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ORIGINAL RESEARCH

Impact of biological therapy in reducing the risk of arthritis development in inflammatory bowel diseases

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ABSTRACT

Objective Evaluate spondyloarthritis (SpA) incidence in inflammatory bowel diseases (IBD) between patients treated with biological disease-modifying antirheumatic drugs (bDMARDs) and conventional DMARDs (cDMARDs) and define risk factors associated with SpA development.

Methods Retrospective cohort study was conducted on patients with Crohn's disease (CD) or ulcerative colitis (UC) and divided into two cohorts: cDMARDs or bDMARDs/targeted synthetic (ts) DMARDs treated patients. Rheumatological assessment was performed in patients presenting musculoskeletal symptoms. Multivariate analysis and Kaplan-Meier curves were used to evaluate the adjusted SpA risk development.

Results 507 patients were included in the study. 176 patients with CD received bDMARDs, 112 cDMARDs and 106 new SpA diagnosies were formulated. Females (OR 1.7 (95% CI 1.1 to 3), adjusted p=0.04), non-stricturing/non-penetrating phenotype (OR 2 (95% CI 1.1 to 3.4), adjusted p=0.01), psoriasis (OR 2.1 (95% CI 1 to 4.6), adjusted p=0.04) and non-infectious uveitis (OR 6.8 (95% CI 1.4 to 33.4), adjusted p=0.01) were associated with increased SpA risk development, while bDMARDs usage was protective (OR 0.4 (95% CI 0.2 to 0.8), adjusted p=0.01), statistically higher than cDMARDs throughout the entire follow-up (effect size 0.47). 98 patients with UC received b-tsDMARDs, 121 cDMARDs and 56 new SpA diagnoses were formulated. Females (OR 2.1 (95% CI 1 to 4.3), adjusted p=0.02) and psoriasis (OR 2.7 (95% CI 1 to 6.8), adjusted p=0.03) were associated with increased SpA risk development, while bDMARDs were protective for SpA development for up to 12 months of treatment compared with cDMARDs (p=0.03).

Conclusions bDMARDs treatment had an impact in reducing SpA development and clinical associated risk factors to transition from IBD to IBD-SpA emerged.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Treatment for both inflammatory bowel diseases (IBD) and spondyloarthritis (SpA) may potentially reduce disease progression and incidence of extraintestinal and extra-articular manifestations and comorbidities. IBD may precede SpA onset and nowadays the therapeutic armamentarium has remarkably expanded, giving clinicians the opportunity to prescribe the best therapy based on patients intestinal and extraintestinal manifestations.

WHAT THIS STUDY ADDS

⇒ We demonstrated that biological disease-modifying antirheumatic drugs (bDMARDs) had an impact on SpA development in patients affected by Crohn's disease (CD) or ulcerative colitis (UC). Moreover, clinical characteristics in patients with IBD have been associated with SpA, suggesting as treatment choice should be influenced by patient phenotype.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Disease interception by bDMARDs and associated risk factors for SpA development in both patients with CD and UC may improve disease management and reduce SpA onset. This was particularly relevant in patients affected by CD for a long follow-up period and for the first year of bDMARDs treatment for patients with UC. A patient's profile risk emerged from the study, suggesting as, in a context of personalised medicine, clinical characteristic at baseline in patients with IBD may be relevant for choosing the best therapeutical approach.

INTRODUCTION

Inflammatory bowel diseases (IBD) such as Crohn's disease (CD) and ulcerative colitis (UC) are characterised by chronic intestinal inflammation frequently associated with extraintestinal manifestations such as spondyloarthritis (SpA).[1] The prevalence of IBD in the general population is up to 1% in industrialised countries[2 3] and studies adopting the former European Spondyloarthropathy Study Group criteria for SpA detected a frequency of IBD ranging between 10%–25% in patients with spondylitis and 30%–36% in patients with sacroilitis, while SpA prevalence

in IBD shows marked variability (6%–46%).[4] The Assessment in Spondyloarthritis International Society (ASAS) formulated the most recent classification criteria, which distinguish axial and peripheral forms of SpA.[5] Generally, peripheral-SpA is more common in patients with IBD (17%–20%), while axial involvement is less frequent (5%–22% in CD, 2%–6% in UC).[6] IBD pathogenesis is not yet fully understood, although an altered innate and adaptive immune response, associated with intestinal microbiome disequilibrium and genetic predisposition, appears to be the most likely hypothesis,[7] suggesting common pathogenic pathways with SpA. Particularly, gut inflammation is considered the basecamp for SpA development and vice versa SpA patients have frequently subclinical gut inflammation.[8] Tumour necrosis factor-alpha (TNFα) and interleukin (IL)-23 have been linked to both diseases pathogenesis, making these inflammatory mediators target of biological disease-modifying antirheumatic drugs (bDMARDs), which are capable of controlling both intestinal and articular manifestations, reducing disease-related damage and progression, and making remission a possible outcome.[9 10] Therefore, IBD-SpA requires a multidisciplinary approach coordinated by both rheumatologist and gastroenterologist for an early diagnosis and combined therapeutic strategy.[11–15] Recently, knowledge on disease interception emerged regarding the role of bDMARDs for psoriasis (PsO) in reducing not only skin inflammation but also the incidence of psoriatic arthritis.[16 17] Considering this hypothesis as biologically and clinically relevant, we aimed at evaluating the incidence of SpA in patients affected by IBD with a follow-up of 10 years, focusing on IBD therapy and associated risk factors to SpA development.

