Use of synthetic and biological DMARDs in patients with enteropathic spondyloarthritis: a combined gastro-rheumatological approach

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Abstract

Objective

The aim of this 2-year prospective study was to assess the diagnostic and therapeutic effect of a combined gastro-rheumatological approach in enteropathic spondyloarthritis (eSpA) patients.

Methods

Inflammatory bowel disease (IBD) patients with joint pain were referred by IBD-dedicated gastroenterologists to a dedicated rheumatologist. At baseline and at 3, 6, 12, 24 months, the following parameters were recorded: clinical and biochemical variables, SpA and IBD activity scores, treatment (conventional synthetic; csDMARDs, biologics; bDMARDs). Associations between treatment and patient characteristics were evaluated by logistic regression (AOR [95% CI]).

Results

Overall, 229 IBD patients were referred to rheumatologists. eSpA was diagnosed in 147 (64.2%) patients: 96 (65.3%) showing peripheral and 51 (34.7%) axial involvement. IBD included Crohn's disease (CD) in 141 (61.6%) and ulcerative colitis (UC) in 88 (38.4%). bDMARD treatment increased over the follow-up (baseline-24 months: 32.7-60%; AOR 3.45 [1.93-6.2], p<0.001). bDMARD use was less frequent in elderly patients (AOR 0.73 [0.56-0.96], p=0.023), in UC (AOR 0.43 [0.2-0.94], p=0.034) and in patients with peripheral involvement (AOR 0.53 [0.3-1.04], p=0.067). csDMARD use was increased in patients with peripheral involvement (AOR 4.65 [2.09-10.33], p<0.001) and in UC (AOR 2.30 [1.13-4.67], p=0.021). CRP, ESR, ASDAS-ESR levels and BASFI significantly decreased over the follow-up, whereas the pMayo score, BASDAI and HAQ-S were unchanged.

Conclusion

In this prospective study in eSpA patients, a multidisciplinary approach was shown to optimise the therapeutic management and outcome (e.g. disease activity scores). bDMARD use paralleled an improvement in disease activity scores and confirmed a good safety profile.

Key words

spondyloarthritis, enteropathic, therapeutic management, biologics

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Introduction

Enteropathic arthritis is an inflammatory chronic arthritis occurring in patients with inflammatory bowel diseases (IBD), classified in the group of spondyloarthritis (SpA) (1–3). IBD includes Crohn's disease (CD) and ulcerative colitis (UC), characterised by chronic intestinal inflammation frequently associated with extra-intestinal manifestations (4, 5). According to the Assessment in Spondyloarthritis International Society (ASAS), SpA is considered as a distinct group of diseases with similar clinical features and a common genetic predisposition, frequently occurring in combination with extra-articular manifestations such as psoriasis, uveitis or IBD (enteropathic SpA, eSpA) (6, 7). Arthritis is the most frequent extra-intestinal manifestation in patients with IBD (8), mainly involving the axial joints (*e.g.* ankylosing spondylitis (AS) and/or isolated sacroileitis or non-radiographic SpA) or peripheral joints and/or peri-articular structures, such as tendons and entheses (9).

The association between SpA and IBD has been established (10, 11). Patients with IBD often show nonspecific markers of inflammation such as C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR). However, CRP seropositivity is also included among the criteria of ASAS classification for axial SpA (12). CRP positivity is also considered a risk factor for radiographic progression (13, 14).

The prevalence of eSpA in IBD varies from 18–45% and may be underestimated by gastroenterologists (15). Although joint pain frequently occurs in IBD patients, only a minority of them are referred to rheumatologists for a proper diagnosis. An integrated assessment by IBD-dedicated rheumatologists and gastroenterologists is therefore required for both diagnosis and management of these patients (16).

Treatment recommendations for active SpA include non-steroidal anti-inflammatory drugs (NSAIDs) and conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs) in patients with peripheral arthritis, followed by biological DMARDs (bDMARDs) in patients with persistently high disease activity unresponsive to conventional treatments (17). Five TNF inhibitors (TNFi) have been approved for SpA treatment, showing similar efficacy for musculoskeletal symptoms, although no head-to-head comparisons are available. However, in IBD patients, the efficacy of TNFi on intestinal inflammation shows marked variations. Monoclonal antibodies (infliximab, adalimumab, golimumab, certolizumab) are efficacious for treating IBD patients with moderate to severe active disease showing inadequate response to conventional therapy. Conversely, etanercept shows no efficacy for treating clinically active IBD (17) and golimumab is only indicated in mild to moderate active UC (15, 16).

