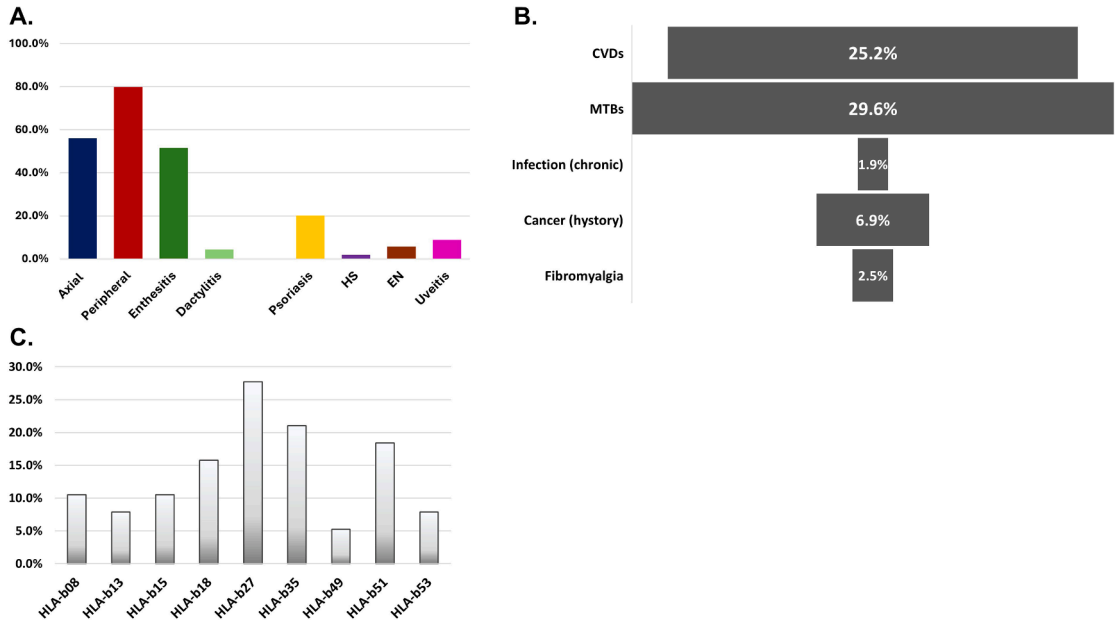

Fig. 1. Baseline characteristics of the SPIB cohort. A. Prevalence of extra-intestinal domain involvement. B. Prevalence of major comorbidities identified within the cohort. C. Distribution of HLA-B alleles among tested patients, expressed as a percentage of the analysed cohort.
Abbreviations: SPIB: Spondyloarthritis in Inflammatory Bowel Disease cohort; HS: hidradenitis suppurativa; EN: erythema nodosum; CVDs: cardiovascular diseases; MTBs: metabolic diseases; HLA: Human Leukocyte Antigen.

patients. Among them, most (72; 80.9%) presented with concomitant peripheral involvement and non-radiographic rather than radiographic disease (43.4%vs 12.6%, respectively).

Among the extra-articular and extra-intestinal domains, psoriasis was the most representative (20.1% of patients), followed by uveitis (8.8%) and erythema nodosum (5.7%).

At baseline, patients in the SPIB cohort exhibited moderate to high disease activity in both rheumatological and gastroenterological assessments.

Patients with pSpA-IBD had mean TJC and SJC scores of 5.3 ± 4.1 and 1.1 ± 1.5, respectively, a mean LEI score of 0.9 ± 1.1, and a mean DAPSA score of 18.1 ± 6.8, indicating moderate peripheral disease activity. Those affected by axSpA-IBD showed high disease activity, with mean ASDAS and BASDAI scores of 2.6 ± 0.8 and 5.5 ± 1.3, respectively.

Regarding IBD, both the mean CDAI and pMAYO scores showed moderate activity in CD and UC patients, respectively.

Finally, baseline laboratory data showed a mean CRP level of 1.1 ± 1.5 mg/dL and a mean faecal calprotectin level of 235.8 ± 326.5 mg/kg, both exceeding their respective upper limits of normal (u.l.n.). HLA-B27 testing was performed in all patients, and 44 (27.7%) resulted positive, most (36/44; 81.8%) with axSpA-IBD.

Longitudinal analysis

The results of the longitudinal analysis are shown in Table 2 and Figs. 2a, 2b, and 3. The primary outcome, combined remission, was achieved in 5.7% of patients at 6 months (T1), but this proportion increased significantly to 22.0% at 1 year (T2). This was maintained through to 4 years (T5), with 26.3% of patients remaining in combined remission.

Considering rheumatologic or gastroenterologic disease activity separately, the proportion of patients with pSpA-IBD achieving DAPSA remission steadily increased from 0.7% at baseline to 9.9% at T1 and 21.1% at T2, reaching 36.7% by T5. A similar pattern was observed in patients with axSpA-IBD reaching ASDAS inactive disease status, rising from 0.0% at baseline to 7.9% at T1 and 20.2% at T2, reaching 38.0% by T5.

The proportion of patients with CD in CDAI remission was already high at baseline (58.5%), but it increased further to 63.4% at T1 and 83.9% at T2, and remained at 77.8% at T5.

The above trend was similar for the proportion of patients with UC in pMAYO remission status, beginning at 54.4% at baseline and rising to 57.6% at T1, 74.2% at T2, and ultimately 80.6% at T5.

The mean difference from baseline (MD) was statistically significant at all time points for both DAPSA and ASDAS scores, as well as for TJC and SJC. Conversely, the MD for the LEI and CDAI scores did not reach statistical significance at T1 but became significant at later time points. For the pMAYO score, a significant MD was observed only at T2, T3 (2 years), and T5.

Regarding laboratory variables, mean CRP levels decreased from baseline at timepoints T2 through T5. Faecal calprotectin levels showed a more variable pattern, with an initial decrease at T2, followed by an increase at T3, and a subsequent decline at T4 (3 years) and T5.

Interestingly, the proportion of patients diagnosed with axSpA-IBD rose from 56.0% at baseline to 71.7% at T5. This increase was driven by the diagnosis of seven new cases of axial involvement during the integrated gastro-rheumatological follow-up.

Drug analysis and adverse events

The results on prescription trends are shown in Figs. 4 and 5. At the baseline visit, data on ongoing therapy *before* the baseline prescriptions were gathered and are reported in Table 1. Most patients (70.5%) had not previously received bDMARDs. Conversely, the remaining 29.5% of patients were receiving biologic therapy: specifically, 26.4% were receiving TNFi, followed by 2.5% and 0.6% receiving vedolizumab and ustekinumab, respectively. No patients had received anti-interleukin-23 (IL-23) or Janus kinase inhibitors (JAKi).

In this study, the following drugs were classified as csDMARDs: sulfasalazine, azathioprine, ciclosporin, methotrexate, and hydroxychloroquine. At the baseline visit, 34.6% of patients were receiving csDMARDs, with azathioprine being the most frequently prescribed (22.0%), followed by sulfasalazine (Azulfidine) and methotrexate

Table 2
Longitudinal Analysis. Longitudinal trends of clinical, laboratory, and disease activity parameters in the SPIB cohort over four years of integrated gastro-rheumatological follow-up. All variables were assessed at baseline (T0) and subsequently at 6 months (T1), 1 year (T2), 2 years (T3), 3 years (T4), and 4 years (T5). Statistical analyses were performed using R software. Differences from baseline for continuous variables were assessed at each timepoint using a linear mixed model (LMM) with Bonferroni correction. P-values < 0.05 are reported in bold.