PATIENTS AND METHODS

Patients and data collected

A monocentric retrospective cohort study was conducted between 1 January 2008 and 31 December 2018 at the Gastroenterology Unit of Policlinico Tor Vergata (Rome, Italy). Adult patients with a new diagnosis of UC or CD according to the European Crohn's and Colitis Organisation Guidelines diagnostic criteria performed by an expert gastroenterologist,[18] in the absence of musculoskeletal symptoms or a diagnosis of SpA at the time of entry into the cohort were included in the study. Conversely, patients with UC or CD with concomitant musculoskeletal symptoms or with a previous diagnosis of SpA or other inflammatory arthritis (eg, rheumatoid arthritis) at the time of cohort entry were excluded. Ppatients with IBD who underwent surgical therapy before the start of the study or during the follow-up were excluded too, both for the small number of cases in our series and above all to eliminate a significant confounding factor for weighing the impact of an exclusively pharmacological therapy. In fact, surgical treatment can improve and even induce a clinical remission of the disease, therefore, patients may not need systemic therapies.[19] Demographic and clinical data collected were sex, body mass index (BMI), smoking habits, age at IBD onset, IBD disease activity using Partial Mayo Score (PMS) for UC and Harvey-Bradshaw Index for CD at IBD onset, UC and CD location by the extent of bowel involvement (proctitis, left-sided colitis, pancolitis for UC; ileal, colonic, ileocolonic for CD according to the Montreal classification),[20] CD phenotypic behaviour (non-stricturing/non-penetrating (NS/NP), stricturing, penetrating according to the Montreal classification),[20] associated comorbidities, PsO, non-infectious uveitis (NIU), SpA family history, human leucocyte antigen (HLA)-B27 positivity, current and previous treatments including bDMARDs therapies and start and end dates of each one of the treatments received. C reactive protein (CRP) values (mg/L) were reported at the time of IBD diagnosis. In all cases, HLA typing was performed on patients' DNA that was extracted from venous EDTA-anticoagulated blood and analysed by using real-time polymerase chain reaction (rtPCR) according to the manufacturer's instructions (XeliGen RT System, Eurospital SPA, Italy, in most cases, and analogous RealTime PCR-based systems in the remaining cases). Data were collected from a dedicated electronic database for the evaluation of patients treated with systemic therapies in accordance to the policy of our university hospital. Patients with relevant clinical missing data (>20% data missing) were excluded from the analysis.

Definition of the cohorts

Patients affected by UC or CD were, respectively, assigned to two different cohorts:

1. Patients treated with conventional DMARDs (cDMARDs) (methotrexate, azathioprine, sulfasalazine) or other immunosuppressive agents (mercaptopurine), with or without associated topical therapies (corticosteroids and/or mesalazine), never exposed to bDMARDs therapies.
2. Patients treated with bDMARDs (TNF-inhibitors, IL12/23-inhibitors, integrin α4β7-inhibitors) or with targeted synthetic DMARDs (tsDMARDs) (Janus kinase (JAK)-inhibitors), with or without t associated topical and/or cDMARDs.

Moreover, IBD onset was stratified according to the Montreal classification for CD, thus each patient was included in one of these three groups: A1, if below 17 years old; A2, if between 17 and 40 years old and A3, if above 40 years old.[20] The comparison between the Montreal classification-based groups was evaluated in order to assess whether the population of patients with CD was heterogeneous and identify any subgroups of patients with a possible greater risk of developing SpA according to their clinical characteristics, particularly in relation to the age of onset of IBD, since extraintestinal manifestations such as SpA tend to be more frequent in early-onset IBD and in younger patients.[21]

Follow-up

Every patient with IBd was assessed periodically according to a standardised protocol of our university hospital, with a clinical evaluation every 3 months. For each patient, bowel disease duration was calculated from IBD diagnosis to SpA diagnoses, if this condition occurred; in the absence of SpA, the bowel disease duration was calculated from the IBD diagnosis to the end of the study or to the loss to follow-up. For each patient, the exposition time to a given treatment was calculated from the moment of drug administration until the diagnosis of SpA, the end of the study or to the loss to follow-up. For patients who received more than one cDMARDs and/or bDMARDs/tsDMARDs, the exposition time to the single treatment was calculated. Furthermore, given that usually the treatment of UC and CD follows a hierarchical order in which topical therapies are generally administered before the systemic ones and cDMARDs before bDMARDs/tsDMARDs, the exposition time to cDMARDs, if administered, was not added to that of the same patients in the bDMARDs/tsDMARDs group.[11 12]

Rheumatological assessment for incident cases of SpA

Rheumatological assessment was performed at the combined gastroenterological and rheumatological outpatients clinic in patients presenting musculoskeletal symptoms, such as peripheral arthralgia or chronic low back pain, by the same experienced rheumatologist over time trough clinical, laboratory and imaging assessment. Patients were classified as affected by SpA if ASAS criteria were satisfied.[5] Incident cases were considered as such if they occurred during and after at least 6 months from the start of the IBD treatment administration defined by the patient's cohort.

Statistical analysis

Continuous variables were presented as mean and SD and compared using the parametric unpaired t-test or Student's t-test when appropriate. Categorical variables were presented with absolute frequencies and percentages and were compared using the χ^2 test or Fisher's exact test when appropriate. A $p<0.05$ was considered significant. A binary logistic regression analysis was used to evaluate the adjusted risk of SpA development by the evaluation of the variables that emerged as statistically significant in the univariate analysis, allowing to calculate OR for single risk factor. An adjusted $p<0.05$ was considered significant. The interactions between the variables included in the regression model were checked through the Wald χ^2 test and the Kendall's Tau-b rank correlation coefficient test. The Kaplan-Meier curve was used to estimate the likelihood of developing SpA during treatment with cDMARDs and b-tsDMARDs. The strength of this relation was assessed by measuring phi (ϕ) effect size. A value of $\phi=0.2$ was considered to be a small effect, 0.5 a medium effect and 0.8 a large effect.[22] All statistical analyses were performed by using IBM SPSS Statistics V.9 (IBM SPSS Software).

