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Original Article

Clinical and patient reported outcomes of the multidisciplinary management in patients with inflammatory bowel disease-associated spondyloarthritis

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ABSTRACT

Objective: Arthritis is the most frequent extra-intestinal manifestation in patients with inflammatory bowel diseases (IBD). The coexistence of intestinal and articular inflammation advocates the need for a multidisciplinary management of patients with IBD-associated spondyloarthritis.

Methods: Consecutive IBD patients were evaluated jointly by the gastroenterologist and the rheumatologist in a combined clinic. All the patients were assessed and screened for articular involvement, disease activity and health related quality of life. After the prescription of a shared treatment, patients with spondyloarthritis were followed up for 24 months.

Results: Two hundred sixty-two IBD patients, including 80 who were classified as affected by spondyloarthritis according to the ASAS criteria, were included in the study. At baseline, patients with both IBD and spondyloarthritis showed worse quality of life in both the physical and mental domains. The multidisciplinary management provided a significant improvement of gastrointestinal and articular manifestations, as well as the health-related quality of life. Moreover, global and gastrointestinal-specific quality of life significantly correlated with articular disease activity.

Conclusion: The multidisciplinary management significantly improves both articular and gastrointestinal disease activities and the quality of life of patients with IBD-associated spondyloarthritis.

An appropriate screening strategy and the integrated management of these patients should be encouraged and employed in clinical practice.

1. Introduction

Arthritis is the most frequent extra-intestinal manifestation in patients with inflammatory bowel disease (IBD) and may develop before, simultaneously, or after the diagnosis of overt IBD [1,2]. IBD-associated spondyloarthritis (SpA/IBD), or enteropathic spondyloarthritis, is included in the group of the spondyloarthritis (SpA), together with ankylosing spondylitis (AS), reactive arthritis, undifferentiated arthritis and psoriatic arthritis [3].

SpA/IBD is often overlooked among other SpAs, despite being burdened with a significant diagnostic delay, and its current therapeutic approach is mainly borrowed from other SpAs [4]. Nevertheless, as it has been recently emphasized, the coexistence of joint and gut inflammation advocates a multidisciplinary management [4,5].

However, in real practice only a small proportion of IBD patients with articular symptoms are properly evaluated by the rheumatologist through a coordinated action with the caring gastroenterologist [6].

In addition, the evaluation of the intestinal and articular disease activities is usually carried out independently, as both specialists employ their own validated instruments. Thus, the choice of the treatment

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may not adequately consider both disease activities at the same time, as well as other therapeutic peculiarities of SpAs as, for example, the earlier need for a biologic treatment in SpA/IBD with axial involvement with respect to SpA/IBD with peripheral involvement.

Hence, an appropriate screening strategy of IBD patients with articular symptoms, a combined clinical evaluation and, thereafter, a therapeutic approach encompassing both intestinal and articular involvements are likely to be beneficial in SpA/IBD patients, especially for the achievement of better clinical outcomes.

In this work, we describe the development and clinical experience of an integrated management approach carried out in the IBD unit, employing a screening strategy and a dedicated consultant rheumatologist, and the impact of such a strategy on our cohort of patients with SpA/IBD, henceforth defined *SPondyloarhritis in Inflammatory Bowel disease* (SPIB) cohort, demonstrating that the multidisciplinary management of patients with SpA/IBD may strengthen the therapeutic approach and improve both disease activity and health related quality of life (HRQoL).

2. Patients and methods

2.1. Patient evaluation, treatment algorithm and follow-up

From June 2014 to April 2018, 422 consecutive patients with IBD, either Crohn's disease (CD) or ulcerative colitis (UC), diagnosed according to the standard criteria [7–8] and followed at the IBD Unit of our hospital, were evaluated together by both the gastroenterologist and the rheumatologist at the same baseline visit. The visits were carried out in the outpatient room and/or in the clinical wards of the Gastroenterology departments.

Demographic and clinical data, including a thorough history and physical examination, were recorded for each patient. Rheumatologic assessment included tender and swollen joint count, current or past history of arthritis, dactylitis, enthesitis and inflammatory back pain. Further laboratory tests, including, among others, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), rheumatoid factor (RF), anti-citrullinated protein antibodies (anti-CCP) and human leukocyte antigen B-27 (HLA−B27), were prescribed as needed. Whenever appropriate, patients with joint symptoms underwent further imaging tests, i.e. ultrasound, conventional X-ray or magnetic resonance imaging (MRI).

Patients with a clinical diagnosis of SpA/IBD and fulfilling the ASAS criteria for axial and/or peripheral SpA were classified respectively as SpA/IBD patients with axial involvement (AxSpA/IBD) and SpA/IBD with isolated peripheral involvement (PerSpA/IBD) [3]. The resulting cohort of patients constituted the SPIB cohort [9].

In addition, from October 2016 IBD patients without a diagnosis of SpA were also screened for articular symptoms using a novel screening tool, the DETAIL (*DETection of Arthritis in Inflammatory boweL diseases*) questionnaire, whose validation process has been described elsewhere [10].

All the patients were thereafter followed and evaluated every 6 months by the two specialists in the outpatient room of the IBD Unit. A control group followed with a non-multidisciplinary approach could not be included for comparison, because the combined clinic had already been active, though not systematically, before study inception.

At each clinical observation, the rheumatologist and the gastroenterologist decided together the therapeutic approach following a shared algorithm, previously described [9], that was designed considering the gastrointestinal and articular disease activities and the pattern of articular involvement at diagnosis (i.e. axial or peripheral arthritis) (Fig. 1).

Available treatment options were: a) conventional drugs, i.e. oral or topical corticosteroids, mesalazine, cyclosporine and azathioprine; b) conventional-synthetic Disease Modifying Anti-Rheumatic Drugs (csDMARDs), i.e. sulfasalazine (SSZ) and methotrexate (MTX); c) biological Disease Modifying Anti-Rheumatic Drugs (bDMARDs), i.e. infliximab (IFX), adalimumab (ADA), golimumab (GOL), ustekinumab (UST) and vedolizumab (VED) [11]. Whenever MTX or bDMARDs were indicated, the dose registered for IBD was used [9].

