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Review

Enteropathic spondyloarthritis: Results from a large nationwide database analysis

Andrea Picchianti-Diamanti[a,*], Roberto Lorenzetti[b], Maria Sole Chimenti[c], Michele Maria Luchetti[d], Paola Conigliaro[c], Claudia Canofari[c], Devis Benfaremo[d], Vincenzo Bruzzese[b], Bruno Laganà[a,1], Roberto Perricone[c,1], on behalf of SIGR (Angelo Zullo[e], Francesco Caso[e], Luisa Costa[e], Paola Tomietto[e], Fischetti Fabio[e], Palma Scolieri[e], Luca Navarini[e], Elisa Cuccagna[e], Luis Severino Martin-Martin[e], Maria Lia Scribano[e], Roberto Faggiani[e], Cristiano Pagnini[e], Giammarco Mocci[e], Mauro Demurtas[e], Antonio Tursi[e], Stefano Festa[e], Giulia Zerboni[e], Roberta Pica[e], Lorenzo Ridola[e], Marino Paroli[e], Flavia Baccini[e], Livia Baincone[e], Armando Gabrielli[e], Antonella Afeltra[e], Raffaele Scarpa[e])

[a] *Department of Clinical and Molecular Medicine, S. Andrea University Hospital, "Sapienza" University, Rome, Italy*
[b] *Department of Internal Medicine, Rheumatology and Gastroenterology, "Nuovo Regina Margherita" Hospital, Rome, Italy*
[c] *Rheumatology, Allergology and Clinical Immunology, Department of Medicina dei Sistemi, University of Rome Tor Vergata, Rome, Italy*
[d] *Clinica Medica, Dipartimento di Scienze Cliniche e Molecolari, Università Politecnica delle Marche, Ancona, Italy*
[e] *Societa' Italiana di GastroReumatologia. Via Michele Mercati 33, Rome, Italy*

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ABSTRACT

Introduction: Spondyloarthrits (SpA) share clinical, genetic and immunological features with Inflammatory Bowel Diseases (IBD), and enteropathic SpA (eSpA) represent the clinical evidence of the association between gut and joint diseases.

This cross-sectional study aimed to report data of eSpA patients collected from the first Italian database.

Patients and methods: A specific web-based interface has been created to insert and collect the main clinical, serologic and imaging data from patients with eSpA, as well as disease activity, comorbidities and treatment, in a real-life scenario.

Results: Data were collected in 14 Italian centers (7 rheumatology and 7 gastroenterology units). A total of 347 eSpA patients were enrolled in the study. Type 1 peripheral eSpA was the most frequent form. Crohn' Disease (CD) was the most represented IBD. CD activity was similar among eSpA, whereas UC activity was slightly higher in the axial and mixed form than in the peripheral eSpA. The disease was active in less than half of axial eSpA patients and in only 18% of patients with peripheral eSpA. Furthermore, most of the patients had an inactive IBD. Nineteen percent of the total eSpA patients were free of therapy at the time of the enrollment and 61% of the patients were receiving biotechnological agents.

Conclusions: The multidisciplinary management of eSpA patients, favored by this *ad hoc* created web-based platform, allowed to obtain data from the largest eSpA cohort. The information coming of this database might advance knowledge of eSpA and improve their standard of care.

Abbreviations: SpA, Spondyloarthritis; eSpA, enteropathic SpA; IBD, Inflammatory Bowel Diseases; CD, Crohn's Disease; UC, Ulcerative Colitis; PsA, Psoriatic Arthritis; SIGR, *Società Italiana di GastroReumatologia*; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; MRI, magnetic resonance imaging; ASDAS, Ankylosing Spondylitis Disease Activity Score; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASFI, Bath Ankylosing Spondylitis Functional Index; LEI, Leeds enthesitis index; HAQ-S, Health Assessment Questionnaire for SpA; HBI, Harvey-Bradshaw Index; csDMARDs, conventional DMARDS; bDMARDs, biotechnological DMARDs; SSA, sulphasalazine; MTX, methotrexate; AZA, azathioprine; CSA, cyclosporine

* Corresponding author at: Department of Clinical and Molecular Medicine, Sant'Andrea University Hospital, Sapienza University of Rome, Rome, Italy.
E-mail addresses: andrea.picchiantidiamanti@uniroma1.it (A. Picchianti-Diamanti), maria.sole.chimenti@uniroma2.it (M.S. Chimenti), mluchetti@univpm.it (M.M. Luchetti), paola.conigliaro@uniroma2.it (P. Conigliaro), claudia.canofari@uniroma2.it (C. Canofari), devis87@gmail.com (D. Benfaremo), vincenzobruzzese@nrm.it (V. Bruzzese), bruno.lagana@uniroma1.it (B. Laganà).