The appropriate management of patients with eSpA requires a joint assessment by dedicated rheumatologists and gastroenterologists (18), aimed to optimise a patient tailored-approach. An attempt to reach a consensus using an integrated approach in these patients has recently been reported (19). However, few data from prospective studies are currently available regarding the efficacy of a multidisciplinary management in terms of clinical outcome in patients with eSpA (19).

Therefore, in the present prospective study we aimed to evaluate the outcome of patients with eSpA following a combined assessment by IBD-dedicated gastroenterologists and rheumatologists over a 2-year follow-up period.

Materials and methods

Patients and study design

In this prospective observational study, all patients with an established diagnosis of IBD referring musculoskeletal pain to an IBD-dedicated gastroenterologist were referred from January 2015 to December 2017, to a combined Gastro-Intestinal and RHEumatologic "GI-Rhe clinic", at the University of Rome Tor Vergata (Italy). Inclusion criteria were: 1) diagnosis of CD or UC according to standard criteria (20, 21), classified according to the Montreal classification (22); 2) joint pain at enrolment ; 3) age ≥18 years; 4) regular follow-up at the tertiary referral IBD Centre of the University of Rome Tor

Vergata, Italy; 5) compliance to follow the study protocol. At baseline, at 3, 6, 12 and 24 months, the following parameters were prospectively reported in a common database: demographic and clinical data, SpA and IBD activity scores (see below), treatments for eSpA and IBD. This study was conducted in accordance with the ethical principles of the Declaration of Helsinki and was consistent with the guidelines for good clinical practice. Written informed consent was obtained from all patients and the Institutional ethics committee approved the study.

Clinical assessment

IBD patients referring musculoskeletal pain during a routine clinical assessment, were enrolled and referred to the combined "GI-Rhe" clinic. In each of the combined GI-Rhe visits at baseline, at 3, 6, 12 and 24 months, the following data were assessed and reported in a common database (23): new diagnosis of eSpA, IBD and SpA activity scores, imaging or endoscopic procedures, laboratory evaluations and adverse events. Rheumatologic assessment included: physical examination with 68 tender and 66 swollen joint count, presence of dactylitis, enthesitis, inflammatory spinal pain and buttock pain. Laboratory tests included ESR and CRP. Joint imaging was requested in order to confirm or deny the diagnosis and included musculoskeletal ultrasound, traditional radiography and magnetic resonance imaging. ASAS criteria were used in order to classify patients affected by axial or/and peripheral SpA and by radiographic or non-radiographic axial SpA (6, 24, 25). Inflammatory findings (arthritis or enthesitis or dactylitis) in patients affected by peripheral SpA were assessed by musculoskeletal ultrasound (25) while sacroiliitis on imaging was detected by traditional radiography, according to the modified NY criteria (26), and/or according to the magnetic resonance imaging consensus definition in patients with axial-SpA (24). Psoriatic arthritis was classified according to CASPAR (ClASsification criteria for Psoriatic ARthritis) criteria (27), rheumatoid arthritis according to ACR criteria (28) and gout according to ACR/EULAR criteria (29). Fibromyalgia and osteoarthritis were diagnosed according to ACR/EULAR classification criteria (30, 31). Polymyalgia rheumatica, systemic sclerosis, inflammatory myopathy, chondrocalcinosis and reactive arthritis were also diagnosed according to respective ACR/EULAR classification criteria (25, 32-34).

Disease activity and function in SpA patients were assessed using the visual analogue scale (VAS, global and pain) (35), Ankylosing Spondylitis Disease Activity Score (ASDAS) (36-38), Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) (39, 40), Bath Ankylosing Spondylitis Functional Index (BASFI) (41), and Health Assessment Questionnaire for SpA (HAQ-S) (42). CD and UC localisation and CD behaviour were recorded according with current guidelines (21, 22). CD activity was evaluated using the CD Activity Index (CDAI) with a score >150 indicating active disease (20, 21). UC disease activity was measured by the partial Mayo (pMayo) score with a score ≥3 indicating active disease (21).