	Baseline (T0)	T1	p T1-T0	T2	p T2-T0	T3	p T3-T0	T4	p T4-T0	T5	p T5-T0
Nr. of patients, global (%)	159 (100.0)	159 (100.0)	/	159 (100.0)	/	159 (100.0)	/	120 (75.5)	/	99 (62.3)	/
Combined Remission, nr. (%)	1 (0.6)	9 (5.7)	/	35 (22.0)	/	47 (29.6)	/	39 (32.5)	/	26 (26.3)	/
Clinimetric Scores, peripheral											
Patients with peripheral involvement, nr. (%)	142 (89.3)	142 (89.3)	/	142 (89.3)	/	142 (89.3)	/	108 (90.0)		90 (90.9)	
Tender Joint Count, mean ± SD	5.3 ± 4.1	3.5 ± 3.2	**<0.0001**	2.5 ± 3.1	**<0.0001**	2.0 ± 3.0	**<0.0001**	1.8 ± 2.6	**<0.0001**	1.5 ± 2.2	**<0.0001**
Swollen Joint Count, mean ± SD	1.1 ± 1.5	0.5 ± 0.9	**<0.0001**	0.4 ± 0.9	**<0.0001**	0.3 ± 0.8	**<0.0001**	0.3 ± 0.9	**<0.0001**	0.1 ± 0.4	**<0.0001**
DAPSA, mean ± SD	18.1 ± 6.8	12.4 ± 6.0	**<0.0001**	10.8 ± 6.4	**<0.0001**	9.9 ± 6.1	**<0.0001**	9.1 ± 6.1	**<0.0001**	7.9 ± 5.7	**<0.0001**
DAPSA LDA, nr. (%)	34/142 (23.9)	61/142 (43.0)	/	54/142 (38.0)	/	57/142 (40.1)	/	39/108 (36.1)	/	34/90 (37.8)	/
DAPSA remission status, nr. (%)	1/142 (0.7)	14/142 (9.9)	/	30/142 (21.1)	/	37/142 (26.1)	/	35/108 (32.4)	/	33/90 (36.7)	/
Leeds Enthesitis Index, mean ± SD	0.9 ± 1.1	0.7 ± 0.8	0.8603	0.4 ± 0.9	**<0.0001**	0.4 ± 0.9	**<0.0001**	0.5 ± 1.1	**0.0037**	0.6 ± 1.1	**0.0289**
Clinimetric Scores, axial											
Patients with axial involvement, nr. (%)	89 (56.0)	89 (56.0)	/	89 (56.0)	/	93 (58.5)		81 (67.5)		71 (71.7)	
ASDAS, mean ± SD	2.6 ± 0.8	2.1 ± 0.6	**<0.0001**	1.8 ± 0.7	**<0.0001**	1.7 ± 0.7	**<0.0001**	1.6 ± 0.7	**<0.0001**	1.5 ± 0.7	**<0.0001**
ASDAS LDA status, nr. (%)	24/89 (27.0)	37/89 (41.6)	/	47/89 (52.8)	/	45/93 (48.4)	/	37/81 (45.7)	/	30/71 (42.3)	/
ASDAS inactive disease status, nr. (%)	0/89 (0.0)	7/89 (7.9)	/	18/89 (20.2)	/	26/93 (28.0)	/	28/81 (34.6)	/	27/71 (38.0)	/
BASDAI, mean ± SD	5.5 ± 1.3	4.7 ± 1.1	**<0.0001**	3.8 ± 1.3	**<0.0001**	3.5 ± 1.5	**<0.0001**	3.4 ± 1.7	**<0.0001**	3.3 ± 1.8	**<0.0001**
Clinimetric Scores, intestinal											
Patients with CD, nr. (%)	93 (58.5)	93 (58.5)	/	93 (58.5)	/	93 (58.5)	/	76 (63.3)		63 (63.6)	
CDAI, mean ± SD	150.0 ± 69.2	134.6 ± 50.3	0.4039	111.0 ± 61.9	**<0.0001**	102.1 ± 54.7	**<0.0001**	88.7 ± 51.3	**<0.0001**	110.8 ± 60.2	**<0.0001**
CDAI remission status, nr. (%)	54/93 (58.1)	59/93 (63.4)	/	78/93 (83.9)	/	79/93 (84.9)	/	72/76 (94.7)	/	49/63 (77.8)	/
Patients with UC, nr. (%)	66 (41.5)	66 (41.5)	/	66 (41.5)	/	66 (41.5)	/	44 (36.7)	/	36 (36.4)	/
pMAYO, mean ± SD	1.8 ± 1.5	1.5 ± 1.1	>0.99	1.2 ± 1.0	**0.0129**	1.2 ± 1.2	**0.0047**	1.3 ± 1.2	0.1631	1.2 ± 1.0	**0.0374**
pMAYO remission status, nr. (%)	36/66 (54.4)	38/66 (57.6)	/	49/66 (74.2)	/	50/66 (75.8)	/	34/44 (77.3)	/	29 (80.6)	/
Laboratory											
C-Reactive Protein (mg/dl), mean ± SD	1.1 ± 1.5	0.8 ± 0.9	0.0621	0.7 ± 1.0	**0.0009**	0.6 ± 0.6	**<0.0001**	0.6 ± 1.3	**0.0001**	0.6 ± 0.7	**<0.0001**
Faecal Calprotectin (mg/kg), mean ± SD	235.8 ± 326.5	153.6 ± 141.4	0.3341	122.7 ± 124.4	**0.0230**	192.4 ± 235.5	0.4647	134.0 ± 178.0	**0.0165**	134.0 ± 160.3	**0.0182**

Abbreviations: Nr.: numbers; DAPSA: Disease Activity in Psoriatic Arthritis; ASDAS: Axial Spondyloarthritis Disease Activity Score; DAPSA/ASDAS LDA: low disease activity as per DAPSA or ASDAS score; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; CDAI: Crohn's Disease Activity Index; pMAYO: partial (without endoscopy) Mayo Clinic score for Ulcerative Colitis.

(Methotrexate).

Oral corticosteroid therapy was ongoing in 44.0% of patients, with a mean prednisone-equivalent dose of 16.7 ± 7.5 mg/day. Finally, mesalazine-based therapy was recorded in 61.6% of patients.

At the baseline visit, the gastroenterologist and rheumatologist jointly decided on the treatment, choosing whether to proceed with the current therapy or initiate a new prescription.

Following baseline prescriptions, the proportion of patients treated with oral corticosteroids decreased to 22.6% (−21.4%), and the mean prednisone-equivalent dose was reduced to 10.0 ± 6.5 mg/day. The proportion of steroid-treated patients continued to decline, reaching a minimum of 6.7% (−37.3%) and 8.1% (−35.9%) at the T4 and T5 visits, respectively. The mean prednisone-equivalent dose prescribed at T4 and T5 was 12.4 ± 6.9 mg/day and 13.0 ± 7.2 mg/day.

In contrast, the prescription trend for b/tsDMARD increased throughout the integrated follow-up. After baseline prescriptions, the proportion of TNFi-treated patients rose to 43.4% (+17.0%), peaking at 61.6% (+35.2%) after the T2 visit, and then remained stable. The proportions of patients treated with anti-IL12/23 or IL-23 and JAKi also grew during follow-up, reaching 7.1% and 6.1%, respectively.