2.2. Clinical assessment and patient reported outcomes

At baseline and at 12 (12mo) and 24 (24mo) months, all the IBD patients that participated in the study were assessed for clinical disease activity and HRQoL measures.

Table 1 summarizes the measurement properties of the tools employed in the study.

Briefly, articular (SpA) disease activity was assessed by the Bath Ankylosing Spondylitis Disease Index (BASDAI) [12] and the Ankylosing Spondylitis Disease Activity Score-C-reactive protein (ASDAS-CRP) [13]; gastrointestinal (IBD) disease activity was assessed with the Crohn's disease activity index (CDAI) for CD [14] and the partial Mayo (pMAYO) score for UC [15]. Patient Global Assessment (PtGA) of disease activity on a numeric rating scale (NRS) from 0 to 10 was also recorded for all patients.

Physical function in patients with SpA/IBD was assessed by means of Bath Ankylosing Spondylitis Functional Index (BASFI) [16] and Health Assessment Questionnaire (HAQ) [17].

Patient-reported outcomes (PROs) measuring HRQoL were administered to all IBD patients, and included specific tests like the Inflammatory Bowel Disease Questionnaire (IBDQ) [18] and the generic instrument Short Form-36 health survey (SF-36), summarized in two summary scores defined Physical Component Score (Sf-36/PCS) and Mental Component Score (Sf-36/MCS) [19].

2.3. Ethical approval and statistical analysis

The study was carried out in compliance with the Declaration of Helsinki on ethical principles for medical research and has been approved by the local Ethic Committee (*Comitato Etico Regionale delle Marche*, protocol n°20170510OR). All the patients that agreed to participate in the study signed a written informed consent.

Data were transferred in an electronic database and anonymized. The D'Agostino and Pearson omnibus test was used to check normality of data. Quantitative variables were summarized as mean ± SD or median (IQR), as appropriate, and Student *t*-test or paired and unpaired non-parametric tests were used to evaluate differences between groups, as appropriate. Qualitative variables were expressed as absolute and percentage frequencies and comparisons were performed by Chi square test. The association between variables was evaluated with the Spearman correlation coefficient. A $p < .05$ was considered significant. Data were analyzed using the GraphPad Prism version 7 (GraphPad software).

3. Results

3.1. Patients

At baseline, 422 patients were screened for articular symptoms. A total of 103 patients reported articular symptoms (24.4% of IBD patients). Upon rheumatologic evaluation, 85 patients (82.5% of the patients reporting articular symptoms and 20.1% of the IBD patients) were classified as affected by SpA/IBD.

Two-hundred and sixty-two (n. 262) patients, including 80 SpA/IBD patients (SPIB cohort) and 182 IBD patients, accepted to participate in the study.

Among the patients reporting articular symptoms, in 18 (17.4%) SpA/IBD was excluded and osteoarthritis (n. 13), fibromyalgia (n. 2), gout (n.1) and calcium pyrophosphate deposition disease (CPPD) (n. 2) were diagnosed.

Table 2 summarizes the baseline characteristics of the patients.