Table 1 Demographic characteristics of the study population

	CD	UC
Patients; n (%)	288 (56.8)	219 (43.2)
Females; n (%)	163 (56.5)	129 (58.9)
Smoking history; n (%)	110 (38.1)	65 (29.6)
Age at IBD diagnosis (years); mean±SD	33.4±14.5	35.7±14.4
Disease duration (months); mean±SD	95.4±74.3	97.1±86.4
SpA family history, n (%)	8 (2.7)	8 (3.6)
Psoriasis; n (%)	39 (13.5)	25 (11.4)
NIU; n (%)	13 (4.5)	4 (1.8)
HLA-B27; n (%)	10/121 (8.2)	7/76 (9.2)
CRP (mg/L); mean±SD	9.8±7.4	7.1±5.7
Comorbidities		
Obesity; n (%)	7 (2.4)	13 (5.9)
Diabetes; n (%)	11 (3.8)	7 (2.4)
Hypertension; n (%)	41 (14.2)	26 (11.8)
MetS; n (%)	4 (1.3)	8 (3.6)
Hypercholesterolaemia; n (%)	7 (2.4)	7 (2.4)

Continuous variables were presented as mean and SD and compared using the parametric unpaired t test or Student's t-test when appropriate. Categorical variables were presented with absolute frequencies and percentages and were compared using the χ^2 test or Fisher's exact test when appropriate. A $p<0.05$ was considered significant.
CD, Crohn's disease; CRP, C reactive protein; HLA, human leucocyte antigen; IBD, inflammatory bowel disease; MetS, metabolic syndrome; NIU, non-infectious uveitis; SpA, spondyloarthritis; UC, ulcerative colitis.

RESULTS

Demographic characteristics of the study cohorts

We included in the study 507 patients, 288 of them (56.8%) with CD and 219 (43.2%) with UC. Conversely, 105 patients were excluded due to an existing SpA diagnosis before the start of the study, while 113 patients were excluded due to the presence of clinical missing data. Data from the study cohorts are summarised in table 1. In both groups, a similar age at IBD onset (33.4±14.5 and 35.7±14.4 years, respectively) and a similar prevalence of female sex (n=163, 56.5% and n=129, 58.9%) were observed, while smoking history was more prevalent among patients with CD (38.1% vs 29.6%, p=0.04). SpA family history, the positivity of HLA-B27, the prevalence of previous or current associated PsO and NIU and CRP values at the moment of cohort entry showed a similar distribution in the two groups. Regarding metabolic comorbidities, obesity (defined as BMI≥30 kg/m^2)[23] was statistically more common in patients with UC (5.9% vs 2.4%, p=0.04). In patients with UC, left colitis was the most common involvement (44%), while proctitis

and pancolitis were found in 26% and 30% of patients, respectively (online supplemental figure 1A). In patients with CD, the ileal involvement was the most frequent one (69%), followed by the ileocolonic (19%) and the colonic (12%) involvement (online supplemental figure 1B). Moreover, the NS/NP phenotype was identified in the majority of patients with CD (51%), followed by the stricturing (37%) and the penetrating (12%) involvement (online supplemental figure 1C).

Analysis of patients with CD

In patients with CD, the stratification by bowel disease onset according to the Montreal classification[20] highlighted the A2 group (onset between 17 and 40 years) as the most prevalent (n=183, 63.5%). Comparing the three groups, CD severity increased significantly over time (p=0.004), as well as the prevalence of ileal involvement (p=0.03), while a concomitant decrease of ileocolonic involvement (p=0.02) was observed. No significant differences in CRP values were detected (online supplemental table 1). Throughout the follow-up (mean time 80.2±24.3 months), 176 (61.1%) patients with CD received a bDMARD (n=173 TNF-inhibitor, n=35 ustekinumab, n=12 vedolizumab; 42 patients received more than one bDMARD), while 112 of them (38.9%) received a cDMARD or immunosuppressor (n=27 methotrexate, n=46 azathioprine, n=46 sulfasalazine, n=25 mercaptopurine; 28 patients received more than one drug). Patients with CD treated with bDMARDs had less frequently an NS/NP phenotype (39.7% vs 58%, p=0.002) but a significantly higher prevalence of stricturing phenotype (38.6% vs 25%, p=0.01). (table 2). During the 10 years of follow-up, 106 new SpA diagnoses were formulated (36.8%), 75 of them (70.7%) with peripheral involvement (online supplemental table 2). The mean time between IBD onset and SpA diagnoses was 98.4±84.3 months and a similar SpA incidence was observed according to Montreal classification and exposition time to cDMARDs and bDMARDs (73.6±38.2 months and 64.3±36.6 months, respectively, p=0.22). In the univariate analysis, patients with CD who developed an SpA during the follow-up were mainly females (p=0.006), presented a higher NS/NP phenotype (p=0.001), SpA family history (p=0.02), associated PsO (p=0.04) and NIU (p=0.002) and were less treated with bDMARDs when compared with patients with CD without SpA (p=0.001). No significant differences in CRP values were detected between the two groups (table 3). In the multivariate analysis, adjusted binary logistic regression analysis showed that female sex (OR 1.7 (95% CI 1.1 to 3), adjusted p=0.04), NS/NP phenotype (OR 2 (95% CI 1.1 to 3.4), adjusted p=0.01), concomitant PsO (OR 2.1 (95% CI 1 to 4.6), adjusted p=0.04) and NIU (OR 6.8 (95% CI 1.4 to 33.4), adjusted p=0.01) were associated with increased risk of developing SpA, while bDMARDs usage was protective (OR 0.4 (95% CI 0.2 to 0.8), adjusted p=0.01). SpA familiarity failed to maintain statistical significance in the multivariate analysis (figure 1). No statistically significant interactions between the variables included in the regression model were detected. Finally, the protective role of bDMARDs for the development of SpA in patients with CD was statistically higher than cDMARDs up to 60 months of treatment (figure 2A) and throughout the entire follow-up, with an effect size of 0.47 (Phi effect (Φ) figure 2B).