Statistical analysis

Data were reported as mean (± standard deviation, SD) for continuous variables, and number and percentage for categorical variables. Comparisons between groups were performed by the Chi-squared test for categorical variables and the 1-way analysis of variance or Wilcoxon test for continuous variables. Adjusted logistic regression models were used to evaluate the independent association between treatment, and individual demographic and clinical characteristics and expressed as Adjusted Odds ratio (AOR) and corresponding 95% confidence intervals [95% CI]. A p-value of <0.05 was considered statistically significant. All analysis was performed using Stata 13.

Results

Baseline demographic and clinical characteristics of enrolled patients

From January 2015 to December 2017, a total of 229 IBD patients were evaluated in a "GI-Rhe" clinic. IBD patients included 141 (61.6%) patients with CD and 88 (38.4%) patients with UC. Among the 229 IBD patients, eSpA was diagnosed in 147 (64.2%) after the combined GI-Rhe clinic and these patients were prospectively followed up for 2 years. The majority of eSpA patients were female (n=99, 67.3%), had a median age of 46 years and mean IBD duration of 14.6±9.7 years. Peripheral involvement was observed in 96 (65.3%), while axial involvement was observed in 51 (34.7%) patients. Among patients with axial involvement, 17 (11.6%) patients had radiographic involvement and 34 (23.1%) patients had non-radiographic involvement. All patients affected by peripheral SpA had inflammatory signs of disease (arthritis, enthesitis or dactylitis) on ultrasound and patients with axial involvement had sacroiliitis either definite radiographic sacroiliitis or active inflammation of sacroiliac joints on magnetic resonance imaging. Among eSpA patients, CRP was elevated (>0.5 mg/dl) in 59 patients (43.4%) at baseline and median disease duration was 6 (3–12) years; CD was mainly localised to the ileum (n=47; 32%), with a slightly higher prevalence of pancolitis (n=30; 20.4%) compared to proctitis (n=9; 6.1%) and left colitis (n=12; 8.2%).

In patients presenting with musculoskeletal diseases (no-eSpA group, n=82), osteoarthritis was diagnosed in 28 patients (34.1%), mechanical low-back pain in 14 patients (17.1%), arthralgias in 8 patients (9.8%), fibromyalgia in 5 patients (6.1%), psoriatic arthritis in 4 patients (4.9%), rheumatoid arthritis in 4 patients (4.9%), and cervical spine pain in 4 patients (4.9%). Other rheumatologic diseases were diagnosed in 12 patients (14.6%) [polymyalgia rheumatica (n=3), aseptic osteonecrosis (n=2), gout (n=2), chondrocalcinosis (n=1), systemic sclerosis (n=1), inflammatory myopathy (n=1), tubercular arthritis (n=1) and reactive arthritis (n=1). At at baseline, 41.5% of musculoskeletal patients (n=34) were treated with mesalazine, 26.8% (n=22) with csDMARDs and 18.3% (n=15) with bDMARDs. Only 3 patients (n=3.7%) were being treated with coxibs at baseline. Once patients with musculoskeletal complaints were diagnosed, they exited the follow-up evalu-

Table I. Baseline clinical characteristics of eSpA and non-eSpA patients.