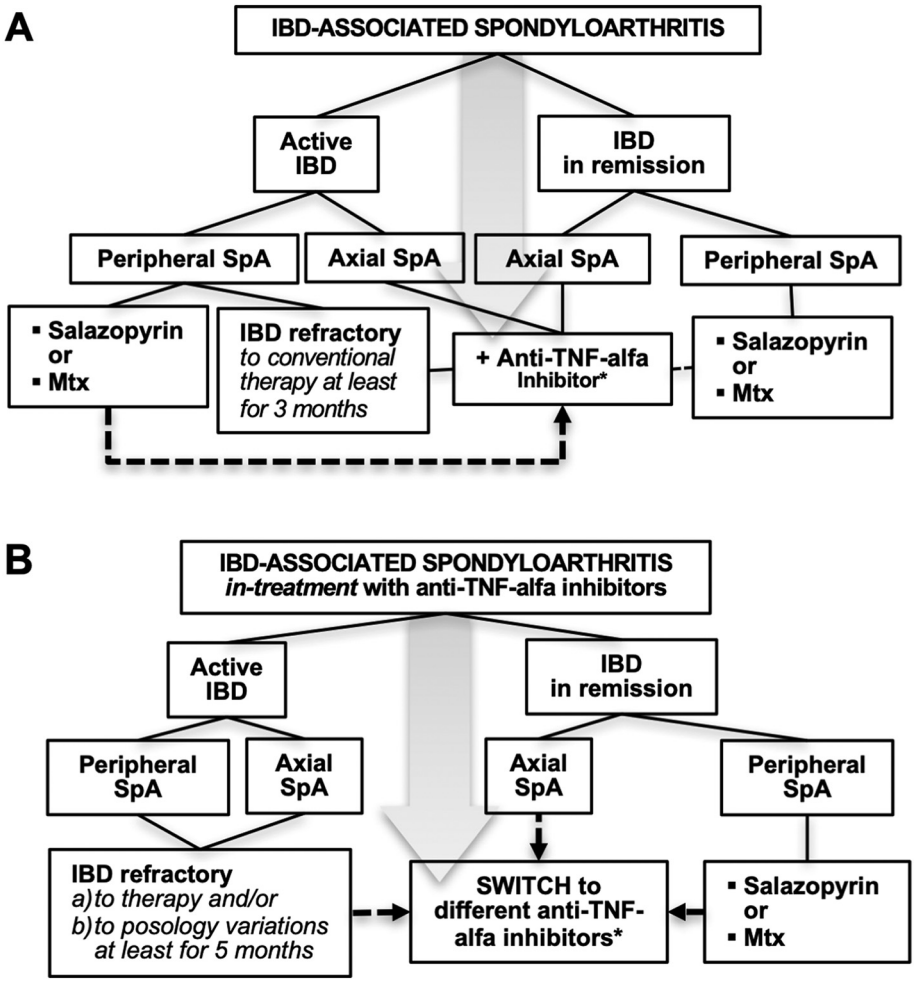

Fig. 1. Therapeutic algorithm employed for the patients affected by inflammatory bowel disease-associated spondyloarthritis.
A. Inflammatory bowel disease-associated spondyloarthritis (SpA/IBD) patients (SPIB cohort) biological drugs-naïve. Briefly, biological drugs-naïve of the SPIB cohort patients were treated, depending on IBD activity and site of the articular involvement, as follow: a) AxSpA/IBD with biologic therapy in first line therapy, due to the absolute contraindication for a long-course treatment with NSAIDs in case of IBD; b) PerSpA/IBD in case of active-IBD and in those patients non-responders to a short course of corticosteroids (not > 3 months) or NSAIDs (not > 2 weeks), with: *i)* a csDMARD, as MTX or SSZ; in case of: ESR > 30 mm/h and/or CRP > 0.5 mg/dl, and polyarticular inflammatory involvement *ii)* biologic therapy; or c) PerSpA/IBD in inactive IBDs, with steroids or DMARDs, depending on the number of inflamed joints and systemic inflammation (evaluated by ESR and/or CRP). B. SpA/IBD patients already in treatment with biologic therapy for the IBD. The SpA/IBD patients already treated with biologic therapy were treated as follow: a) PerSpA/IBD with active IBD were switched to another biologic therapy; b) PerSpA/IBD with IBD in remission were treated adding a csDMARD to the biologic therapy already in use; c) AxSpA/IBD were switched to another biologic therapy, regardless of IBD activity. Dashed arrows: patients refractory to the therapy on course.
*Using the attack dose and the dosage approved for the therapy of IBD in case of active IBD. Abbreviations. IBD: inflammatory bowel disease. NSAID: non-steroidal anti-inflammatory drug. AxSpA/IBD: patients with axial spondyloarthritis, PerSpA/IBD: patients with peripheral spondyloarthritis. csDMARD: conventional synthetic disease modyfing anti-rheumatic drug, MTX: methotrexate, SSZ: salazopiryn. ESR: erythrocyte sedimentation rate, CRP: C-reactive protein.

There were no differences between SpA/IBD and IBD cohorts with regard to the relative frequency of CD/UC, mean age and mean duration of IBD, whereas in the SpA/IBD cohort there was a higher proportion of women and a higher prevalence of current or previous extra-intestinal manifestations besides the joint involvement.

The intestinal disease resulted active in a higher proportion of patients with SpA/CD than patients with CD, whereas the UC disease activity was similar between the two groups.

Among patients with SpA/IBD, 39 (48.7%) had axial involvement (AxSpA/IBD), with or without concomitant peripheral arthritis or enthesitis, and 41 (51.3%) had isolated peripheral involvement (PerSpA/IBD), that included oligoarticular (29.2%), polyarticular (46.3%) and enthesitic (24%) manifestations.

In the SPIB cohort, only 7 (8%) patients were HLA-B27 positive. These patients were all classified to be affected by AxSpA/IBD according to ASAS criteria and fulfilled at the same time the modified New-York criteria (mNYC) for AS. The remaining 32 patients (82%) had non-radiographic sacroiliitis detected on MRI.

With regard to the diagnostic delay, the mean duration of articular symptoms in the SpA/IBD cohort was about 4 years, but it was significantly longer for the patients with axial than those with isolated peripheral involvement (5.5 vs. 2.3 years, $p = .003$).

3.2. Treatment approach

At baseline, 19% of patients were taking a bDMARD in the SpA/IBD group, compared to 25% of patients with IBD (p = not significant, ns). Upon the multidisciplinary evaluation, a bDMARD was prescribed in 58 (72.5%) patients with SpA/IBD and at the 12mo follow-up 13 patients were receiving IFX, 41 ADA, 2 GOL, 1 UST and 1 VED. MTX was prescribed in 5 and SSZ in 7 patients with PerSpA/IBD.

Eight AxSpA/IBD patients declined treatment with a bDMARD. The main reasons were major safety concerns, major contraindications (i.e. recent history of prostate cancer), pregnancy planning or a very low articular disease activity associated with a deep remission of the intestinal disease.

3.3. Clinical evaluation at baseline

At the time of first evaluation, intestinal disease was active in 52% of SpA/CD patients in comparison with 24% of CD patients ($p < .01$) as well as in 62.5% of SpA/UC patients vs. 55% of UC patients (p = ns), as assessed respectively by CDAI and pMAYO scores.

As expected, median CDAI resulted significantly higher in the SpA/CD group than in CD patients (158 (84.3) vs 110 (85), respectively, $p < .001$). However, there were no differences between the median CDAI of the SpA/CD vs. the CD group if in the calculation the item n. 4, reporting the presence of extra-intestinal manifestations (in such a case joint pain), was not incorporated into the final score (133 (82.8) vs 110 (85), p = ns) (Fig. 2).

Conversely, UC disease activity did not significantly differ between SpA/UC and UC patients (2 (2) vs 2 (2), p = ns).

With regard to the PROs of HRQoL, the SPIB cohort reported a poorer gastrointestinal (IBDQ, 157 (50) vs. 179 (51), $p < .001$) and

Table 1
Measurement properties of the disease activity and patient reported outcomes employed in the SPIB study.