Analysis of patients with UC

During the combined follow-up (mean time 75.2±27.3 months), 98 (44.7%) patients with UC received a bDMARD or tsDMARD (n=87 TNF-inhibitor, n=2 ustekinumab, n=28 vedolizumab, n=1 JAK-inhibitor; 20 patients received more than one bDMARD), while 121 of them (55.2%) received a cDMARD or immunosuppressor (n=24 methotrexate, n=51 azathioprine, n=75 sulfasalazine, n=29 mercaptopurine; 45 patients received more than one cDMARD). Patients with UC treated with bDMARDs/tsDMARDs have been diagnosed with IBD at a younger age than patients treated with cDMARDs (p=0.01) and presented a significantly higher prevalence of pancolitis (p=0.008) and PMS severity at disease onset (p=0.02) (table 2). During the follow-up, after a mean time of 94.5±81.4 months, a significantly lower number of new SpA diagnoses were formulated in the UC group when compared with the CD group (56 vs 106, respectively; p=0.007), without differences in the phenotypic SpA presentation. Moreover, a similar exposition time to cDMARDs and bDMARDs (76.8±36.4 months and 68.7±35.1 months, respectively, p=0.18) was detected. In the univariate analysis, patients with UC who developed SpA during the follow-up were mainly females (p=0.01) and presented more frequently PsO (p=0.02). Patients without SpA showed an incidence of pancolitis significantly higher than SpA patients (p=0.02). Neither cDMARDs nor bDMARDs had an impact on the development of SpA (table 3). The multivariate analysis confirmed that female sex (OR 2.1 (95% CI 1 to 4.3), adjusted p=0.02) and concomitant PsO (OR 2.7 (95% CI 1 to 6.8), adjusted p=0.03) were associated with increased risk of developing SpA (figure 3). No statistically significant interactions between the variables included in the regression model were detected. Finally, also in the multivariate analysis, bDMARDs failed to reach statistical significance as a protective factor on the development of SpA throughout the whole follow-up (p=0.05 and p=0.16, respectively) (table 2, figure 3). Nevertheless, up to 12 months of treatment, patients treated with bDMARDs had a statistically lower SpA incidence compared with patients treated with cDMARDs (p=0.03) (figure 4A,B).

DISCUSSION

General overview

Here, we described the clinical characteristics of patients affected by CD or UC referring to a single tertiary-level centre who were evaluated in the combined gastroenterological and rheumatological outpatients clinic. As expected, IBD mainly affected young people, who are

Table 2 Comparison between biological disease-modifying antirheumatic drugs (bDMARDs) and conventional synthetic disease-modifying antirheumatic drugs (cDMARDs) therapy in patients with Crohn's disease (CD) and ulcerative colitis

CD			
	bDMARDs	**cDMARDs**	**P value**
Patients; n (%)	176 (61.1)	112 (38.9)	–
Females; n (%)	92 (52.2)	71 (63.3)	0.06
Obese; n (%)	5 (2.8)	5 (4.4)	0.46
Smoking history; n (%)	73 (41.4)	37 (33)	0.15
Age at IBD diagnosis (years); mean±SD	32.4±14.2	35±14.9	0.07
Ileum involvement; n (%)	115 (65.3)	83 (74.1)	0.11
Colon involvement; n (%)	24 (13.6)	12 (10.7)	0.46
Ileocolon involvement; n (%)	37 (21)	17 (15.1)	0.21
NS/NP phenotype; n (%)	70 (39.7)	65 (58)	0.002
Stricturing phenotype; n (%)	68 (38.6)	28 (25)	0.01
Penetrating phenotype; n (%)	24 (13.6)	8 (7.1)	0.08
SpA family history; n (%)	1 (0.5)	7 (6.2)	0.004
Psoriasis; n (%)	28 (15.9)	11 (9.8)	0.14
NIU; n (%)	5 (2.8)	8 (7.1)	0.08
HLA-B27; n (%)	8/66 (12.1)	2/55 (3.6)	0.09
CRP (mg/L); mean ± SD	12.6 ± 9.2	4.3 ± 2.8	0.09
Moderate-severe HBI at onset; n (%)	52 (29.5)	23 (20.5)	0.08
Ulcerative colitis			
	bDMARDs	**cDMARDs**	**P value**
Patients; n (%)	98 (44.7)	121 (55.2)	–
Females; n (%)	56 (57.1)	73 (60.3)	0.63
Obese; n (%)	8 (8.1)	10 (8.2)	0.97
Smoking history; n (%)	29 (29.5)	36 (29.7)	0.97
Age at IBD diagnosis (years); mean±SD	31.5±12.3	35.7±15.4	0.01
Proctitis; n (%)	20 (20.4)	37 (30.5)	0.08
Left colitis; n (%)	39 (39.7)	57 (47.1)	0.27
Pancolitis; n (%)	38 (38.7)	27 (22.3)	0.008
SpA family history; n (%)	4 (4)	4 (3.3)	0.76
Psoriasis; n (%)	10 (10.2)	15 (12.3)	0.61
NIU; n (%)	2 (2)	2 (1.6)	0.83
HLA-B27; n (%)	5/35 (14.2)	2/41 (4.8)	0.15
CRP (mg/L); mean±SD	11.2±8.4	4.5±2.7	0.15
Moderate-severe PMS at onset; n (%)	25 (25.5)	17 (14)	0.03