Clinical characteristic	Total (n=229)	No eSpA (n=82)	eSpA (n=147)	*p*-value
Female, n (%)	148 (64.6)	49 (59.8)	99 (67.3)	0.25
Age (years), median and range	48 (39-59)	52.5 (41-62)	46 (37-56)	**0.022**
Smokers, n (%)	55 (24)	16 (19.8)	39 (27.5)	0.43
Familial history (IBD/psoriasis): n (%)	46 (20.1)	17 (20.7)	29 (19.7)	0.99
Crohn's disease, n (%)	141 (61.6)	45 (54.9)	96 (65.3)	
Ulcerative colitis, n (%)	88 (38.4)	37 (45.1)	51 (34.7)	0.12
IBD disease duration (years)	14.8 ± 10.7	15.3 ± 12.3	14.6 ± 9.7	0.72
CD Localisation, n (%)				
L1: ileum	76 (33.2)	29 (35.4)	47 (32)	
L2: colon	21 (9.2)	5 (6.1)	16 (10.9)	
L3: ileum-colon	42 (18.3)	11 (13.4)	31 (21.1)	
L4: upper	1 (0.4)	0 (0)	1 (0.68)	0.38
CD behaviour, n (%)				
B1: non-stricturing, non penetrating	72 (31.4)	23 (28)	49 (33.3)	
B2: stricturing	56 (24.5)	18 (22)	38 (25.9)	
B3: penetrating	8 (3.5)	2 (2.4)	6 (4.1)	
P: perianal disease	5 (2.2)	2 (2.4)	3 (2)	0.95
CDAI, median and range	74 (50-113)	60 (48-75)	84.5 (50-138)	**0.004**
UC localisation, n (%)				
Proctitis	19 (8.3)	10 (12.2)	9 (6.1)	0.14
Left colitis	23 (10)	11 (13.4)	12 (8.2)	0.25
Pancolitis	46 (20.1)	16 (19.5)	30 (20.4)	1.0
pMAYO score, median and range	0 (0-1)	1 (0-2)	1 (0-2)	**0.042**
Type of eSpA, n (%)				
Axial			51 (34.7)	
Peripheral			96 (65.3)	
Radiographic (axial), n (%)			17 (11.6)	
Non-radiographic (axial), n (%)			34 (23.1)	
Duration of eSpA, years (median and range)			6 (3-12)	
ESR (mm/h), median and range	20 (9-31)	18 (9-30)	22 (8-34)	0.25
CRP (mg/dl), median and range	0.5 (0.09-0.95)	0.58 (0.1-1.13)	0.4 (0.05-0.95)	0.27
Comorbidities, n (%)				
Cardiovascular	50 (21.8)	22 (26.8)	28 (19)	0.17
Metabolic	15 (6.6)	7 (8.5)	8 (5.4)	0.36
Osteoporosis/osteopenia	14 (6.1)	4 (4.9)	10 (6.8)	0.56
Gastrointestinal	18 (7.9)	7 (8.5)	11 (7.5)	0.78
Infective	12 (5.2)	4 (4.9)	11 (7.5)	0.45
Respiratory	11 (4.8)	3 (3.7)	9 (6.1)	0.42
Neoplastic	8 (3.5)	2 (2.4)	6 (4.1)	0.52
Autoimmune	25 (10.9)	7 (8.5)	18 (12.2)	0.39
Medication, n (%)				
bDMARDs	63 (27.5)	15 (18.3)	48 (32.7)	**0.02**
csDMARDs	60 (26.2)	22 (26.8)	38 (25.9)	0.87
Coxib	7 (3.1)	3 (3.7)	4 (2.7)	0.69
Mesalazine	82 (35.8)	34 (41.5)	48 (32.7)	0.18
None	17 (7.4)	8 (9.8)	9 (6.1)	0.32
Biologic line, n (%)				
1°	45 (19.7)	12 (14.6)	33 (22.4)	
>1°	18 (7.9)	3 (3.7)	15 (10.2)	0.4

ASDAS: ankylosing spondylitis disease activity score; bDMARD: biological disease-modifying anti-rheumatic drugs; csDMARD: conventional synthetic disease-modifying anti-rheumatic drugs; CD: Crohn's disease; CDAI: Crohn's disease activity index; IBD: inflammatory bowel disease; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate, pMAYO: partial Mayo score; UC: ulcerative colitis.

ation phase and were referred to the relevant ambulatory.

Baseline clinical characteristics of patients with and without eSpA are compared in Table I. Clinical characteristics were similar between patients with compared to those without eSpA. Statistical significant differences emerged with regard to age, disease activity and treatment: IBD patients with eSpA were younger (median age 46 [37–56 years] *vs*. 52.5 [41–62 years]; p=0.022), had a higher CDAI (84.5 [50–138]; *vs*. 60 [48–75]; p=0.004), and greater use of bDMARDs at baseline (32.5% *vs*. 18.3%, p=0.02).

Therapeutic management in eSpA patients

The decision to treat was always a shared decision as suggested by the treat-to-target recommendation for SpA (43). All treatments were administered as indicated with a rheumatological indication, apart from active gastrointestinal disease where they had double indication (gastro and rheuma). At baseline, almost one-third (32.7%) of eSpA patients (n=48) were receiving bDMARDs: adalimumab, (n=30; 62.4%), infliximab, (n=18; 37.5%). The remaining 86 IBD patients were treated with either mesalazine (n=48; 32.7%) or with csDMARDs (n=38; 25.9%): sulfasalazine, (n=32; 84.2%) azathioprine (n=5; 13.2%), methotrexate (n=3; 7.9%) or hydroxychloroquine (n=2; 6.3%).