Test	Items and interpretation
Bath ankylosing spondylitis disease index [9]	6 items: [1] fatigue, [2] back pain, [3] peripheral pain/swelling, [4] discomfort at pressure, [5] morning discomfort, and [6] duration of morning stiffness; Range from 0 to 10, with lower number representing less severe disease activity; Score > 4 = active disease.
Ankylosing spondylitis disease activity score [10]	5 items: [1] back pain, [2] morning stiffness, [3] patient global, [4] peripheral pain/swelling, and [5] C-reactive protein; Score < 1.3 = inactive disease; Score 1.3 to < 2.1 = low disease activity; Score 2.1 to ≤3.5 = high activity; Score > 3.5 = very high activity; Change ≥1.1 = clinically important improvement; Change ≥2.0 = major improvement.
Crohn's disease activity index [11]	8 items: [1] liquid stools, [2] abdominal pain, [3] general well-being, [4] extra-intestinal manifestations (including arthralgia), [5] use of anti-diarrheals, [6] abdominal masses, and [7] hematocrit, 8) weight; Final score is the sum of items, weighted by different factors; Score < 150 = non-active disease; Score > 150 = active disease; Score > 450 = extremely severe disease.
Partial MAYO score [12]	3 items: [1] stool frequency, [2] rectal bleeding, and [3] physician global assessment; Range from 0 to 9; Score < 2 = disease remission; Score 2–4 = mild disease activity; Score 5–7 = moderate disease activity; Score > 7 = severe disease activity.
Bath ankylosing spondylitis functional index [13]	10 questions designed to determine the degree of functional limitation; Final score ranges from 0 to 10, with a lower score indicating less functional limitation.
Inflammatory bowel disease questionnaire [14]	32 questions divided into 4 subscales: [1] bowel symptoms (10 questions); [2] systemic symptoms, including sleep disorders and fatigue (5 questions); [3] emotional function, such as depression, aggression and irritation (12 questions); and [4] social function, meaning the ability to participate in social activities and to work (5 questions); The patient is invited to choose from 1 to 7 for every question; Total score ranges from 32 to 224 points, with lower scores reflecting worse quality of life.
Patient global assessment (PtGA)	Collected on a numeric rating scale ranging from 0 to 10 for the question asking the patient: "Considering all the ways your disease affects you, how much do you think is active today?"
Short form-36 health survey [15]	Generic health status instrument with 8 domains: [1] physical function, [2] body pain, [3] role limitations–physical, [4] general health, [5] vitality, [6] social function, [7] role limitations–emotional, and [8] mental health; Greater scores reflect better health status; Summarized in two summary scores defined as the [1] physical component score (Sf-36/PCS) and [2] mental component score (Sf-36/MCS).

global HRQoL (Sf-36 PCS and MCS, 40.9 (12.4) vs 52.7 (13) and 35.9 (20) vs 44.2 (16.2), respectively, both p < .001), in both the physical and mental well-being summary scores (Fig. 3, A-C). All the domains of the Sf-36 assessment (physical activity, role-physical, bodily pain, global health, vitality, social activities, role-emotional and mental health) were significantly worse in SpA/IBD than in IBD patients ($p < .001$ for all comparisons) (Fig. 3D).

SpA/IBD patients also perceived a higher disease activity (PtGA, 60 (30) vs 40 (30), p < .001) compared to patients with IBD without articular involvement.

No differences were found between AxSpA/IBD and PerSpA/IBD patients for both articular disease activity and HRQoL PROs assessed at baseline (data not shown).

Moreover, even if the median disease activity and HRQoL scores were similar between male and female SpA/IBD patients, women showed a non-significant trend towards worse scores in all measures, especially for Sf-36/MCS (33 (22) vs 38 (17.5), $p = .08$).

3.4. Assessment of disease activity at follow-up evaluations

All SpA/IBD patients were evaluated at 12 months, but 13 missed the 24mo follow-up.

In the SPIB cohort, articular disease activity significantly improved, compared to baseline, at the 12mo (BASDAI, 5 (2) vs 3.7 (3), $p < .001$; ASDAS-CRP, 2.9 (1.2) vs 2.2 (0.9), p < .001) and the 24mo follow-up (5 (2) vs 3.8 (3), p < .001; ASDAS-CRP, 2.9 (1.2) vs 2.2 (1.3), p < .001) (Fig. 4A).

Gastrointestinal disease activity was significantly improved compared to baseline only in patients with SpA/CD but not SpA/UC both at the 12mo (CDAI, 158 (84.3) vs 120 (88.2), $p = .005$; pMAYO, 2 (2) vs 1.5 (1), p = ns) and the 24mo follow up evaluations (CDAI, 158 (84.3) vs 120 (106), $p = .02$; pMAYO, 2 (2) vs 1 (2), p = ns). However, as discussed in the previous section, this could be a misleading interpretation due to the presence of the item reporting joint pain in the CDAI score.

3.5. Assessment of function and health related quality of life

In patients with SpA/IBD, physical function as assessed by BASFI (2.1 (3) vs 1.5 (2), $p = .002$) and HAQ (0.25 (0.75) vs 0 (0.5), $p = .01$) was significantly improved compared to baseline at 12mo, but the differences were non statistically significant at the 24mo assessment (BASFI, 2.1 (3) vs 2 (2); HAQ, 0.25 (0.75) vs 0 (0.37)).

Patients with SpA/IBD experienced a significant amelioration of the global HRQoL, with particular regard to physical and mental health both at the 12mo (Sf-36/PCS, 40.9 (12.4) vs 47 (16), $p = .003$; Sf-36/MCS, 35.9 (20) vs 41.5 (15.2), $p = .001$) and the 24mo (Sf-36/PCS, 40.9 (12.4) vs 44.3 (14.6), $p = .02$; Sf-36/MCS, 35.9 (20) vs 41.3 (13), p = .02) follow-up visits (Fig. 4B).

At the 12mo assessment, 42 (52.5%) patients experienced a clinically important improvement of the Sf-36/PCS, defined as a positive difference of at least 3.0 points between the follow-up and baseline score. The rate of clinically meaningful improvement of the Sf-36/MCS score was slightly lower, as it was seen in 38 (47.5%) patients. Similar percentages of improvement were confirmed for both scores at the 24mo follow-up.