Continuous variables were presented as mean and SD and compared using the parametric unpaired t test or Student's t-test when appropriate. Categorical variables were presented with absolute frequencies and percentages and were compared using the $\chi 2$ test or Fisher's exact test when appropriate. A $p<0.05$ was considered significant.
CRP, C reactive protein; HBI, Harvey-Bradshaw Index; HLA, human leucocyte antigen; IBD, inflammatory bowel disease; NIU, non-infectious uveitis; NS/NP, Non-stricturing/non-penetrating; PMS, Partial Mayo Score; SpA, spondyloarthritis.

also at greater risk of having a higher severity of bowel disease and developing extraintestinal manifestations, including SpA.[24–26] Nevertheless, in our study, elderly patients with CD had a significantly higher disease activity, regardless of the extent of the intestinal location, and this is probably due to an early treatment with bDMARDs of young patients with IBD, as expected in a context of personalised medicine. Since the activity of CD was independent from the intestinal extent the choice to start a bDMARD in these patients was mainly conditioned by the disease phenotype. In particular, the stricturing phenotype is a driver of intestinal disease severity, being associated with more aggressive forms of CD.[27] Therefore, even in our study, stricturing patients with CD received mostly

Table 3 Comparison between patients with Crohn's disease and ulcerative colitis with and without spondyloarthritis

Crohn's disease			
	SpA yes	SpA no	P value
Patients; n (%)	106 (36.8)	182 (63.1)	–
Females; n (%)	71 (66.9)	92 (50.5)	**0.006**
Obese; n (%)	4 (3.7)	6 (3.2)	0.83
Age at IBD diagnosis (years); mean±SD	32.8±13.1	33.8±15.2	0.31
Disease duration (months); mean±SD	98.4±84.3	90.6±73.2	0.16
Smoking history; n (%)	42 (39.6)	68 (37.1)	0.7
Ileum involvement; n (%)	80 (75.4)	118 (64.8)	0.06
Colon involvement; n (%)	15 (14.1)	21 (11.5)	0.51
Ileocolon involvement; n (%)	11 (10.3)	43 (23.6)	**0.005**
NS/NP phenotype; n (%)	67 (63.2)	67/157 (42.6)	**0.001**
Stricturing phenotype; n (%)	29 (27.3)	68/157 (43.3)	**0.008**
Penetrating phenotype; n (%)	10 (9.4)	22/157 (14)	0.26
SpA family history; n (%)	6 (5.6)	2 (1)	**0.02**
Psoriasis; n (%)	20 (18.8)	19 (10.4)	**0.04**
NIU; n (%)	10 (9.4)	3 (1.6)	**0.002**
HLA-B27; n (%)	9/87 (10.3)	1/34 (2.9)	0.18
CRP (mg/L); mean±SD	16.5±13.6	6.8±5.5	0.16
Moderate-severe HBI at onset; n (%)	32 (30.1)	43 (23.6)	0.22
bDMARDs; n (%)	52 (49.1)	124 (68.1)	**0.001**
Ulcerative colitis			
	SpA yes	SpA no	P value
Patients; n (%)	56 (25.5)	163 (74.4)	–
Females; n (%)	41 (73.2)	88 (53.9)	**0.01**
Obeses; n (%)	5 (8.9)	13 (7.9)	0.82
Age at IBD diagnosis (years); mean±SD	36.5±13.9	32.8±14.3	0.05
Disease duration (months); mean±SD	94.5±81.4	95.6±80.3	0.49
Smoking history; n (%)	19 (33.9)	46 (28.2)	0.41
Proctitis; n (%)	18 (32.1)	39 (23.9)	0.22
Left colon; n (%)	28 (50)	68 (41.7)	0.28
Pancolitis; n (%)	10 (17.8)	55 (33.7)	**0.02**
SpA family history; n (%)	3 (5.3)	5 (3)	0.43
Psoriasis; n (%)	11 (19.6)	14 (8.5)	**0.02**
NIU; n (%)	2 (3.5)	2 (1.2)	0.25
HLA-B27; n (%)	5/46 (10.8)	2/21 (9.5)	0.86
CRP (mg/L); mean±SD	9.6±6.2	6.8±4.9	0.32
Moderate-severe PMS at onset; n (%)	11 (19.6)	31 (19)	0.91
bDMARDs; n (%)	19 (33.9)	79 (48.4)	0.05

Continuous variables were presented as mean and SD and compared using the parametric unpaired t test or Student's t-test when appropriate. Categorical variables were presented with absolute frequencies and percentages and were compared using the $\chi 2$ test or Fisher's exact test when appropriate. A $p<0.05$ was considered significant.
bDMARDs, biological disease-modifying antirheumatic drugs; CRP, C reactive protein; HBI, Harvey-Bradshaw Index; HLA, human leucocyte antigen; IBD, inflammatory bowel disease; NIU, non-infectious uveitis; NS/NP, non-stricturing/non-penetrating; PMS, Partial Mayo Score; SpA, spondyloarthritis.

bDMARDs, with respect to NS/NP patients with CD who were treated more frequently with cDMARDs. Conversely, the intestinal extension in UC is directly proportional to the intestinal disease activity,[27] confirmed again in our study as the main factor determining the usage of bDMARDs.