Finally, the proportion of patients treated with csDMARDs or vedolizumab remained stable throughout the follow-up period. In contrast, the use of mesalazine-based therapy declined from 61.6% before baseline to 23.2% after T5 evaluation.

Throughout the follow-up period, a total of 35 AEs were recorded and deemed "possibly drug-related" by the treating physicians. The most frequently reported AEs were classified as "skin and subcutaneous tissue disorders" (28.6%), followed by "gastrointestinal disorders" (14.3%) and "infections and infestations" (11.4%). Ten AEs (28.6%) were attributed to csDMARDs, and 25 (71.4%) to bDMARDs.

Most AEs were assessed as mild to moderate in severity; however, 9 out of 35 (25.7%) were classified as "severe" (grade 3, according to CTCAE v5.0). These included: two ileal abscesses (possibly related to adalimumab and infliximab), one CD flare (possibly related to

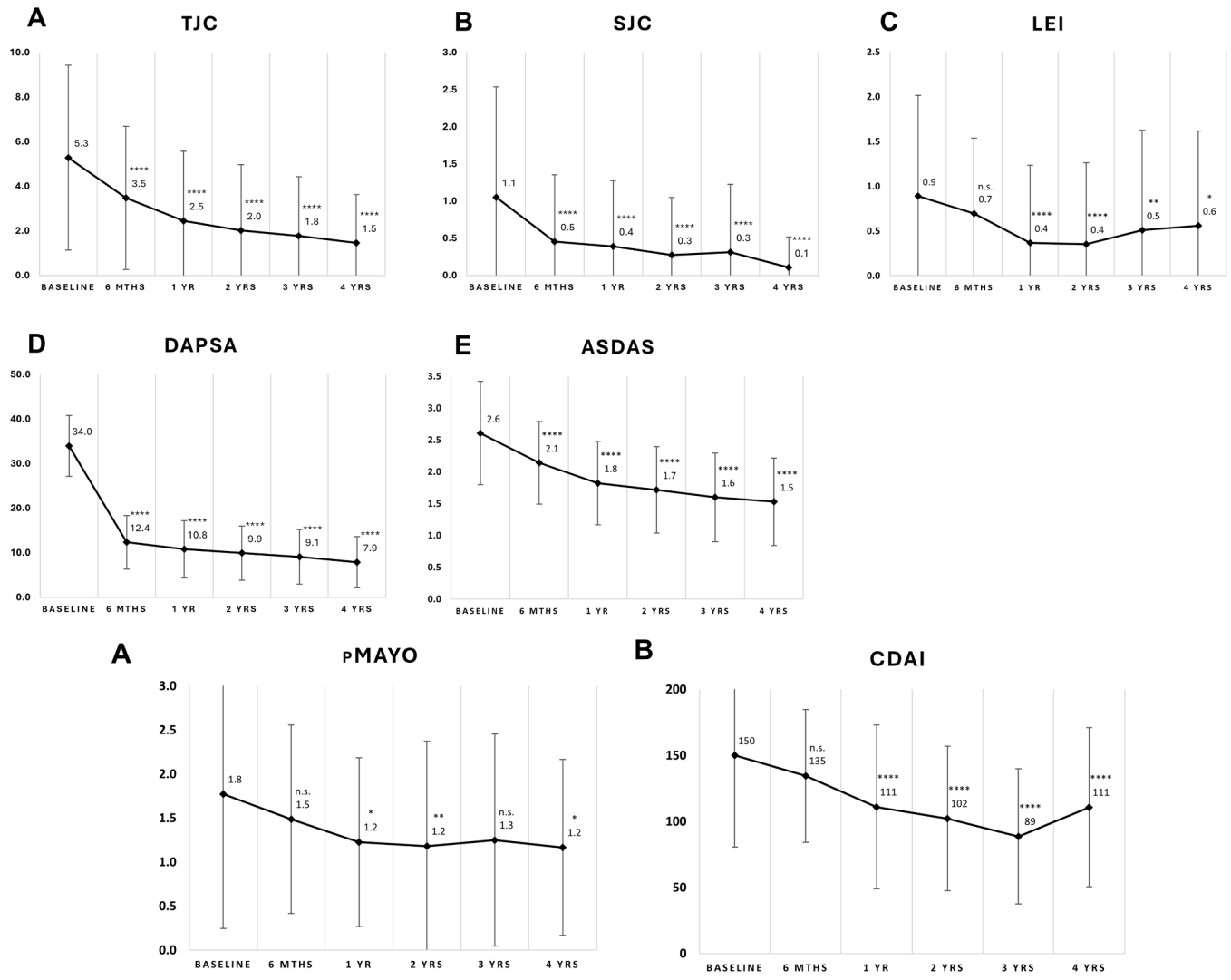

Fig. 2. A Longitudinal trend of SpA-related disease activity scores in the SPIB cohort over four years of integrated gastro-rheumatological follow-up. Mean scores (± SD) are shown at baseline, 6 months, 1 year, 2 years, 3 years, and 4 years for: A. Tender Joint Count (TJC); B. Swollen Joint Count (SJC); C. Leeds Enthesitis Index (LEI); D. Disease Activity in Psoriatic Arthritis (DAPSA); E. Axial Spondyloarthritis Disease Activity Score (ASDAS). Differences from baseline were assessed at each timepoint using a linear mixed model with Bonferroni correction. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$, **** $p < 0.0001$; n.s., not significant.
Abbreviations: SPIB: Spondyloarthritis in Inflammatory Bowel Disease cohort; SpA: spondyloarthritis; mths: months; yr: year; yrs: years.
Figure 2b Longitudinal trend of IBD-related disease activity scores in the SPIB cohort over four years of integrated gastro-rheumatological follow-up. Mean scores (± SD) are shown at baseline, 6 months, 1 year, 2 years, 3 years and 4 years for: A. partial Mayo score (pMAYO); B. Crohn's Disease Activity Index (CDAI). Differences from baseline were assessed at each timepoint using a linear mixed model with Bonferroni correction. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$, **** $p < 0.0001$; n.s., not significant. Abbreviations: IBD: Inflammatory Bowel Diseases; SPIB: Spondyloarthritis in Inflammatory Bowel Disease cohort; mths: months; yr: year; yrs: years.

etanercept), one case of breast cancer (possibly related to infliximab), two paradoxical psoriasis flares (possibly related to infliximab and adalimumab), and three severe cutaneous reactions (possibly related to infliximab, adalimumab, and sulfasalazine). Additionally, three cases of anaphylaxis, including one resulting in shock, were recorded following intravenous infliximab administration, and were classified as life-threatening AEs (grade 4, CTCAE v.5.0).

Subgroup analysis

Subgroup analyses were performed to evaluate differences in baseline characteristics between patients with axSpA-IBD and pSpA-IBD, as well as between those with CD or UC. The findings are shown in Table 3.

Regarding the rheumatological side, baseline characteristics were similar between the axSpA-IBD and pSpA-IBD groups, except for HLA-B27 positivity, which was more common in patients with axial involvement (40%vs 12.5%, $p = 0.044$).

On the gastroenterological side, patients with UC were older and had a shorter duration of articular symptoms compared to those with CD (54.5 ± 13.1 vs 45.3 ± 12.8 years, $p < 0.001$; and 2.9 ± 3.7 vs 3.9 ± 5.0 years, $p = 0.002$, respectively).