[1] these authors contributed equally to the manuscript.

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1. Introduction

Spondiloarthrytis (SpA) belong to a heterogeneous group of inflammatory chronic diseases sharing common pathogenic, clinical and radiologic features such as the presence of inflammatory back pain, dactylitis and enthesitis, the association with the HLAB27 and the frequent extra-articular involvement mainly cutaneous, ocular and intestinal. SpA affect mainly young subjects and can lead to functional impairment and deterioration in patients' quality of life and life expectancy. SpA include ankylosing spondylitis, psoriatic arthritis (PsA), reactive arthritis, acute anterior uveitis, axial non-radiographic SpA and SpA associated to inflammatory bowel disease (IBD). The worldwide estimated prevalence for PsA is 1% [1], whereas for AS is 0.24% in Europe and 0.31% in North America [2].

It has been noted that up to 60% of patients with SpA presents subclinical gut inflammation and 10% an overt inflammation evolving to Crohn's disease (CD). On the other hand, arthritis is the most frequent extra-intestinal manifestation in patients with IBD [3–5]. IBD include CD and ulcerative colitis (UC) which may onset at any age, with a peak of incidence between 20 and 40 and 50–60 years, and a prevalence of 300/100.000 subjects has been reported in Western populations [6]. Symptoms include diarrhoea, generally with blood and mucus, abdominal pain, weight loss and fever, evolving to severe impairment in quality of life and reduction of life expectancy if not timely and adequately treated.

Joint involvement in enteropathic SpA (eSpA) can manifest as axial (sacroileitis and/or spondylitis), peripheral, or mixed (axial and peripheral). The peripheral involvement was empirically classified in type 1 or pauciarticular (< 5 joints, usually self-limiting and related to the IBD activity) and type 2 or polyarticular (≥ 5 joints, generally independent from IBD activity) [7]. The reported prevalence is highly variable ranging from 1 to 25% for sacroileitis and 3 to 30% for peripheral involvement [8]. At least in part, such a variability could depend on a lack of homogeneity among eSpA patients, different classification criteria and diverse diagnostic tools used. Indeed, the high clinical variability of eSpA, combined with the absence of specific markers and the multi-organ involvement, make challenging a prompt diagnosis with detrimental consequences on patients' management.

In this context, a multidisciplinary approach coordinated by rheumatologist and gastroenterologist is expected to be advantageous for patients with eSpA. This study aimed to report data from the first web-based rheumatologic and gastroenterologic integrated platform on eSpA patients managed in clinical practice.

2. Patients and methods

This is a cross sectional multicenter study with patients from 14 Italian centers (having an IBD/SpA integrated outpatient unit) participating in the Italian database for eSpA. Data were collected from consecutive patients from January 2017 to March 2018.

To be included in the database the patients had to present a diagnosis of eSpA confirmed through standard criteria and subgrouped using the Montreal classification for CD and UC, combined with a diagnosis of peripheral and/or axial arthritis confirmed in accordance with the ASAS criteria; age $>$ 18 years, available clinical data and compliance to follow the study protocol [9–13].

A web-based interface was created *ad hoc* to insert the data from all the participating centers. The software is an independent database that was established by the *Società Italiana di GastroReumatologia* (SIGR) in December 2016 to collect the main clinical, serologic and imaging data from patients with eSpA as well as disease activity, comorbidities and treatment in a real-life scenario.

It is focused on a multidisciplinary approach and divided into three domains:

the patient domain with the non-sensitive demographic data that had to be filled in by the first specialist who performed the visit. After that, the clinician obtained a unique code to identify the patient and then proceeded on to the specific rheumatologic or gastroenterologic domain.