Treatment with bDMARDs significantly increased over the follow-up period at 12 months vs. baseline (32.7% *vs*. 46.7%; AOR 1.85 [1.21–2.83]) and at 24 months (32.7% *vs*. 60%; AOR 3.45 [1.93–6.2] (Fig. 1). Adalimumab (60.4%; n=29) and infliximab (37.5%; n=18) accounted for almost all (97.9%) bDMARD use. Based on the characteristics of our IBD study cohort, bDMARD use was less frequent in older patients (increase in 10-year intervals; AOR 0.73 [0.56–0.96]), in UC *vs*. CD patients (AOR 0.43 [0.2–0.94]) and in patients with peripheral *versus* axial involvement (AOR 0.53 [0.3–1.04]).

csDMARD use was unchanged over the 2 year follow-up period (Fig. 1), although csDMARDs were used by a higher proportion in patients with peripheral *vs*. axial involvement (AOR 4.65 [2.09–10.33]) and in patients with UC *vs*. CD (2.30 [1.13–4.67]). One-third of eSpA patients receiving bDMARDs (n=48) were also treated in combination with a csDMARD (n=16; 33.3%) with a slight (non-significant) increase observed over the follow-up period (33.3% *vs*. 50% at 24 months). In contrast, when compared with baseline, treatment with mesalazine significantly decreased at 3 months (32.7% *vs*. 16.4%; AOR 0.34 [0.18–0.66]), 6 months (32.7% *vs*. 17.1%; AOR 0.42

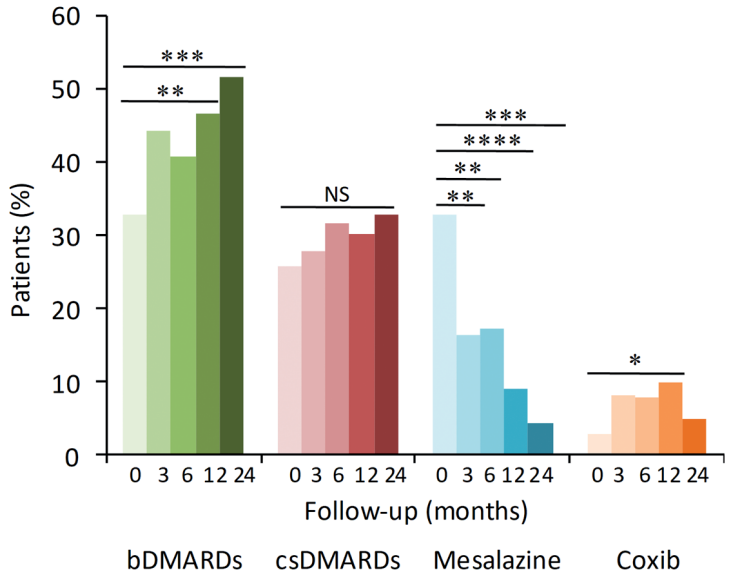

Fig. 1. Therapeutic management of eSpA patients. Data are presented as number and %. Asterisks represent level of statistical significance compared to baseline where *p<0.05, **p<0.01, ***p=0.001 and ****p<0.001. bDMARDs: biological disease-modifying anti-rheumatic drugs; csDMARDs: conventional synthetic disease-modifying anti-rheumatic drugs; Coxib: cyclooxygenase-2 inhibitors.

[0.23–0.74]), 12 months (32.7% *vs*. 8.9%; AOR 0.19 [0.09–0.41]) and 24 months (32.7% *vs*. 1.7%; AOR 0.03 [0–0.23]) (Fig. 1). The proportion of IBD patients treated with cyclooxygenase-2 inhibitors (coxibs) significantly increased at 12 months *vs*. baseline (2.72% *vs*. 10%; AOR 3.82 [1.19–12.25]) (Fig. 1).