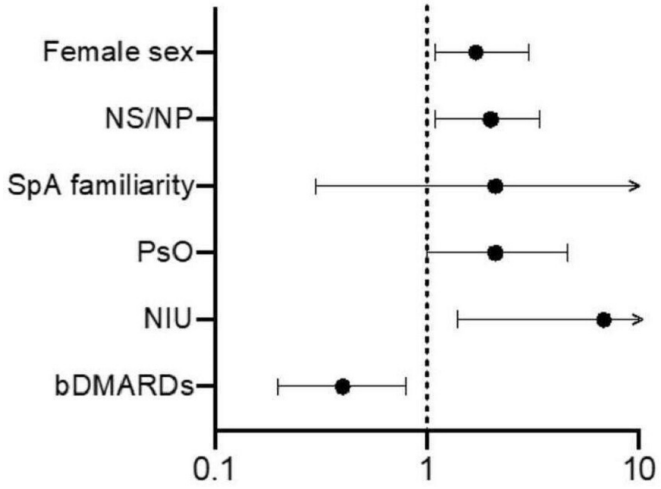

Figure 1 Risk factors for spondyloarthritis in Crohn's disease (CD). Forest plot representing the OR of SpA in patients with CD, calculated by adjusted binary logistic regression analysis: bDMARDs 0.4 (95% CI 0.2 to 0.8, adjusted p=0.01); NIU 6.8 (95% CI 1.4 to 33.4, adjusted p=0.01); PsO 2.1 (95% CI 1 to 4.6, adjusted p=0.04); SpA familiarity 2.1 (95% CI 0.3 to 12.5, adjusted p=0.4), NS/NP phenotype 2 (95% CI 1.1 to 3.4, adjusted p=0.01), female sex 1.7 (95% CI 1.1 to 3, adjusted p=0.04). A p<0.05 was considered significant. bDMARDs, biological disease-modifying antirheumatic drugs; NIU, non-infectious uveitis; NS/NP, non-stricturing/non-penetrating; PsO, psoriasis; SpA, spondyloarthritis.

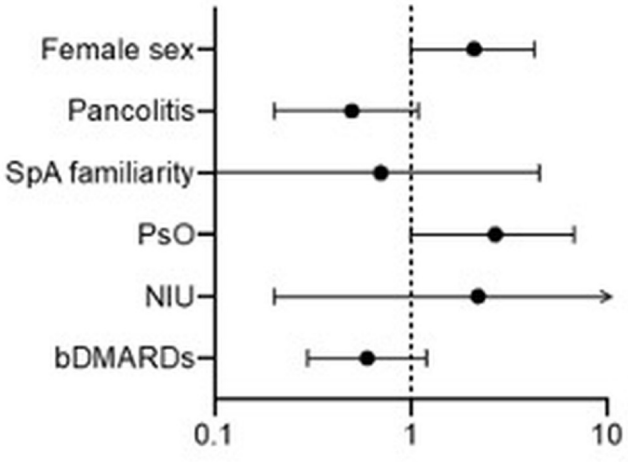

Figure 3 Risk factors for spondyloarthritis in ulcerative colitis. Forest plot representing the OR of SpA development in patients with UC, calculated by adjusted binary logistic regression analysis: bDMARDs 0.6 (95% CI 0.3 to 1.2, adjusted p=0.16); NIU 2.2 (95% CI 0.2 to 20.1, adjusted p=0.46); PsO 2.7 (95% CI 1 to 6.8, adjusted p=0.03); SpA familiarity 0.7 (95% CI 0.1 to 4.5, adjusted p=0.79); pancolitis 0.5 (95% CI 0.2 to 1.1, adjusted p=0.09); female sex 2.1 (95% CI 1 to 4.3, adjusted p=0.02). bDMARDs, biological disease-modifying antirheumatic drugs; NIU, non-infectious uveitis; PsO, psoriasis; SpA, spondylarthritis; UC, ulcerative colitis.

SpA development

Approximately 8 years after the diagnosis of IBD, 36.8% of patients with CD and 25.5% of UC developed SpA. These incidence rates were slightly higher in both diseases than those reported in literature and could be related to the fast referral to the rheumatologist due to the combined outpatients clinic, but also by the fact that generally in a tertiary-level centre more severe forms of IBD are managed, which present a potential greater risk of developing extraintestinal manifestations of the disease.[28 29] Moreover, our study confirmed that patients with CD developed SpA more frequently than those with UC, and that peripheral SpA was more prevalent than the axial one in both CD and UC, counting between 70% and 78% of all SpA.[30] On the other side, no significant effect of age at IBD onset or IBD severity in both patients with CD and UC on the risk of SpA development was observed. Focusing on CD location, colonic involvement has been associated with a higher presence of extraintestinal manifestations, particularly SpA, compared with patients affected from ileitis,[31] while SpA is more common