Regarding the related conditions, erythema nodosum was more frequently observed in patients with CD than in those with UC (9.7%vs 0.0%, $p = 0.010$), and in patients with perSpA/IBD compared to those with axSpA/IBD (10.0%vs 2.2%, $p = 0.043$).

Finally, before the integrated gastro-rheumatological assessment, patients with UC were less likely to be treated with csDMARDs but more likely to receive oral mesalazine than those with CD (22.7%vs 43.0%, $p = 0.013$; and 77.3% vs 50.5%, $p = 0.001$, respectively).

Predictors of remission

A univariable analysis was performed to identify potential baseline predictors of combined remission at any timepoint, then a multivariable

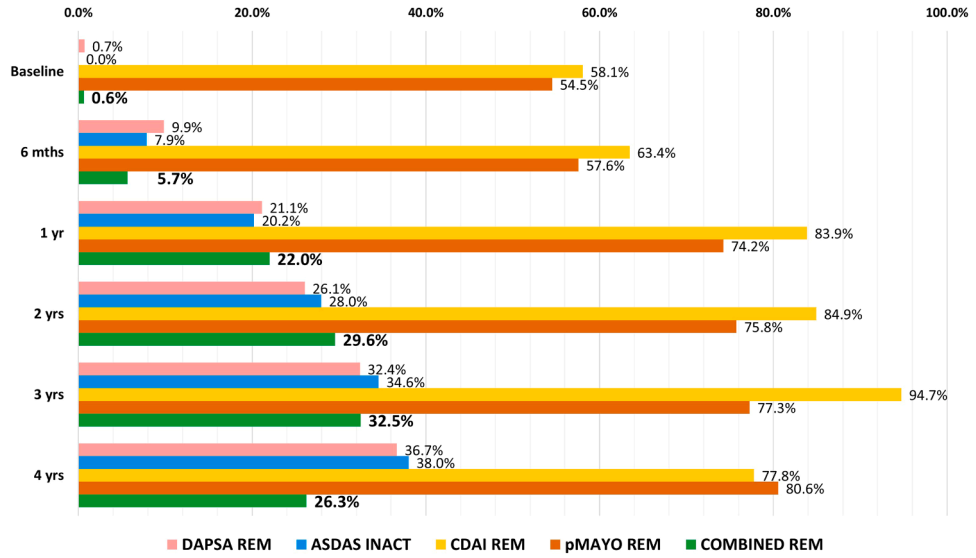

Fig. 3. Longitudinal remission rates in the SPIB cohort over four years of integrated gastro-rheumatological follow-up. Bars represent the proportion of patients achieving (from left to right): DAPSA remission (DAPSA $\leq$ 4), ASDAS inactive disease (ASDAS $<$ 1.3), CDAI remission (CDAI $<$ 150), pMAYO remission (pMAYO $<$ 2), and combined remission (simultaneous attainment of all applicable remission criteria). Data are shown at baseline, 6 months, 1 year, 2 years, 3 years and 4 years. The proportions of combined remission are highlighted in bold.
Abbreviations: SPIB: Spondyloarthritis in Inflammatory Bowel Disease cohort; DAPSA: Disease Activity in Psoriatic Arthritis; ASDAS: Axial Spondyloarthritis Disease Activity Score; CDAI: Crohn's Disease Activity Index; pMAYO: partial (without endoscopy) Mayo Clinic score for Ulcerative Colitis; DAPSA/CDAI/pMAYO REM: remission status as per DAPSA, CDAI, or pMAYO score; ASDAS INACT: inactive disease status as per ASDAS score; COMBINED REM: combined remission; mths: months; yr: year; yrs: years.

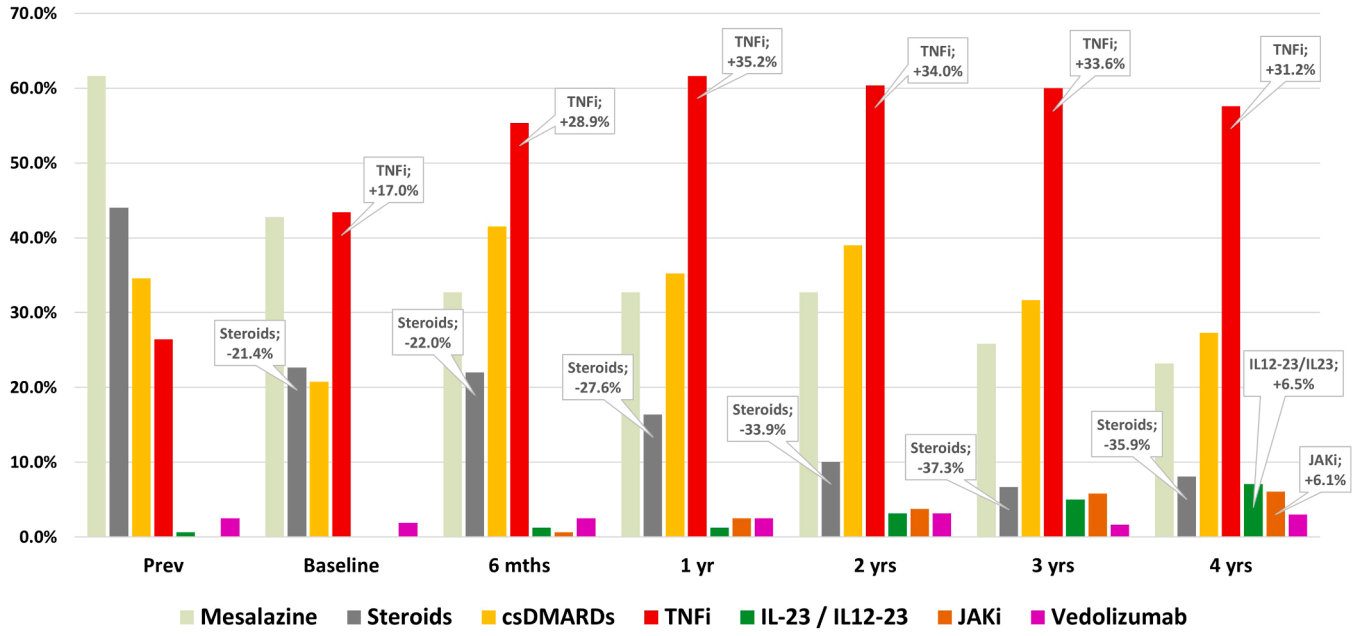

Fig. 4. Longitudinal prescription trends in the SPIB cohort before and during integrated gastro-rheumatological follow-up. Bars represent the proportion of patients receiving (from left to right): mesalazine, oral corticosteroids, csDMARDs, TNFi, Anti IL-12/23 or Anti IL-23 agents, JAKi, and vedolizumab. Prescription data are displayed at multiple timepoints: prior to the first integrated evaluation (Prev), and after each integrated assessment at baseline, 6 months, 1 year, 2 years, 3 years, and 4 years. Abbreviations: SPIB: Spondyloarthritis in Inflammatory Bowel Disease cohort; csDMARDs: conventional synthetic disease modifying anti-rheumatic drugs; TNFi: Inhibitors of Tumor Necrosis Factor α; IL-12/23: Interleukin 12/23; JAKi: Janus Kinase Inhibitors; mths: months; yr; year; yrs: years.

analysis using stepwise logistic regression was carried out to confirm the findings, incorporating variables considered relevant based on univariate analysis and expert clinical judgement; the results are shown in Table 4.