Disease activity measures in eSpA patients

Normalisation of ESR (≤20 mm/h) *vs*. baseline was observed in patients at 6 months (n=43, 61.4%; AOR 0.52 [0.32–0.85]), 12 months (n=51, 62.9%; AOR 0.49 [0.29–0.81]) and 24 months (n=35, 60.3%, AOR 0.54 [0.31–0.95]; Fig. 2A). CRP seronegativity (≤0.5 mg/dl) was observed at 12 (n=59, 71.9%, AOR 0.5 [0.29–0.88]) and 24 months (n=41, 71.9%, AOR 0.49 [0.27–0.9]; Fig. 2B). Although CD activity remained largely stable over the follow-up period, clinical remission of CD as assessed by a CDAI ≤150 was observed at 12 months (n=51, 85%, AOR 0.2 [0.04–0.95]; Fig. 2C). Similarly, clinical activity of UC, as assessed by the pMAYO score, remained stable over–the follow-up period (Fig. 2D). BASFI was significantly reduced at 24 months (2.9±2.1 *vs*. 2.1±2.1; AOR -1.21; [-2.85-0.42]; Fig. 2F), while ASDAS decreased at 12 months compared with baseline (2.96±0.85 *vs*. 2.57±0.95; AOR 0.56 [0.32–1]; Fig. 2G). A trend towards a reduction in global VAS was observed at 12 and 24 months (compared to baseline) (Fig. 2E) while BASDAI and HAQ-S remained stable over the follow-up period (Fig. 2H-I).

Safety

Treatment-related adverse events (AEs) registered in eSpA patients during the follow–up period are summarised in Table II. A total of 55 AEs were reported, 6 (10.9%) being graded as serious, while other AEs were mainly related to intolerance (n=25; 45.5%), infection (n=13; 23.6%) or allergic reaction (n=11; 20%). AEs were more frequently reported in patients treated with bDMARDs (n=27; 49.1%) followed by csDMARDs (n=15; 27.3%) and coxibs (n=7; 12.7%). In particular, infection and allergic reaction were mainly associated to bDMARDs (n=11 and n=7, respectively). Two cases of neoplasia were registered (one during bDMARD and one during csDMARD treatment). Coxibs, given based on diagnosis and during the follow-up in the presence of inflammatory pain, were used for 4 weeks and then re-evaluated according to the follow-up. One case of gastrointestinal bleeding and four of intolerance were reported during treatment with coxib.

Discussion

Extra-intestinal manifestations, including joint pain may be misdiagnosed by experienced gastroenterologists. Therefore, a multidisciplinary approach is currently suggested for IBD patients with articular manifestations (18, 19, 23). Supporting our previous study (23), a shared gastroenterology-rheumatology approach was associated with a significant improvement of SpA disease activity, no major IBD complications and a good safety profile during the 2 years follow-up.

Findings revealed that from a total of 229 IBD patients who referred joint pain and attended at least one follow-up visit after baseline, a diagnosis of eSpA was made in 64.2% of patients (n=147). A comparable proportion was reported in our previous joint gastro-rheumatologic assessment (23). Therefore, one of the main findings from this study is that almost one third (36.7%) of IBD patients referred to rheumatologists by dedicated gastroenterologists, due to musculoskeletal pain, had no eSpA related to IBD. This implies that quite often articular manifestations related to IBD are misdiagnosed and therefore not properly treated, even in tertiary referral IBD centres.

The higher proportion of eSpA patients treated with biologics (compared to non-eSpA patients) is not surprising, since anti-TNF agents are indicated for both IBD and SpA with proven efficacy, particularly in patients with axial involvement (44). Interestingly, csDMARD remained unchanged, while mesalazine use decreased, most likely due to the absence of efficacy of mesalazine on articular involvement. bDMARD treatment significantly increased over the follow-up period in both peripheral and axial-SpA patients. Interestingly, patients with axial eSpA and CD were more likely to receive bDMARDs than peripheral eSpA and UC patients. This approach was probably related to the recognised efficacy of anti-TNF agents in axial disease compared with csDMARDs, and to the frequent use of anti-TNFs in refractory or fistulising CD