2.1. Clinical assessment

Rheumatologic assessment included: physical examination with 68 tender and 66 swollen joint count, presence of dactylitis, enthesitis, inflammatory spinal and buttock pain. Laboratory tests included erythrocyte sedimentation rate (ESR, mm/h), C-Reactive Protein (CRP, mg/l) and HLAB27.

Imaging data included: ultrasonography (US) (defined as positive in the presence of synovial hyperthrophy, tenosynovitis or enthesitis according to the OMERACT definition criteria), traditional radiography (only for the axial involvement; sacroileitis according to the New York criteria, presence of syndesmophites or parasyndesmophites) and magnetic resonance imaging (MRI) (only for the axial involvement; active or inactive sacroileitis according to the ASAS definition) [14–17].

ASAS criteria were used to classify patients as affected by axial or/and peripheral SpA [13]. The Oxford Criteria were used to classify the joint involvement in eSpA patients as type 1 peripheral and type 2 peripheral; the combination of both axial and peripheral involvement was defined as mixed according to Smale et al. [7,8].

Disease activity and function in eSpA patients were assessed using the Ankylosing Spondylitis Disease Activity Score (ASDAS CRP-based), Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), Bath Ankylosing Spondylitis Functional Index (BASFI), tender and swollen joints count, Leeds Enthesitis Index (LEI) and Health Assessment Questionnaire for SpA (HAQ−S) [18–21].

CD and UC localization and CD behavior were registered according to the Montreal Classification. For CD localization: L1 = ileum, possibly involving cecum; L2 = colon; L3 = ileocolon and L4 = upper gastrointestinal tract; for CD behavior: B1 = no stricturing and no penetrating, B2 = stricturing and B3 = penetrating; for UC involvement: E1 = ulcerative proctitis, E2 = left sided UC (distal UC), E3 = extensive UC (pancolitis) [9–11].

CD activity was evaluated using the Harvey-Bradshaw Index (HBI). UC disease activity was measured by the partial and full Mayo score with a score ≥ 3 indicating active disease according to the European Crohn's and Colitis' Organization criteria [22].

Data regarding the current rheumatologic and gastroenterologic therapeutic regimen (*i.e.* route of administration, dose and dose interval) were also recorded.

2.2. Statistical analysis

Continuous variables were compared using the parametric unpaired *t*-test. Categorical variables were compared using the Chi-squared test or Fisher' exact test when appropriate, and P values $< .05$ were considered statistically significant. All statistical analyses were performed using GraphPad Prism version 7 (GraphPad software).

3. Results

Clinical, demographic, serologic and imaging data of the 347 enrolled eSpA patients are resumed in Table 1.

One hundred and eighty-four patients (53%) had a peripheral eSpA of which 105 (57%) pauciarticular and 79 (43%) polyarticular; 69 (20%) patients presented an axial eSpA and 94 (27%) had a mixed form. Peripheral eSpA was the most represented form both in CD (51%) and in UC patients (61%).

Two hundred and forty-four patients out of 347 (70.5%) had CD, 71 (20.5%) patients had UC, whereas 32 (9%) patients presented unclassified colitis. The most prevalent localization of CD was L1 (42%), and the most prevalent behavior was B1 (50%), whereas in UC patients the most prevalent localization was E3 (42%).

Table 1
Demographic, clinical, serologic and imaging data of the total eSpA patients.

			Peripheral		
	Axial	Mixed	Pauci	Poli	
Total (n)	69	94	105	79	347
Male (n)	44	38	34	23	139
Age (mean)	51	48	51	50	50
Smokers (n)	41	44	57	45	187
Familial history (n)	10	9	6	11	36
SpA disease duration (mean;years)	7	7	4	4	5
IBD disease duration (mean;years)	17	16	14	14	15
CD total (n)	53	66	66	59	244
All localizations	38	46	56	52	192
L1	15	19	21	25	80
L2	5	7	12	11	35
L3	16	17	23	13	69
L4	2	3	0	3	8
All behaviors	38	41	55	52	186
B1	18	23	28	24	93
B2	16	14	20	18	68
B3	3	3	6	10	22
P	1	1	1	0	3
UC total (n)	9	19	24	19	71
All localizations	6	4	14	2	26
E1	2	1	4	0	7
E2	2	2	4	0	8
E3	2	1	6	2	11
Unclassified Colitis	7	9	15	1	32
ESR (mm/h; mean)	24,96	16,07	23,11	20,74	20,86
CRP (mg/l; mean)	7,34	7,98	5,59	7,97	7,20
B27 tot/pos (n)	42/10	61/10	60/3	36/0	199/23
X-Ray tot/pos (n)	29/25	37/32	14/1	19/1	99/59
MRI tot/pos (n)	38/34	46/42	28/0	27/0	139/76
US tot/pos (n)	6/1	43/1	52/49	60/60	161/111
All comorbidities (n)	13	25	11	21	70
Uveitis	6	7	1	4	18
Dactylitis	0	3	2	5	10
Psoriasis	7	20	8	17	52