Male gender was linked to higher odds of achieving remission during follow-up (OR 2.80, 95% CI 1.21–6.76, p = 0.018). Conversely, axial and entheseal involvement were associated with lower odds of remission (OR 0.41, 95% CI 0.17–0.96, p = 0.041; and OR 0.26, 95% CI 0.11–0.59, p = 0.002; respectively). Notably, the presence of erythema nodosum was independently connected to increased odds of remission (OR 6.70, 95% CI 1.46–37.9, p = 0.018); however, the small number of events observed warrants cautious interpretation.

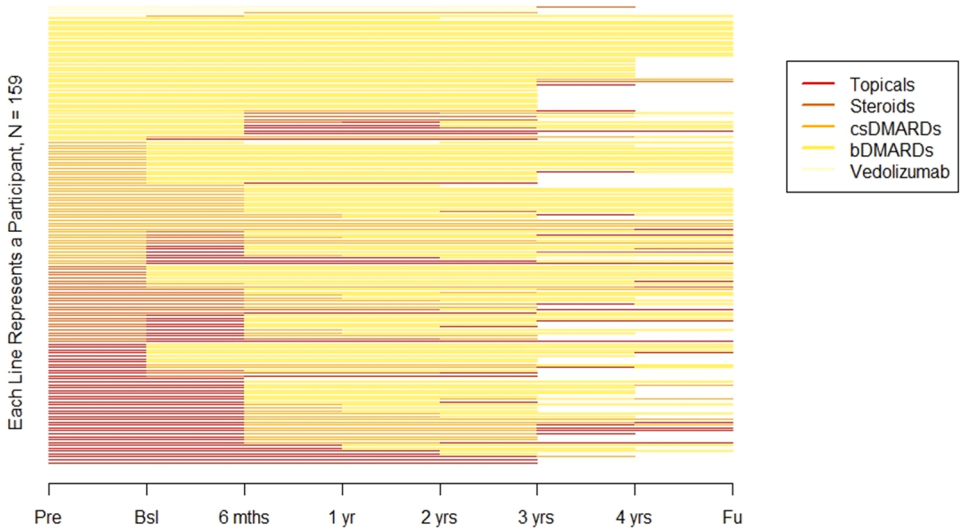

Fig. 5. Heatmap of individual treatment trajectories in the SPIB cohort over the integrated follow-up period. Each horizontal line represents one of the 159 participants, with columns corresponding to timepoints: before the first integrated assessment (Pre), and after each assessment at baseline (Bsl), six months, one year, two years, three years, and four years. Continuous shading along a line indicates treatment persistence, while changes in colour reflect treatment modifications over time. Abbreviations: SPIB: Spondyloarthritis in Inflammatory Bowel Disease cohort; mths: months; yr: year; yrs: years; Fu: follow-up.

Discussion

Spondyloarthritis associated with inflammatory bowel disease (SpA-IBD) is a chronic immune-mediated condition in which, due to pathogenetic similarities [3], joint inflammation may be clinically associated with active intestinal disease.

Although SpA-IBD has been included by Moll and Wright in the SpA classification since 1973, there remains surprisingly limited evidence-based guidance on the optimal approach to diagnosis and management, particularly regarding therapeutic and follow-up integrative management [25]. Importantly, SpA-IBD may not simply represent the coexistence of two independent diseases, but rather a multidomain inflammatory condition in which intestinal and musculoskeletal manifestations intersect and may respond differently to therapy. In this context, close collaboration between rheumatologists and gastroenterologists is essential, as csDMARDs and b/tsDMARDs may exhibit different efficacy and safety profiles in SpA-IBD. Furthermore, treatment response requires domain-specific clinimetric assessment depending on the specialist field [26].

However, no randomized controlled trials have included SpA-IBD patients so far; therefore, the limited clinical and therapeutic data are derived from non-controlled studies.

Our study presents long-term real-world data from one of the largest cohorts of Spa-IBD patients managed within an integrated gastro-rheumatology clinic and highlights three main clinical implications.

First, the multidisciplinary treat-to-target approach led to sustained improvements in both intestinal and musculoskeletal domains. This structured approach differs from standard care, where patients are usually referred sequentially without coordinated follow-up or shared decision making between specialists.

Second, therapeutic patterns progressively shifted towards greater use of b/tsDMARDs, alongside a reduction in corticosteroid exposure during follow-up.

Third, male sex and the absence of axial or entheseal involvement emerged as independent predictors of combined remission.

In this study, we describe a composite outcome, termed “combined remission”, defined as the simultaneous achievement of intestinal and articular remission based on validated disease activity scores for both diseases. Although this composite outcome has never been formally validated, it was conceived to reflect the integrated multidomain assessment applied at each follow-up visit.

At baseline, only one patient was in combined remission, and about half of the cohort was in intestinal remission. During the integrated follow-up, the proportion of patients achieving combined remission increased steadily, reaching approximately one-quarter of the cohort at year four.

The treatment patterns evolved alongside clinical improvements. A notable proportion of patients (29.5%) entered the cohort while already receiving biologic therapy for IBD, reflecting the heterogeneity of real-world SpA-IBD populations and the variable timing of symptom onset, diagnosis, and treatment initiation. The proportion of patients receiving TNFi increased from 26% at baseline to 62% at two years, then stabilised. Conversely, prescriptions of anti-IL-23 and JAKi showed a modest increase during follow-up. In this regard, the extended enrolment period allowed the SPIB cohort to capture not only the evolution of integrated care strategies, but also a rapidly changing therapeutic landscape. Over the last decade, the introduction of drugs with domain-selective efficacy has increased the complexity of managing inflammation across intestinal and musculoskeletal manifestations. For example, IL-17 inhibition has demonstrated robust efficacy in articular disease but remains contraindicated in IBD [27,28]. Conversely, vedolizumab is gut-selective and may provide limited efficacy on musculoskeletal inflammation [29]. Similarly, IL-12/23 and IL-23 inhibitors are effective in intestinal disease and in peripheral musculoskeletal domains, but their role in axial involvement remains debated [30]. More recently, JAKi have shown efficacy in both SpA and IBD, offering a broader therapeutic approach; however, their use requires consideration of patient comorbidities, particularly cardiovascular risk. In this context, recognition of SpA-IBD as a multidomain inflammatory condition has become increasingly relevant, as non-integrated therapeutic strategies may preferentially target one domain while insufficiently addressing another.

The b/tsDMARD escalation observed during the study period coincided with a significant reduction in corticosteroid use and dosage. These findings suggest that progressive treatment optimization with targeted b/tsDMARD therapy within an integrated setting may increase disease control while minimising reliance on systemic corticosteroids.

The reported AEs aligned with known safety profiles: skin reactions were most common, severe infections were rare, and anaphylaxis occurred only with intravenous infliximab. Importantly, no unexpected safety signals were identified from the integrated escalation strategy.