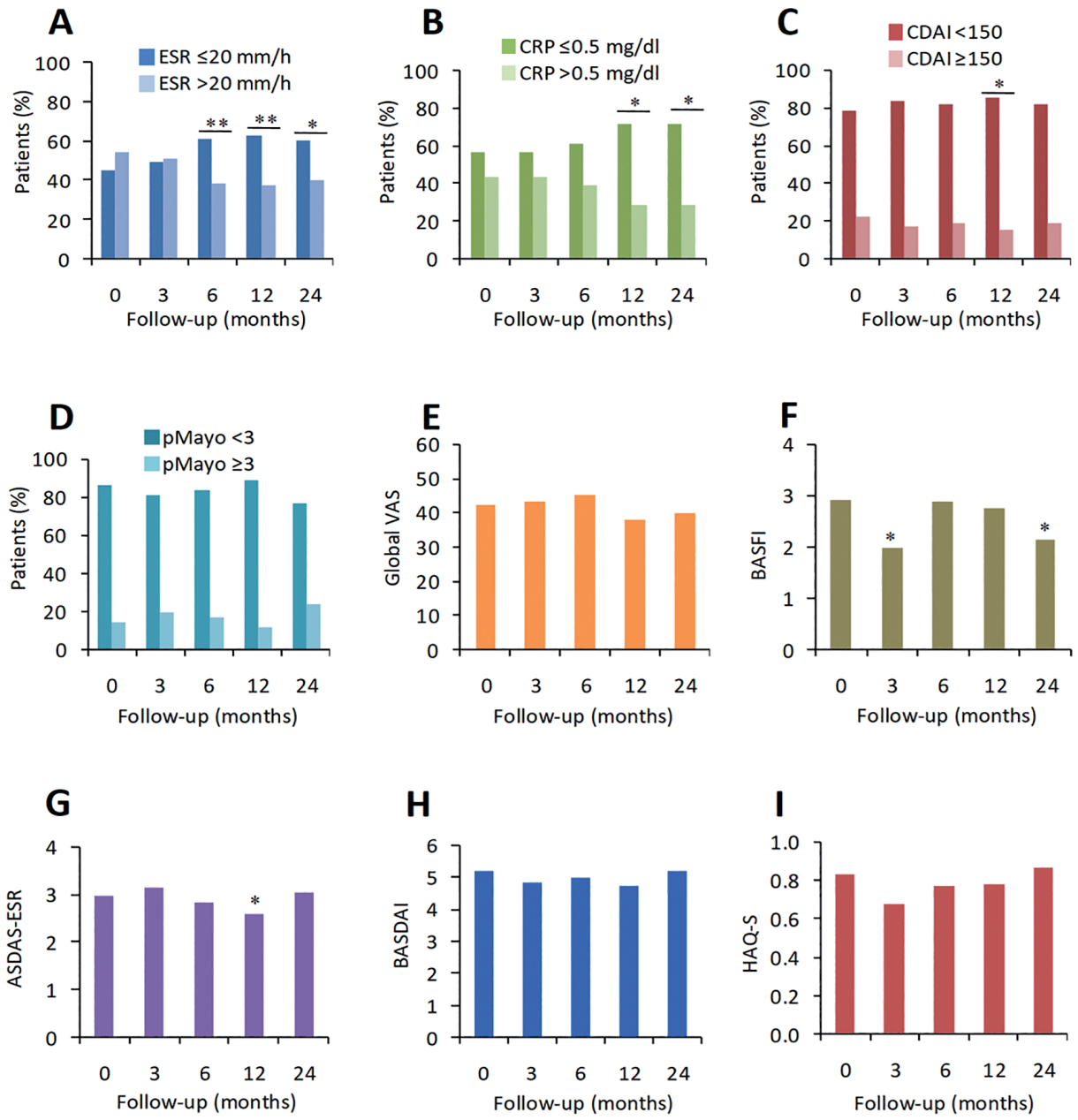

Fig. 2. Normalisation and change in levels of disease activity measures over 2-year follow-up in eSpA patients. Data are presented mean values or number and %. BASDAI: Bath Ankylosing Spondylitis Disease Activity Index, BASFI: Bath Ankylosing Spondylitis Functional Index, CDAI: Crohn's disease activity index, CRP: C-reactive protein, ESR: erythrocyte sedimentation rate, HAQ-S: Health Assessment Questionnaire for Spondyloarthropathies and VAS: visual analogue scale. Asterisks represent level of statistical significance between levels at baseline and follow-up time points where *p<0.05 and **p<0.01.

Table II. Summary of adverse events in eSpA population.