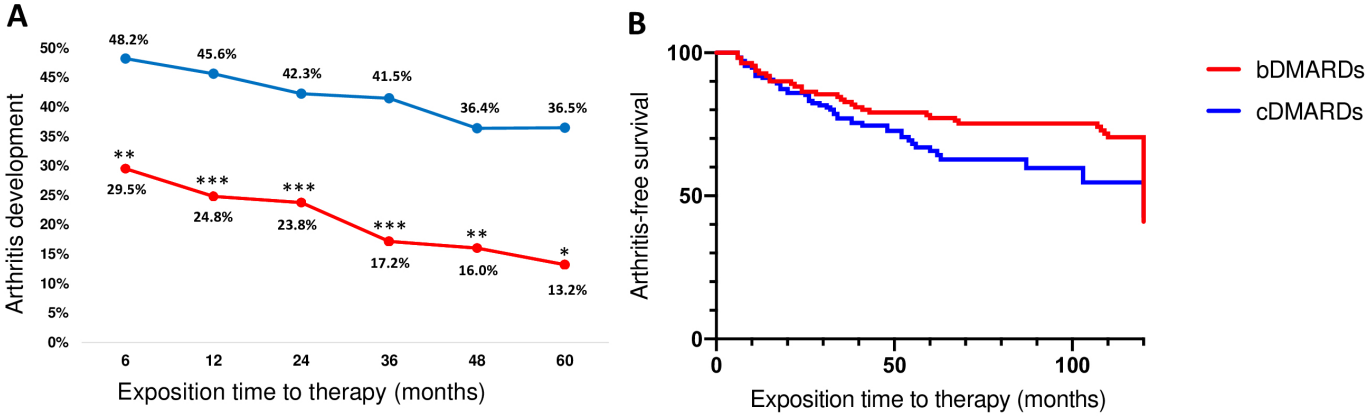

Figure 2 (A) Arthritis development in Crohn's disease patients up to 60 months of treatment. (B) The Kapla-Meier curve shows the rate of arthritis development in patients with Crohn's disease treated with bDMARDs (red) and cDMARDs (blue). Phi effect (Φ): 0.47. Categorical variables were presented with absolute frequencies and percentages and were compared using the $\chi 2$ test or Fisher's exact test when appropriate. A p<0.05 was considered significant: *p<0.05; **p<0.01; ***p<0.001. bDMARDS, biological disease-modifying antirheumatic drugs; cDMARDs, conventional disease-modifying antirheumatic drugs.

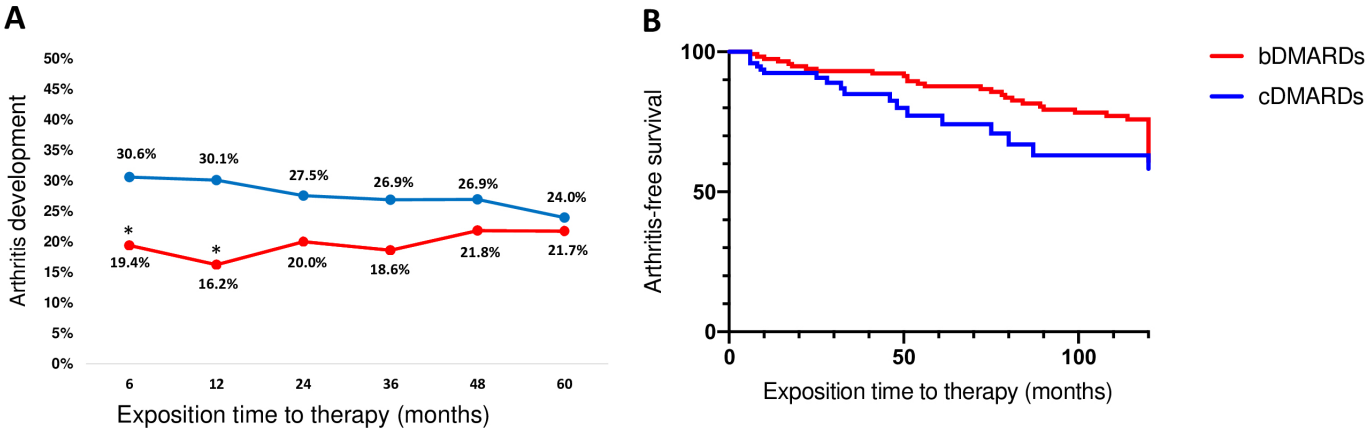

Figure 4 (A) Arthritis development in ulcerative colitis patients up to 60 months of treatment. (B) The Kaplan-Meier curve shows the rate of arthritis development in ulcerative colitis patients treated with bDMARDs (red) and cDMARDs (blue). Phi effect (Φ): 0.53. Categorical variables were presented with absolute frequencies and percentages and were compared using the $\chi 2$ test or Fisher's exact test when appropriate. A $p<0.05$ was considered significant: *$p<0.05$. bDMARDs, biological disease-modifying antirheumatic drugs; cDMARDs, conventional disease-modifying antirheumatic drugs.

in patients with UC with pancolitis rather than with left-colitis and proctitis.[32 33] Data from our analysis showed no significant differences between CD location and SpA incidence, while pancolitis in patients with UC seemed to be less associated with SpA development. However, this latter evidence is conditioned by the fact that patients with pancolitis received more frequently bDMARDs, compared with patients with a less bowel extension, which could have played a key role in preventing SpA development. Furthermore, patients with CD with the stricturing phenotype developed SpA less frequently, particularly when compared with patients with the NS/NP phenotype. These data are in contrast with what emerges in literature, where the stricturing phenotype is characterised by a greater disease severity.[27] However, the greater severity of IBD is generally referred to the intestinal disease sensu stricto, such as local severity or complications, or the need to surgical approach, and not necessarily to the probability of developing extraintestinal manifestations, including SpA. In our study, the NS/NP phenotype was a predictor of the development of SpA in both univariate and multivariate analysis, confirming the fundamental role of systemic inflammation in the pathogenesis of SpA. However, NS/NP patients with CD received bDMARDs less frequently than patients with CD with other phenotypes, thus their higher incidence of SpA could also be influenced by the different pharmacological approach adopted.