The proportion of patients classified as axSpA-IBD increased over

Table 3
Patient's Subgroups. Comparison of clinical characteristics between subgroups of the SPIB cohort. The left section displays differences between patients with axial involvement (with or without peripheral involvement – i.e. axSpA-IBD) and those with exclusive peripheral involvement (arthritis, enthesitis, and/or dactylitis; i.e. perSpA-IBD). The right section presents differences between patients with Crohn's Disease and those with Ulcerative Colitis. a. Ischemic Cardiomyopathy, Heart Failure, Cardiac Arrhythmias (any), valvular disease (any), Stroke, Venous Thromboembolism, Pericardial Disease, other Cardiomyopathies. b. Diabetes (type I or type II), Obesity, Dyslipidaemia, Osteoporosis. c. csDMARDs include Sulfasalazine, Azathioprine, Ciclosporin, Methotrexate, and Hydroxychloroquine. # Refers to treatment ongoing before baseline prescriptions. Statistical analysis was conducted by "R" software. Subgroup comparisons were conducted using the Mann-Whitney U test for continuous variables and Pearson's chi-square test for categorical variables. P-values < 0.05 are reported in bold.

Patients n. (%)	**axSpA-IBD 89 (56.0)**	**perSpA-IBD 70 (44.0)**	**p**	**Crohn's Disease 93 (58.5)**	**Ulcerative Colitis 66 (41.5)**	**p**
Gender (F/M), n. (%)	46(51.7)/43(48.3)	48(68.6)/22(31.4)	0.046	56(60.2)/37(39.8)	38(57.6)/28(42.4)	0.865
Age, yrs ± SD	48.4 ± 13.7	50.0 ± 13.8	0.399	45.3 ± 12.8	54.5 ± 13.1	***<0.001***
Smoke, active, n. (%)	9 (10.1)	15 (21.4)	0.079	16 (17.2)	8 (12.1)	0.511
IBD disease duration, years ± SD	13.2 ± 11.6	10.3 ± 10.6	0.715	11 ± 11.5	13.1 ± 10.8	0.095
Msk symptoms duration, years ± SD	4.4 ± 5.0	2.4 ± 3.7	0.002	3.9 ± 5.0	2.9 ± 3.7	***0.002***
IBD type (CD/UC), n. (%)	50(56.2)/39(43.8)	43(61.4)/27(38.6)	0.613	93(100)/0(0.0)	0(0.0)/66 (100)	/
HLA-B27, n. (%)	36 (40.5)	8 (11.4)	***<0.001***	21 (22.6)	23 (34.9)	0.088
Comorbidities, n. (%)						
CVD[a], n. (%)	27 (30.3)	13 (18.6)	0.130	21 (22.6)	19 (28.8)	0.482
MTB[b], n. (%)	27 (30.3)	20 (28.6)	0.946	23 (24.7)	24 (36.4)	0.159
Disease Domains						
r-axSpA, n. (%)	20 (22.5)	0 (0.0)	/	14 (15.1)	6 (9.1)	0.382
nr-axSpA, n. (%)	69 (77.5)	0 (0.0)	/	36 (38.7)	33 (50.0)	0.210
Peripheral involvement, n. (%)	72 (80.9)	70 (100)	***<0.001***	85 (91.4)	57 (86.4)	0.452
Peripheral Arthritis, n. (%)	57 (64.0)	70 (100)	***<0.001***	75 (80.6)	52 (78.8)	0.931
Entesitis, n. (%)	50 (56.2)	32 (45.7)	0.249	45 (48.4)	37 (56.1)	0.428
Dactylitis (ever), n. (%)	4 (4.5)	3 (4.3)	>0.99	5 (5.4)	2 (3.0)	0.700
Psoriasis (ever), n. (%)	19 (21.3)	13 (18.6)	0.814	21 (22.6)	11 (16.7)	0.474
Uveitis (ever), n. (%)	9 (10.1)	5 (7.1)	0.708	10 (10.8)	4 (6.1)	0.456
Erythema Nodosum (ever), n. (%)	2 (2.2)	7 (10.0)	***0.043***	9 (9.7)	0 (0.0)	***0.010***
Disease Activity, baseline						
Tender Joint Count, mean ± SD	5.4 ± 3.9	5.2 ± 4.4	0.638	5.4 ± 4.4	5.2 ± 3.8	0.996
Swollen Joint Count, mean ± SD	1.0 ± 1.5	1.1 ± 1.5	0.694	1.1 ± 1.6	0.9 ± 1.2	0.628
DAPSA, mean ± SD	18.1 ± 7.4	18.1 ± 6.4	0.784	18.2 ± 7.2	18.0 ± 6.3	0.785
LEI, mean ± SD	0.8 ± 1.0	1.1 ± 1.3	0.491	1.0 ± 1.3	0.7 ± 0.9	0.492
ASDAS, mean ± SD	2.6 ± 0.8	/	/	2.6 ± 0.8	2.7 ± 0.8	0.548
CDAI, mean ± SD	143.1 ± 70.9	157.9 ± 67.1	0.255	150.0 ± 69.2	/	/
pMAYO, mean ± SD	1.7 ± 1.4	1.9 ± 1.7	0.967	/	1.8 ± 1.5	/
CRP (mg/dl), mean ± SD	1.2 ± 1.5	1.1 ± 1.5	0.901	1.3 ± 1.7	0.9 ± 1.1	0.902
Calprotectin (mg/kg), mean ± SD	166.5 ± 161.2	311.0 ± 433.1	0.376	207.4 ± 202.9	278.4 ± 457.2	0.377
Treatment, baseline #						
Mesalazine, n. (%)	55 (61.8)	43 (61.4)	>0.99	47 (50.5)	51 (77.3)	***0.001***
Corticosteroids (oral), n. (%)	37 (41.6)	33 (47.1)	0.588	43 (46.2)	27 (40.9)	0.614
csDMARDs[c], n. (%)	29 (32.6)	26 (37.1)	0.665	40 (43.0)	15 (22.7)	***0.013***
TNFi	26 (29.2)	16 (22.9)	0.381	27 (29.0)	15 (22.7)	0.395

Abbreviations: ax/perSpA-IBD: Spondyloarthritis associated with Inflammatory Bowel Diseases with axial/peripheral involvement; F: females; M: males; IBD: Inflammatory Bowel Diseases; msk: musculoskeletal; CD: Crohn's Disease; UC: Ulcerative Colitis; HLA-B27: Human Leukocyte Antigen B-27; CVD: cardiovascular diseases; MTB: metabolic diseases; r/nr-axSpA: radiographic/non-radiographic axial SpA; DAPSA: Disease Activity in Psoriatic Arthritis; LEI: Leeds Enthesitis Index; ASDAS: Axial Spondyloarthritis Disease Activity Score; CDAI: Crohn's Disease Activity Index; pMAYO: partial (without endoscopy) Mayo Clinic score for Ulcerative Colitis; CRP: C-reactive protein; csDMARDs: conventional synthetic disease modifying anti-rheumatic drugs; TNFi: Inhibitors of Tumor Necrosis Factor α; yrs: years; SD: standard deviation.

time due to new diagnoses, highlighting the sometimes insidious evolution of axial involvement and the importance of serial rheumatological assessments, even in apparently "peripheral-only" disease at presentation. In this context, the high prevalence of peripheral involvement observed among axSpA-IBD patients in our cohort requires careful interpretation. Our data suggest that peripheral involvement in axSpA-IBD may be heterogeneous, with variable contributions from arthritis and enthesitis. In this regard, enthesitis may be difficult to assess in real-word settings and may lead to some overestimation of peripheral involvement. Furthermore, this cohort was initially screened using a validated questionnaire, which may have had lower sensitivity in detecting subclinical or atypical axial involvement and may have preferentially identified patients with more evident peripheral manifestations. Finally, SpA-IBD may represent a distinct clinical entity compared with classical axSpA and may share closer clinical similarities with other peripheral SpA, including PsA, in which axial and peripheral involvement frequently coexist. However, this interpretation remains largely speculative, and further dedicated studies are needed to better explore this concept.