Adverse event	Total	bDMARDs	csDMARDs	Coxib	Mesalazine	Serious AE
Infection	13 (23.6)	11 (20.0)	0 (0)	2 (3.6)	0 (0)	0 (0)
Neoplasia	2 (3.6)	1 (1.8)	1 (1.8)	0 (0)	0 (0)	2 (3.6)
Intolerance	25 (45.5)	7 (12.7)	9 (16.4)	4 (7.3)	5 (9.0)	0 (0)
Allergic reaction	11 (20.0)	7 (12.7)	4 (7.3)	0 (0)	0 (0)	0 (0)
GI bleeding	1 (1.8)	0 (0)	0 (0)	1 (1.8)	0 (0)	1 (1.8)
Myelotoxicity	2 (3.6)	0 (0)	1 (1.8)	0 (0)	1 (1.8)	2 (3.6)
Surgical intervention	1 (1.8)	1 (1.8)	0 (0)	0 (0)	0 (0)	1 (1.8)
Total	55 (100)	27 (49.1)	15 (27.3)	7 (12.7)	6 (10.9)	6 (10.9)

AE: adverse event; bDMARDs: biological disease-modifying anti-rheumatic drugs; csDMARDs conventional synthetic disease-modifying anti-rheumatic drugs; GI: gastrointestinal.

(45). Conversely, bDMARDs were less frequently used in older eSpA patients. The reported higher risk of infections in older IBD patients using biologics (46) and the frequent comorbidities contraindicating their use may well account for these findings. In our study population, bDMARDs included only adalimumab or infliximab, adalimumab accounting for 62.4% of bDMARD use in these patients. It is tempting to speculate that the observed improvement in several disease activity scores during the follow-up, including ESR, CRP and ASDAS is mainly related to the immunomodulatory effects of anti-TNFs. However, considering the fact that this was a real-life observational study, where patients could have received combined therapy, sub-analysis of outcome variables by drug type and indication was not performed to avoid significant bias. The effect of anti-TNFs is well established in other settings, but rarely demonstrated in the eSpA population (18). The observed reduction in CRP during the follow-up, related to a decrease in inflammatory status, might be associated with a reduced risk for radiographic progression, in agreement with previous evidence in SpA (11). Luchetti and colleagues recently demonstrated that adalimumab treatment over a period of 1 year could significantly improve a wide range of both articular and gastrointestinal inflammatory measures by employing a multidisciplinary (gastro-rheumatologic) evaluation (18). Similarly, we observed a significant reduction in inflammatory (ESR and CRP), gastrointestinal (CDAI) and articular (ASDAS and BASFI) scores up to 12 months. During the 2 years follow-up, clinical scores and inflammatory markers were further reduced. The lack of a significant improvement of several outcome parameters early after enrolment may be due to the long disease duration in our study population. The development of other, more sensitive composite scores may be necessary in this setting, as already suggested (18) and developed for other multidisciplinary diseases, such as psoriatic arthritis (47).

Concerning IBD, no flares, no steroid consumption or tolerability issues emerged over the follow-up period. eSpA patients treated with adalimumab for 1 year were also observed to have few adverse events in the study by Luchetti *et al*. (18). However, in the present study over 2 years, 55 (24%) AEs were reported. Although the majority of AEs (n=49, 89.1%) were mild and required drug discontinuation only in one case of malignancy (prostatic neoplasia). The development of AEs following long-term treatment with bDMARDs may occur and should be monitored. In our population, a good tolerability of coxibs was observed in eSpA patients, supporting few and discrepant findings providing evidence of the safety of coxibs in IBD patients (48, 49). In the present study, rheumatologists and gastroenterologists share a common experience for managing patients with eSpA, significantly improving awareness of both specialists, thus optimising the diagnosis of the often complex symptoms associated with IBD and eSpA. This will in turn help reduce the diagnostic delay, thus allowing a prompt and appropriate therapeutic intervention and a better prognosis of the affected patients (19, 50, 51).

Furthermore, the combined approach may lead to better compliance of patients, reduced cost and reduced loss of working days for patients, saving time for both patients and physicians.

This study provides prospectively collected data from a homogeneous cohort of patients with eSpA followed up for 24 months.

Among the major limitations that need to be addressed, weaknesses of observational studies including the lack of blinding when evaluating the efficacy of treatment and incompleteness of data in some patients have previously been described (52, 53). Consistent with limitations of an observational design, our study provides important clinical insights regarding the diagnosis and treatment of eSpA, providing preliminary information regarding the efficacy of treatments of both intestinal and articular symptoms. Among limitations of the study, stratification of patients who attended all visits at 2 years reduced the sample size. However, specific endpoints still showed favourable treatment efficacy and our findings are in agreement not only with our previous study (23), but also with other observations (18, 54). A longer follow-up of a larger study population, together with additional measures of disease outcome (*e.g*. radiological measures) may provide further information.

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