Gastrointestinal specific HRQoL, assessed by IBDQ, was also improved throughout the study period in the whole SPIB cohort (157 (50) vs 180.5 (48) and 185 (49) at the 12mo and the 24mo follow-up, respectively, both $p < .001$) (Fig. 4C).

3.6. Comparisons between biological or conventional therapy

With regard to baseline treatment, SpA/IBD patients already receiving a biologic drug showed similar disease activity, function and HRQoL compared to patients receiving conventional treatment (p = ns for all comparisons).

Patients who were assigned to a bDMARD after the integrated evaluation at baseline drove the global amelioration of disease activity, function and quality of life seen at the 12mo and the 24mo assessments, whereas patients treated with csDMARDs did not experience such a

Table 2
Baseline characteristics of the patients with inflammatory bowel disease-associated spondyloarthritis and inflammatory bowel disease without articular involvement included in the SPIB study.

	SpA/IBD (n = 80)	IBD (n = 182)	p
Crohn's disease: Ulcerative colitis	48 (60%): 32 (40%)	118 (65%): 64 (35%)	0.45
Males: Females	34 (42.5%): 46 (57.5%)	110 (60%): 72 (40%)	0.007
Age, in years	48.4 ± 14.1	46 ± 14.7	0.21
Mean duration of IBD, in years	12 ± 10.3	11 ± 9.8	0.49
Mean duration of joint symptoms, in years	3.9 ± 4.8	N/A	/
Current smokers: Ex-smokers	15 (19%): 28 (35%)	59 (32.5%): 34 (18.5%)	0.69
HLA-B27 positivity	7 (8%)	N/A	/
Prior surgical intervention for the IBD	21 (26%)	55 (30%)	0.51
Previous or concurrent extra-intestinal manifestations	12 (15%)	10 (6%)	0.01
Psoriasis	4	2	
Eritema nodosum	4	8	
Uveitis	6	8	
Pioderma gangrenosum	1	0	
Crohn's disease activity (according to CDAI)			
Remission	23 (48%)	90 (76%)	< 0.001
Moderate	16 (33%)	16 (13.5%)	0.003
Moderate-to-Severe	9 (19%)	12 (10.5%)	0.13
Ulcerative colitis activity (according to pMAYO)			
Remission	12 (37.5%)	29 (45%)	0.46
Mild	18 (56.5%)	28 (44%)	0.24
Moderate-to-severe	2 (6%)	7 (11%)	0.45
Current medication at baseline			
NSAIDs	3	2	
Sulfasalazine	4	2	
Mesalazine	32	85	
Cyclosporine	1	0	
Azathioprine	11	31	
Oral steroids	20	31	
Topical steroids	4	5	
Methotrexate	2	1	
Infliximab	12	24	
Adalimumab	3	20	
Golimumab	0	2	
Features of axial spondyloarthritis patients	n = 39	N/A	
Ankylosing spondylitis	7 (18%)		
Non-radiographic Axial-SpA	32 (82%)		
Concomitant Peripheral involvement	20 (51%)		
Syndesmophytosis	8 (20%)		
Bamboo spine	2 (5%)		
Sacroiliitis on imaging	39 (100%)		
Features of peripheral spondyloarthritis patients	n = 41		
Oligoarticular involvement	12 (29.2%)		
Poliarticular involvement	19 (46.3%)		
Enthesitis	10 (24%)		

Data are presented as n, n (%) or mean ± SD. Abbreviations: SpA/IBD: cohort of patients with inflammatory bowel disease associated spondyloarthritis (SPIB cohort); IBD: cohort of patients with inflammatory bowel disease without articular disease; CDAI: Crohn's Disease Activity Index; pMAYO: partial Mayo score: NSAIDs: Non-steroidal anti-inflammatory drugs.

significant improvement. In fact, at the 12mo assessment IBDQ (186 (44) vs 158 (49), $p < .001$), Sf-36/PCS (48 (13) vs 43 (12), $p = .002$), Sf-36/MCS (42.7 (16) vs 36 (19.5), $p < .001$), BASDAI (3 (2.1) vs 6 (2.5), $p < .001$), BASFI (1.1 (1.1) vs 2.1 (3), $p < .001$) and ASDAS-CRP (2 (0.8) vs 3.1 (1.2), $p < .001$) were significantly improved only in the group of patients treated with bDMARDs. The improvement was also maintained at the 24mo assessment (data not shown).

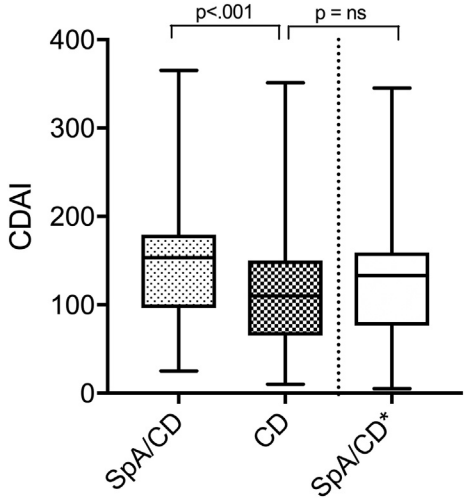

Fig. 2. Comparison of median CDAI of CD patients vs SpA/CD patients with or without the incorporation of CDAI item n. 4. There are no differences between the median CDAI of the SpA/CD vs. the CD group if in the calculation the item n. 4, reporting the presence of extra-intestinal manifestations (in such a case joint pain), is not incorporated into the final score (SpA/CD*). CDAI: Crohn's Disease Activity Index; CD: Crohn's disease; SpA/CD: Crohn's disease associated spondyloarthritis.