Improving detection of axial involvement remains challenging in real-world practice, particularly in patients with IBD in whom gastrointestinal symptoms may overshadow musculoskeletal manifestations, and may therefore require a multidisciplinary screening strategy based on risk stratification and selective imaging.

The comparison with previous studies is complicated by the limited reproducibility of SpA-IBD research, mainly due to the absence of disease-specific outcomes and classification criteria [31]. In this study, we employed the disease activity scores endorsed by recent studies [17, 18] and by the latest Italian consensus on SpA-IBD [2].

Baseline characteristics in our cohort align with those reported in other studies on patients with concomitant SpA and IBD diagnoses [32–37]. Furthermore, our findings regarding remission and clinical improvement are consistent with those reported by Dalal [38] and Savin [39], although those studies had substantially shorter follow-up.

The analysis of predictors of combined remission revealed that male sex was associated with a higher likelihood of treatment response, whereas axial disease and enthesitis were negative predictors of remission.

From a clinical perspective, axial disease and enthesitis are recognised as domains associated with higher inflammatory burden and long-

Table 4
Regression Analysis for Combined Remission. Univariable (left) and multivariable stepwise logistic regression (right) to identify baseline clinical predictors of combined remission (both rheumatological and gastrointestinal). a. Ischemic Cardiomyopathy, Heart Failure, Cardiac Arrhythmias (any), valvular disease (any), Stroke, Venous Thromboembolism, Pericardial Disease, other Cardiomyopathies. b. Diabetes (type I or type II), Obesity, Dyslipidaemia, Osteoporosis. c. csDMARDs include Sulfasalazine, Azathioprine, Ciclosporin, Methotrexate, and Hydroxychloroquine. # Refers to treatment ongoing before baseline prescriptions. Statistical analysis was conducted by "R" software. Subgroup comparisons were conducted using the Mann-Whitney U test for continuous variables and Pearson's chi-square test for categorical variables. The p value was highlighted in bold if <0.05.

	Univariable analysis		Multivariable analysis	
	OR (95% CI)	***p value***	**OR (95% CI)**	***p value***
Sex (male vs female)	1.64 (0.80–3.40)	0.177	2.80 (1.21–6.76)	***0.018***
Age, years	1.00 (0.97–1.02)	0.827	/	/
Smoke habit (present vs absent)	0.38 (0.09–1.18)	0.133	0.25 (0.05–0.92)	0.059
IBD disease duration, years	0.23 (0.01–1.85)	0.217	/	/
Musculoskeletal symptoms duration, years	0.99 (0.99–1.00)	0.650	/	/
IBD type (CD vs UC)	1.67 (0.80–3.63)	0.184	/	/
HLA-B27 (present vs absent)	0.88 (0.19–3.07)	0.857	/	/
Comorbidities, n. (%)				
CVD[a] (present vs absent)	1.64 (0.73–3.58)	0.218	/	/
MTB[b] (present vs absent)	0.74 (0.31–1.63)	0.466	/	/
Disease Domains				
Axial involvement (present vs absent)	0.48 (0.23–0.99)	***0.049***	0.41 (0.17–0.96)	***0.041***
Peripheral arthritis (present vs absent)	1.01 (0.43–2.60)	0.982	/	/
Entheseal involvement (present vs absent)	0.30 (0.13–0.63)	***0.002***	0.26 (0.11–0.59)	***0.002***
Dactylitis domain (present vs absent)	1.20 (0.17–5.82)	0.832	/	/
Psoriasis (present vs absent)	0.80 (0.30–1.93)	0.633	/	/
Uveitis (present vs absent)	1.75 (0.51–5.41)	0.345	/	/
Erythema nodosum (present vs absent)	6.82 (1.71–33.69)	***0.009***	6.70 (1.46–37.9)	***0.018***
Disease Activity, baseline				
Tender Joint Count	0.94 (0.84–1.04)	0.268	/	/
Swollen Joint Count	0.94 (0.69–1.23)	0.652	/	/
DAPSA	0.94 (0.88–1.00)	0.053	/	/
LEI	0.95 (0.51–1.60)	0.848	/	/
ASDAS	0.64 (0.29–1.28)	0.244	/	/
CDAI	1.00 (0.99–1.01)	0.812	/	/
pMAYO	0.91 (0.58–1.36)	0.677	/	/
CRP (mg/dl)	0.79 (0.52–1.05)	0.172	0.73 (0.48–0.99)	0.080
Calprotectin (mg/kg)	1.00 (0.99–1.00)	0.468	/	/
Treatment, baseline #				
Mesalazine (present vs absent)	1.05 (0.50–2.23)	0.896	/	/
Corticosteroids (oral) (present vs absent)	0.80 (0.38–1.65)	0.554	/	/
csDMARDs[c] (present vs absent)	0.76 (0.34–1.61)	0.481	/	/
TNFi (present vs absent)	0.87 (0.37–1.93)	0.737	/	/

Results are presented as Odds Ratios (ORs) with 95% confidence intervals (CIs). P-values < 0.05 were considered statistically significant.
Abbreviations: IBD: Inflammatory Bowel Diseases; CD: Crohn's Disease; UC: Ulcerative Colitis; HLA-B27: Human Leukocyte Antigen B-27; CVD: cardiovascular diseases; MTB: metabolic diseases; DAPSA: Disease Activity in Psoriatic Arthritis; LEI: Leeds Enthesitis Index; ASDAS: Axial Spondyloarthritis Disease Activity Score; CDAI: Crohn's Disease Activity Index; pMAYO: partial (without endoscopy) Mayo Clinic score for Ulcerative Colitis; CRP: C-reactive protein; csDMARDs: conventional synthetic disease modifying anti-rheumatic drugs; TNFi: Inhibitors of Tumor Necrosis Factor α; OR: odds ratio; CI:.

term disability [40]. As highlighted by McGonagle et al. [41], enthesitis is a biologically heterogeneous domain, with potential differences across disease settings. In SpA-IBD, the pathogenic mechanisms underlying entheseal involvement remain poorly understood and may involve inflammatory pathways that could respond differently to targeted therapies. Moreover, in our cohort, advanced therapies were predominantly represented by TNFi, which may have limited treatment effectiveness in patients with a predominant entheseal phenotype, as evidence from PsA suggest a favourable effect of interleukin-targeted therapies on enthesitis [42]. Furthermore, the potential contribution of widespread pain to elevated LEI scores cannot be excluded and may explain the association between entheseal involvement and reduced likelihood of clinical remission. Finally, the association with male sex is consistent with previous observations in SpA populations [43–45]; whether sex-related differences in remission reflect underlying biological mechanisms, differences in disease perception and psychosocial factors, or, likely, an interaction between these elements, remains uncertain [46].

The strengths of our study include its long-term follow-up, careful patient classification, and repeated dual assessment by rheumatologists and gastroenterologists using recommended and reproducible disease activity scores.