IBD: Inflammatory Bowel Disease; SpA: Spondyloarthritis; CRP:C-reactive protein;
ESR: Erythrocyte sedimentation rate; CD: Crohn's disease; UC: Ulcerative colitis; US: Ultrasonography; MRI: Magnetic Resonance Imaging.

The prevalence of males was higher in the axial eSpA (62%) than in the mixed (40%) or peripheral group (31%) (axial *vs* peripheral $p < .0001$). The smoking habits were similar among the eSpA groups with the axial one having the highest percentage (59%).

ESpA disease duration was higher in the axial and mixed types compared to the peripheral one ($p < .001$), furthermore the disease duration was significantly higher in the IBD than in the eSpA patients ($p < .0001$).

The ESR and CRP values were not significantly different between axial and peripheral eSpA. The HLAB27 was positive in 12% of the total examined eSpA patients and 24% of the axial eSpA, whereas only three patients with type 1 peripheral involvement resulted positive.

Considering comorbidities, psoriasis was present in 15% of the total eSpA patients with a higher prevalence in the mixed group (21%); uveitis and dactylitis were present in 5% and 3% of the total eSpA patients, respectively, with the axial form having the highest and lowest prevalence respectively.

Imaging data were available in a subgroup of patients. In particular, among axial and mixed eSpA, X-ray was positive in 57/66 patients (86%), MRI was positive in 76/84 patients (90%) (five of who had a negative X-ray) and US was positive in 2/49 patients (4%).

With regard to type 1 and 2 peripheral eSpA, X-ray was positive in 2/33 patients (6%), MRI in none out of 55 patients, whereas US was positive in 109/112 patients (97%) (see Table 1 for more details).

3.1. Disease activity and therapeutic regimen

Fifty-one and 46% percent of axial eSpA presented an inactive disease considering the ASDAS (< 2.1) and BASDAI (< 4) respectively; 82% of the patients with peripheral eSpA presented < 4 active joints. Regarding IBD activity, 94% of CD and 74% of UC patients were in clinical remission (HBI < 5; Mayo score ≤ 3).

The number of tender joints of mixed and type 2 eSpA was significantly higher than the type 1, whereas the activity of the axial involvement was not significantly different among axial and mixed eSpA (Fig. 1).

CD activity was similar among eSpA, whereas UC activity was slightly higher in the axial and mixed form than in the peripheral eSpA (Fig. 1).

Concerning quality of life, the HAQ and BASFI of eSpA was not significantly different between CD and UC patients.

A relevant rate (19%) of eSpA patients was free from therapy at the time of the enrollment, 20% was receiving conventional DMARDS (csDMARDs) alone, whereas 61% of the total eSpA patients were treated with biotechnological DMARDs (bDMARDs) alone (70%) or in combination with csDMARDs (30%) (Fig. 2). Sulphasalazine (SSA) was the most frequently used csDMARDs followed by methotrexate (mtx), azathioprine (AZA), hydroxychloroquine, cyclosporine (CSA) and 6-mercaptopurine. Among bDMARDs, adalimumab (ADA) was the most used (60%), followed by infliximab (30%) and golimumab (GOL) (10%) [23,24] In particular, bDMARDs were more frequently adopted in patients with mixed and type 1 eSpA than in patients with the other subtype of eSpA (Fig. 2).

4. Discussion

ESpA represent the clinical evidence of a shared pathophysiology between IBD and SpA.