3.7. Association between disease activity and patient reported outcomes

In the SPIB cohort, articular disease activity assessed by ASDAS-CRP significantly correlated with physical function (BASFI, rho 0.48, $p < .001$) and HRQoL PROs (IBDQ, rho −0.37; Sf-36/MCS, rho −0.42, both with $p < .01$), both at baseline and at follow-up assessments. BASDAI showed a similar correlation for BASFI (rho 0.54, $p < .01$) and IBDQ (rho −0.27, $p = .01$), but not Sf-36 summary scores (Table 3).

In addition, considering the whole cohort of 262 IBD patients, intestinal disease activity significantly correlated with HRQoL PROs, such as IBDQ (rho −0.57 and − 0.47 for CDAI and pMAYO, respectively, $p < .001$), Sf-36/MCS (rho −0.38 and − 0.26, for CDAI and pMAYO respectively, $p < .001$ and $p = .01$), and Sf-36/PCS (rho −0.43 and − 0.20, $p < .001$ and $p < .05$).

These observations suggest that the global amelioration of both gastrointestinal and articular manifestations is tightly associated with the amelioration of the global HRQoL of the patients.

4. Discussion

The association between SpAs and IBDs, known since the beginning of the last century, is highly suggestive of a shared pathogenic pathway [20]. Indeed, IBDs and SpAs share several features, including genetic susceptibility and clinical manifestations [5].

Such overlap between SpA and IBD, and the consequent heterogeneity of SpA/IBD manifestations, strongly advocates a shared decision-making and a multidisciplinary approach.

However, the prevalence and disease burden of SpA in patients with an overt or occult IBD is still rather underestimated by both gastroenterologists and rheumatologists, and accordingly in clinical practice they use to evaluate separately patients with both articular and gastrointestinal involvement.

To our knowledge, this is the first study reporting the clinical and patient reported outcomes of a multidisciplinary gastro-rheumatologic approach in a large cohort of SpA/IBD patients over a two-year follow-up.

As demonstrated in our study, patients with both SpA and IBD have a worse health related quality of life (HRQoL), as assesses by the scoring

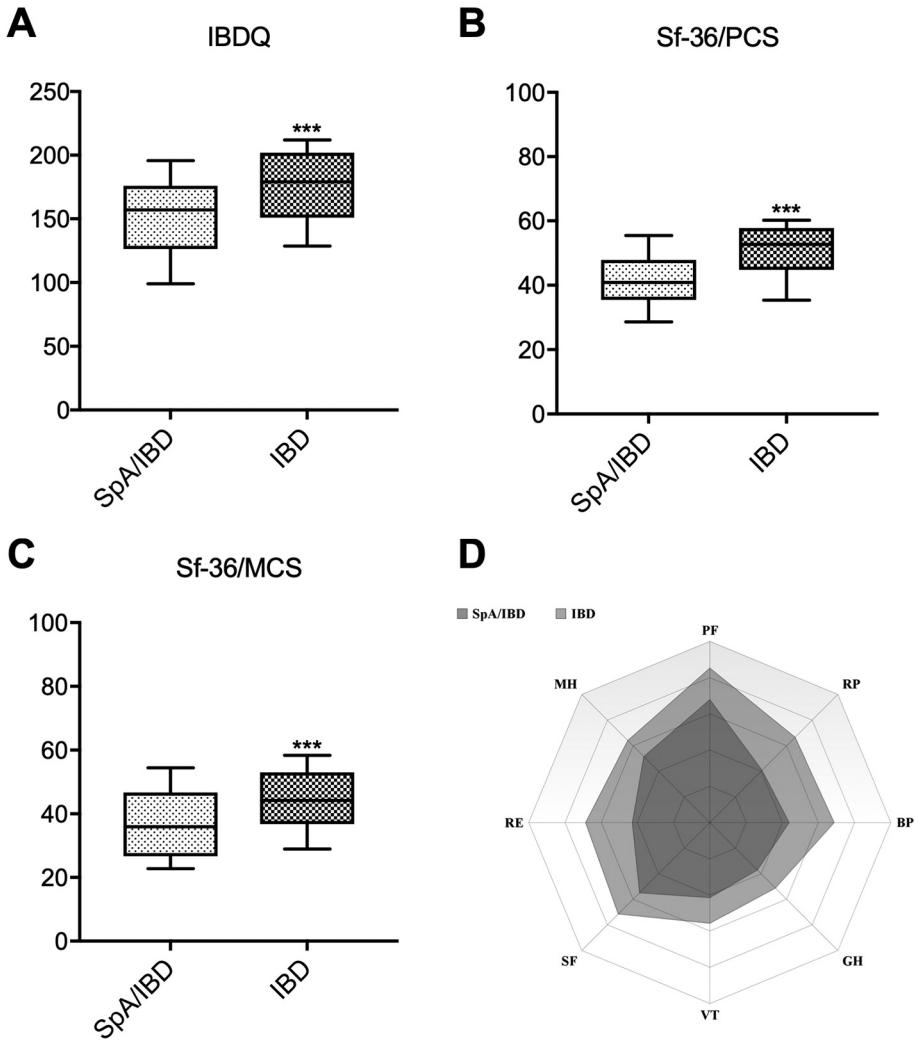

Fig. 3. Evaluation of the health-related quality of life (HRQoL) at baseline in patients with inflammatory bowel disease-associated spondyloarthritis (SpA/IBD) compared to patients with inflammatory bowel disease without spondyloarthritis (IBD). HRQoL was assessed by A. Inflammatory Bowel Disease Questionnaire (IBDQ), B. Short-Form 36 Physical Component Score (Sf-36/PCS) and C. Short-Form 36 Mental Component Score (Sf-36/MCS). D. Radar diagram showing the distribution of Sf-36 subscales in patients with SpA/IBD vs patients with IBD: physical function (PF), role limitation–physical (RP), body pain (BP), general health (GH), vitality (VT), social function (SF), role limitation–emotional (RE), and mental health (MH).
* $p < .05$ ** $p < .01$ ***$p < .001$.

of both generic (Sf-36) and specific (IBDQ) questionnaires. Moreover, the observation that HRQoL is tightly related to disease activity suggests that an earlier treatment and a tighter control may achieve better health outcomes.