Risk factors associated to SpA onset

The most impactful predictor of SpA in patients with CD was the concomitant presence of NIU (OR 6.8). NIU is one of the most frequent extraintestinal manifestations of IBD and IBD themselves increase the risk of developing NIU up to 10 times compared with the general population.[34 35] NIU may occur even before the IBD onset, and a recent study showed that up to 19% of NIU patients attending the combined ophthalmologist-rheumatologist clinic had an underlying IBD-SpA.[36] The impact of NIU was not as significant in patients with UC, in contrast to PsO, which showed to be a relevant predictor of SpA in both our CD and UC cohorts (OR 2.1 in CD and OR 2.7 in UC). PsO and IBD notoriously share molecular signatures in their pathogenesis, such as TNF and IL-23, therefore, it is reasonable to assert that the hyperactivation of these cytokine axes both on the cutaneous and intestinal fronts may have a cumulative effect and enhance the transition of inflammation towards the joint structures.[37] Moreover, female sex was for the first time associated with the incidence of SpA in both patients with CD and UC (OR 1.7 in CD and OR 2.1 in UC). Typically, SpA was considered as a male disease, but recently SpA phenotype and SpA management was partially redefined in female sex.[38–40] However, further studies are needed in these aspects. The development of SpA in patients with IBD was independent from SpA familiarity and HLA-B27 positivity, although its presence may contribute to a higher prevalence of axial involvement.[41]

The role of biological therapy

Therapy with bDMARDs was demonstrated to be extremely effective in preventing the incidence of SpA in patients with CD (OR 0.4) regardless of the exposition time. In fact, 6 months of treatment are enough to significantly reduce this risk, and this effectiveness is maintained up to 60 months. Furthermore, 60 months of therapy reduced the probability of developing SpA from about 1 case in 3 patients (36.8%) to about 1 case in 10 patients (13.2%). In our study, TNF-inhibitors were the most prevalent bDMARD administered, and nearly all patients who received IL-23-inhibitors and/or integrin α4β7-inhibitors had received prior TNF-inhibitor therapy. Therefore, it was not possible to carry out a subanalysis on the impact of the single classes of bDMARDs on SpA prevention. Nowadays, the therapeutic armamentarium has remarkably expanded with new molecules, giving clinicians the opportunity to set studies in order to quantify the effective impact of individual drug classes.[11 12] These brilliant

results were not found in patients with UC. In fact, while the univariate analysis reached the limit of statistical significance, the multivariate analysis did not confirm this protective effect. However, this result is conditioned by the fact that the multivariate analysis took into consideration the entire observation period. Indeed, bDMARDs and/or tsDMARDs therapy significantly reduced the development of SpA in the first 12 months of treatment, when compared with cDMARDs therapy (figure 4A), and subsequently, this preventive effect was lost. Currently, there are no concrete elements that can explain this condition and further prospective studies are needed. The hypothesis related to the reduction of SpA development in patients with IBD treated with bDMARDs are two: (1) bDMARDs may prevent the development of SpA via inhibition of key cytokines involved in the pathogenesis of both conditions[7–10] or (2) bDMARDs may suppress clinical symptoms related to SpA, thus postponing SpA diagnoses and not really preventing its onset. Between these two possibilities, as we have not observed differences in SpA development timing between the two groups of patients evaluated (cDMARDs vs bDMARDs), we can suppose that bDMARDs may prevent rather than suppress SpA development, but prospective studies are certainly needed to concretely support this hypothesis.

Final considerations

In this study, we demonstrated the close correlation between IBD and SpA development, regardless of the age of onset of IBD, as highlighted by a recent Swedish study.[42] Therefore, it is necessary to pay attention to all age groups of patients with IBD as potentially at risk of developing SpA, although treatment with bDMARDs may prevent the onset of this extraintestinal manifestation in a real-life clinical setting. The limitations of this study include: (1) the retrospective nature of the study, even if monocentric and the clinician assessor was the same during the follow-up period; (2) a relevant number of patients with missing data were excluded from the study; (3) the radiographic and ultrasound characteristics of SpA patients were not reported; (4) we were not able to report a serological biomarker, as CRP values have not emerged as a risk factor for SpA development and faecal calprotectin was not reported in all the time points of the follow-up period. Moreover, as reported in literature, its role may be relevant in detecting subclinical bowel inflammation in patients with SpA, rather than in being a predictor of SpA in patients with IBD.[43 44] In conclusion, here, we demonstrated how bDMARDs therapy reduced the risk of SpA development in an IBD monocentric cohort of patients. This was particularly relevant in patients affected by CD for a long follow-up period and for the first year of bDMARDs treatment for patients with UC. A patient's profile risk emerged from our analysis, suggesting as, in a context of personalised medicine, clinical characteristic at baseline in patients with IBD may be relevant for choosing the best therapeutical approach.

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Contributors MF, BM and PC performed the statistical analyses and wrote the manuscript. PT, AD'A and SE helped in writing the manuscript. EC and MSC designed the study and supervised in writing the manuscript. EC, AB, LB and GM contributed in writing the manuscript. EC and MSC visited the patients included in the study.

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