The primary limitation of this study lies in its observational, real-world design, which lacks a parallel control group and therefore prevents formal statistical inference regarding the impact of the integrated care model compared with standard care. In our setting, eligible patients with SpA-IBD were systematically referred to the integrated clinic, precluding the creation of a contemporaneous "usual-care" pathway. Randomisation to integrated versus non-integrated management was considered inappropriate in a non-interventional context, as stated by our Ethics Committee. In fact, this limitation reflects the current literature, in which integrated SpA–IBD models are mostly evaluated in uncontrolled observational cohorts [47]. To mitigate this limitation, we explored available data on diagnostic delay in SpA-IBD. Combined analyses from the REGISPONSER and RESPONDIA cohorts reported a mean diagnostic delay of 5.3 years in patients with ankylosing spondylitis and IBD, compared with the mean musculoskeletal symptom duration of 3.5 years observed in the SPIB cohort [48]. Similarly, patients diagnosed before implementation of the SPIB pathway in our centre showed a mean diagnostic delay of 6.1 years. Although these comparisons are indirect and not suitable for formal statistical inference, they may provide contextual support for the potential role of structured multidisciplinary evaluation in facilitating earlier diagnosis.

Additional limitations should also be recognised. The study was conducted at a single tertiary referral centre. Since the screening strategy was implemented in an IBD Unit focusing on the tight management of such patients, the SPIB cohort included only patients with confirmed IBD, not SpA patients with incident IBD. This may limit the

generalisability of the findings. Lastly, endoscopic disease activity was not consistently assessed, as in our real-world practice endoscopic procedures are performed based on clinical indications and resource availability, and are almost never performed in patients in clinical remission. As a result, mucosal healing data were unavailable for most patients, and intestinal remission was mainly evaluated using clinical scores.

Considering all the remaining gaps in this peculiar disease that acts as a bridge between two distinct conditions, sharing pathogenetic and therapeutic challenges, a research agenda for SpA-IBD should include: *a)* a thorough analysis of the shared pathogenetic pathways to develop new therapies effective for both conditions; *b)* consensus-driven classification of patients and definition of the clinimetric tools for integrated management to achieve a formal "composite remission"; c) consequently, broader application of the integrated management model for SpA-IBD patients; d) propensity score matching or multicentre data to compare the likely improved clinical outcomes of integrated management versus standard routine care; e) observational studies and RCTs specifically designed for such patients.

Conclusion

To our knowledge, this study presents the largest real-world cohort of SpA-IBD patients evaluated over a four-year period using an integrated gastro-rheumatological approach. Our findings support a multidisciplinary model of care and emphasise the importance of treatment strategies that explicitly address both joint and gut involvement. Within this context, we observed a progressive increase in b/tsDMARD use accompanied by a reduction in corticosteroid exposure. ACKNOWLEDGMENTS.

Ethical statement

The study protocol was approved by the Ethics Committee of Marche (Protocol number 267–2024, Comitato Etico Territoriale delle Marche, Azienda Ospedaliero Universitaria delle Marche, Ancona, Italy) and was conducted in accordance with Good Clinical Practice guidelines. All participants provided written informed consent for participation in the study and for the use of their clinical data for research and publication purposes.

Data availability

The data underlying this article will be shared on reasonable request to the corresponding author.

Glossary

AIC – Akaike Information Criterion.
AE(s) – Adverse Event(s).
AEs – Adverse Events.
ASAS – Assessment of SpondyloArthritis International Society.
ASDAS – Axial Spondyloarthritis Disease Activity Score. axSpA – Axial Spondyloarthritis. axSpA-IBD – Axial Spondyloarthritis associated with Inflammatory Bowel Disease.
BASDAI – Bath Ankylosing Spondylitis Disease Activity Index. bDMARDs – Biologic Disease-Modifying Anti-Rheumatic Drugs.
CD – Crohn's Disease.
CDAI – Crohn's Disease Activity Index.
CI – Confidence Interval.
CRP – C-Reactive Protein.
CTCAE – Common Terminology Criteria for Adverse Events. csDMARDs – Conventional Synthetic Disease-Modifying Anti-Rheumatic Drugs.
DAPSA – Disease Activity in Psoriatic Arthritis.
DETAIL – DETection of Arthritis in Inflammatory boweL diseases questionnaire.
ECCO – European Crohn's and Colitis Organisation.
HLA-B27 – Human Leukocyte Antigen B27.
IBD – Inflammatory Bowel Disease.
IL-12/23 – Interleukin 12/23.
IL-23 – Interleukin 23.
JAKi – Janus Kinase inhibitors.
LMM – Linear Mixed Model.
LEI – Leeds Enthesitis Index.
MRI – Magnetic Resonance Imaging. mNY – Modified New York criteria.
NSAIDs – Non-Steroidal Anti-Inflammatory Drugs.
OR – Odds Ratio. pMAYO – Partial Mayo score for ulcerative colitis. pSpA – Peripheral Spondyloarthritis. pSpA-IBD – Peripheral Spondyloarthritis associated with Inflammatory Bowel Disease.
PhGA – Physician Global Assessment.
PtGA – Patient Global Assessment.
REDCap – Research Electronic Data Capture.
SD – Standard Deviation.
SIJ – Sacroiliac Joints.
SJC – Swollen Joint Count.
SpA – Spondyloarthritis.
SpA-IBD – Spondyloarthritis associated with Inflammatory Bowel Disease.
SPIB – SPondyloarthritis in Inflammatory Bowel disease cohort.
STROBE - Strengthening the Reporting of Observational Studies in Epidemiology.
TJC – Tender Joint Count.
TNFi – Tumor Necrosis Factor inhibitors.
UC – Ulcerative Colitis.
VAS – Visual Analogue Scale.
VIF – Variance Inflation Factor.

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CRediT authorship contribution statement

Valentino Paci: Conceptualization, Methodology, Software, Validation, Formal analysis, Investigation, Data curation, Writing – original draft, Visualization. **Giulia Marchionni:** Conceptualization, Methodology, Software, Validation, Formal analysis, Investigation, Data curation, Writing – original draft, Visualization. **Alen Zabotti:** Writing – review & editing. **Lucia Perini:** Data curation. **Valentina Marconi:** Data curation. **Alice Agostinelli:** Data curation. **Ilaria Cimaroli:** Data curation. **Federico Fiorini:** Data curation. **Raissa Di Zio:** Data curation. **Leonardo Massaccesi:** Data curation. **Raffaella Sordillo:** Data curation. **Diego Bartoli:** Data curation. **Valeria Manuale:** Data curation. **Daniele Balducci:** Resources, Data curation. **Michele Montori:** Resources, Data curation. **Laura Bolognini:** Resources, Data curation. **Emanuele Bendia:** Resources, Data curation. **Devis Benfaremo:** Writing – review & editing. **Antonio Benedetti:** Resources, Data curation. **Luca Quartuccio:** Writing – review & editing. **Gianluca Moroncini:** Conceptualization, Methodology, Validation, Investigation, Resources, Writing – review & editing, Supervision, Project administration. **Dennis Poddubnyy:** Writing – review & editing. **Michele Maria Luchetti Gentiloni:** Conceptualization, Methodology, Validation, Investigation, Resources, Writing – review & editing, Supervision, Project administration.

Declaration of competing interest

Valentino Paci reports speaking and/or consulting fees from AbbVie, Eli Lilly and Johnson & Johnson. Alen Zabotti reports speaking and/or

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.semarthrit.2026.153005.

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