In our SPIB cohort, the diagnostic delay is about 4 years, but significantly different between patients with axial and peripheral SpA. This could be related to the fact that inflammatory back pain (IBP) is frequently misdiagnosed as non-specific or mechanic back pain, whereas the rheumatologic referral may be earlier and easier for peripheral joints complains [21]. Other Authors found a slightly longer lag time (5.2 years) between the onset of joint symptoms and SpA diagnosis in patients with IBD [5], even if shorter than the estimated diagnostic delay for SpA in general, which is 8.8 years for women and 6.5 years for men [22].

In light of this, the first important issue in SpA/IBD is the need for an early and definite diagnosis of spondyloarthritis.

The establishment of a gastro-rheumatological clinic is certainly useful and probably effective in shortening diagnostic delay, as shown in previous studies [5]. However, since a combined approach is not always feasible, especially in smaller realities, the validation of simpler referral tools is necessary.

The systematic application of a simple and effective screening questionnaire to all IBD patients complaining articular symptoms, with a consequent appropriate referral to the rheumatologist, may be an easy and practical solution. So far, few questionnaires to screen IBD patients for the presence of SpA have been developed and validated [23]. However, these instruments often lack simplicity and are difficult to employ in routine clinical practice.

For this reason, we recently developed and preliminary validated the DETection of Arthritis in Inflammatory boweL diseases questionnaire (DETAIL), a six-item questionnaire that has been tested in IBD patients not already diagnosed having a SpA [10]. In the validation study, the DETAIL demonstrated an excellent performance, referring to the rheumatologist a significant number of patients reporting articular symptoms and could, therefore, represent a novel tool to achieve the early diagnosis of SpA/IBD. Indeed, the systematic evaluation of all patients that are followed in IBD Units is resource and time consuming, whereas the systematic application of an easy screening questionnaire is surely a feasible and effective approach even in a gastroenterological setting.

In our real-life IBD cohort, the prevalence of SpA is around 20%, slightly higher than expected from literature studies [24]. Among 80 patients with SpA/IBD, about 50% had axial involvement and the other 50% isolated peripheral joints involvement.

Of patients with AxSpA/IBD, the vast majority (82%) were diagnosed to have non-radiographic AxSpA. All of these patients were HLA-B27 negative and fulfilled the imaging arm of the ASAS classification criteria.

Indeed, the diagnosis of nr-AxSpA is challenging and the accuracy of ASAS criteria has been questioned several times in recent years. The ASAS criteria, which are classification and not diagnostic criteria, have been developed in 2009 to allow earlier identification of patients at risk to develop AS.

However, several studies demonstrated that not all nr-AxSpA will

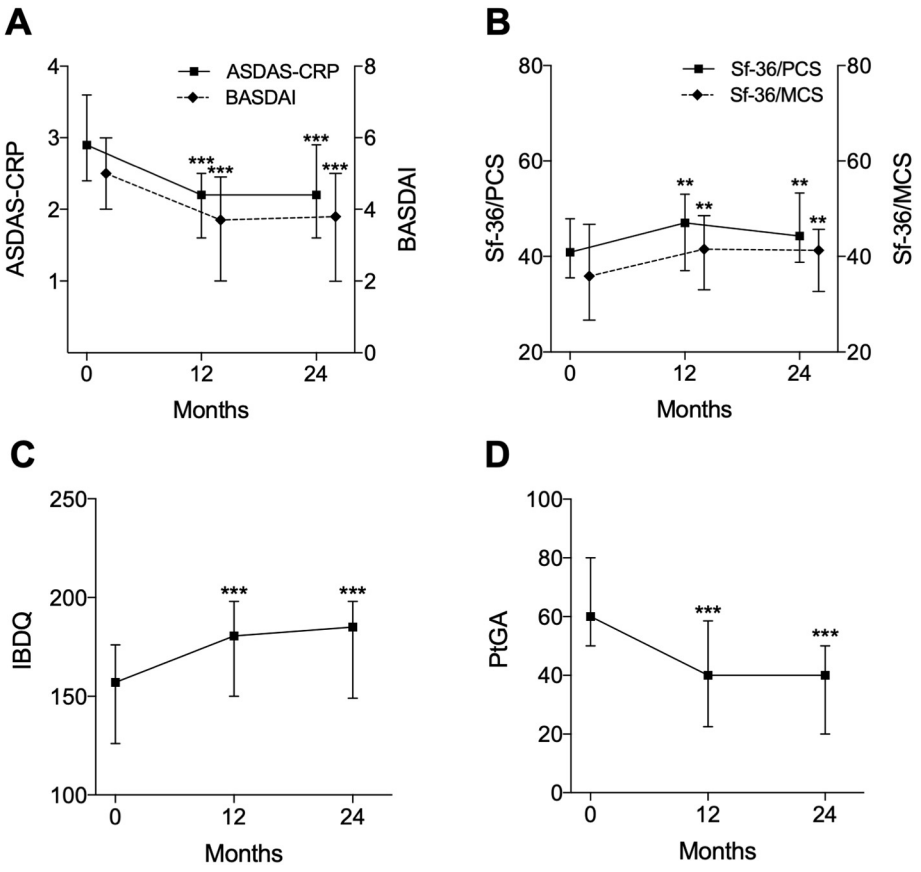

Fig. 4. Median articular disease activity and quality of life scores trough 24 months in patients with inflammatory bowel disease-associated spondyloarthritis.
A. Articular disease activity as assesses by Ankylosing Spondylitis Disease Activity Score-C-reactive protein (ASDAS-CRP) and Bath Ankylosing Spondylitis Disease Index (BASDAI); B. General health-related quality of life as assessed by Short Form-36 health survey Physical Component Score (Sf-36/PCS) and Mental Component Score (Sf-36/MCS); C. Gastrointestinal-specific health related quality of life as assessed by the Inflammatory Bowel Disease Questionnaire (IBDQ); D. Patient's global assessment of disease activity (PtGA).
* p < .05 **p < .01 ***p < .001.

progress to AS (10–40% over a period of 2–10 years) [25]. Moreover, several concerns were raised due to clinical differences between the clinical and imaging arms, which subtend different risk for radiographic progression, and perform differently in validation studies [26].

Another issue to be considered is the low specificity of the sacroiliac joints MRI findings, which may lead to misclassification in populations with low axSpA prevalence. Nevertheless, the pretest probability of SpA in patients with IBD is expected to be high, as several studies confirmed [24]. Moreover, one in six IBD patients may have asymptomatic or subtle sacroiliitis that can be already detected on imaging, a finding that is often overlooked by both the radiologist and the gastroenterologist [27].

The prevalence of HLA-B27 in our cohort is extremely low (20% of AxSpA/IBD), but this is not surprising since a similar prevalence has been reported in other SpA/IBD cohorts [5], differently to other nrAxSpA cohorts, for which the presence of the HLA-B27 was considered an entry criterion [28]. The different rate of HLA-B27 positivity in patients with AS, nr-AxSpA and SpA/IBD is yet to be explained and further research is needed to identify the diagnostic and prognostic implications of these findings.

Indeed, another important observation of our study, that confirms previous observations that male to female ratio is quite different between AS and other SpAs [29], is the fact that female patients are represented in a higher proportion, even in the AxSpA subset. Moreover, despite the differences are not statistically significant, in the SPIB cohort there is a trend towards a significantly worse quality of life reported by female patients. This observation seems to confirm recent literature data derived from large SpA cohorts, in which women show a higher disease activity and worse quality of life scores, as well as lower response rates and adherence to biological treatment [30,31].

The second important issue in patients with SpA/IBD is the optimization of treatment.

In fact, the different guidelines employed by the two specialists may lead to different therapeutic decisions for the same patient and, probably, to different disease outcomes.

As emphasized by our operational algorithm, every patient was evaluated by both the gastroenterologist and the rheumatologist, who considered simultaneously both the gastrointestinal and articular disease activities and the pattern of articular inflammation (axial or peripheral). Thus, for example, initiation of TNF-inhibitors is highly

Table 3
Association between disease activity and health related quality of life at baseline in the SPIB cohort.

	IBDQ	Sf-36/PCS	Sf-36/MCS	HAQ	BASDAI	BASFI	ASDAS-CRP
IBDQ		0,34*	0,53*	−0,13	−0,27*	−0,37*	−0,37*
Sf-36/PCS	0,34*		0,10	−0,50*	−0,14	−0,50*	−0,21
Sf-36/MCS	0,53*	0,10		−0,00	−0,15	−0,18	−0,42*
HAQ	−0,13	−0,50*	−0,00		0,06	0,33*	0,15
BASDAI	−0,27*	−0,14	−0,15	0,06		0,54*	0,58*
BASFI	−0,37*	−0,50*	−0,18	0,33*	0,54*		0,48*
ASDAS-CRP	−0,37*	−0,21	−0,42*	0,15	0,58*	0,48*	

Data were analyzed trough Spearman correlation coefficient. *$p < .05$.

recommended in patients with AxSpA/IBD, following ASAS guidelines [32]. Indeed, the simultaneous consideration of both intestinal and articular disease activities in the phase of treatment decision-making invariably led to the prescription of a biological drug in a high number of patients, in order to use a single compound for the management of the different disease domains of SpA/IBD, as well as to achieve an optimal adherence to treatment and less adverse events [11,33]. It is important to note that a similar approach is suggested for the treatment of a multifaceted SpA like psoriatic arthritis [34–36].

Another important issue raised by our study is the discriminative capacity of the measurement tools that are routinely applied for the clinical evaluation of disease activity in both IBD and SpA. Indeed, in patients with SpA/CD the gastrointestinal disease activity, assessed using the CDAI, resulted worse than those affected by CD but, notably, such a difference disappeared when in the CDAI calculation the item exploring the presence of articular symptoms was not considered. Therefore, the presence of articular symptoms may mislead the gastroenterologist to overestimate the CD disease activity.

Conversely, clinimetric tests exploring articular disease may overestimate the SpA activity if, for example, IBD patients report higher levels of fatigue (BASDAI item n.1) or have higher serum levels of CRP (ASDAS-CRP item n.5).

In light of this issues, we think there may be a need to develop a unifying score to specifically assess the disease activity in the peculiar group of SpA/IBD patients.

The results of our study reinforce the need to reconsider in a new light the patients affected by SpA/IBD: not only a subset of the large families of IBD and SpA, but a distinct and rather peculiar disease requesting a tailored clinical evaluation and therapeutic approach. The lower prevalence of HLA-B27 positive patients in the SPIB and other SpA/IBD cohorts compared to AS patients may represent a further clue to investigate the different clinical and pathogenic peculiarities of SpA/IBD [5,37,38,28].

The lack of a control group, which may affect the generalizability of the study results, is the main limitation of our report. However, the design of such a study could have been problematic in our institution, since the integrated clinic had been common practice long before study inception. As a result, patients would have been subjected to the observer effect bias with a high probability even in case of randomization.

In conclusion, we demonstrated that the early diagnosis and the multidisciplinary management of SpA in IBD patients are feasible in clinical practice and that a tight cooperation between gastroenterologists and rheumatologists improves both the disease activity and the quality of life of SpA/IBD patients.

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Conflict of interest

The authors declare no conflict of interest with regard to this work.

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