A possible link between the gut and the joints was hypothesized for the first time by Smith in 1922 who described an improvement of the articular symptoms in patients with chronic arthritis after colectomy [25]. Only 42 years later, the American Rheumatism Association classified arthritis associated with IBD as an independent clinical form and in 1976 eSpA was included in the SpA group by Moll and Wright [26,27]. In the last 20 years, there has been a growing interest in understanding the immunological basis and the clinical expression of the gut-joint axis [28–30]. Abnormalities in the gut microbiota has indeed been reported both in patients with IBD and SpA, suggesting a tight interrelationship between microbiota, rheumatic and gastroenterology pathologies [31,32]. It has been hypothesized that in SpA patients the increased intestinal permeability, probably induced by genetic factors (HLA−B27) could lead to a disruption of the basal membrane, hyperplasia of goblet cells and activation of Paneth cells producing high levels of AMPs and IL-23 [33]. Moreover, there is evidence in increased IL-23 expression in inflamed tissues including the gut of SpA patients without an overt IBD [34,35].

Several authors evaluated the prevalence of eSpA among IBD and the characteristics of the different clinical phenotype [[8,36–43]]. However, the reported prevalence is highly variable, since current studies are characterized by a lack of homogeneity in patient's characteristics and by different classification criteria as well as imaging tools adopted.

In this cross-sectional study, we aimed at collecting a large comprehensive and standardized database of eSpA patients in a real-life scenario.

To obtain such a target, a specific web-based interface was created to insert and collect the main clinical, serologic and imaging data from patients with eSpA, as well as disease activity, comorbidities and treatment from 14 IBD/SpA integrated out-patient units.

Confirming previous studies, in our cohort of eSpA we found out that the type 1 was the most frequent form of eSpA and CD was more

TD = Tender, SW= Swollen
BASDAI = Bath Ankylosing Spondylitis Disease Activity Index
ASDAS = Ankylosing Spondylitis Disease Activity Score
HBI = Harvey-Bradshaw Index
Data are expressed as mean. *P<0.004 mixed vs type 1 **P< 0.001 type 2 vs type 1

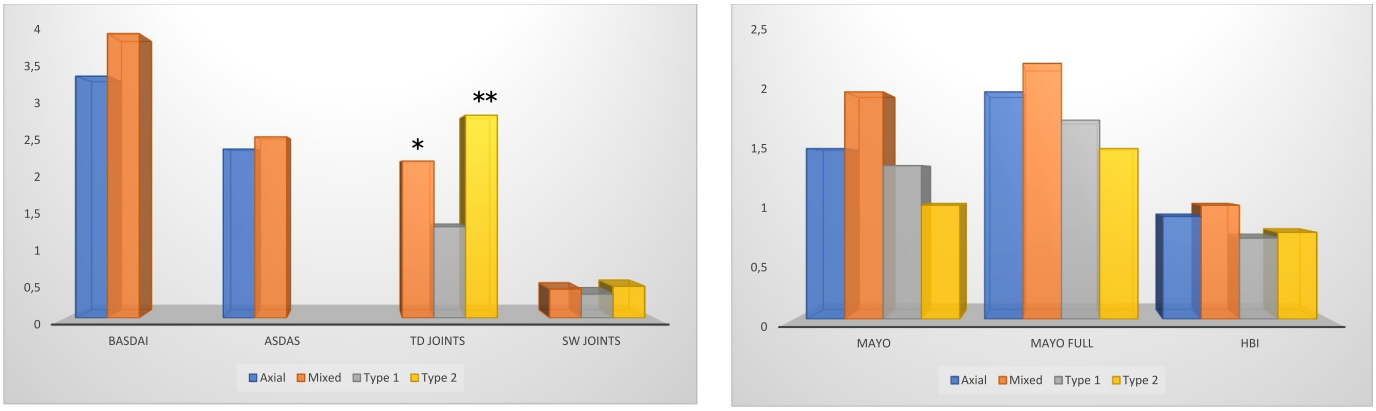

Fig. 1. Disease activity in axial, mixed, type 1 and type 2 eSpA. Panel A = Axial and peripheral disease activity status, Panel B = Crohn's Disease and Ulcerative Colitis disease activity status.

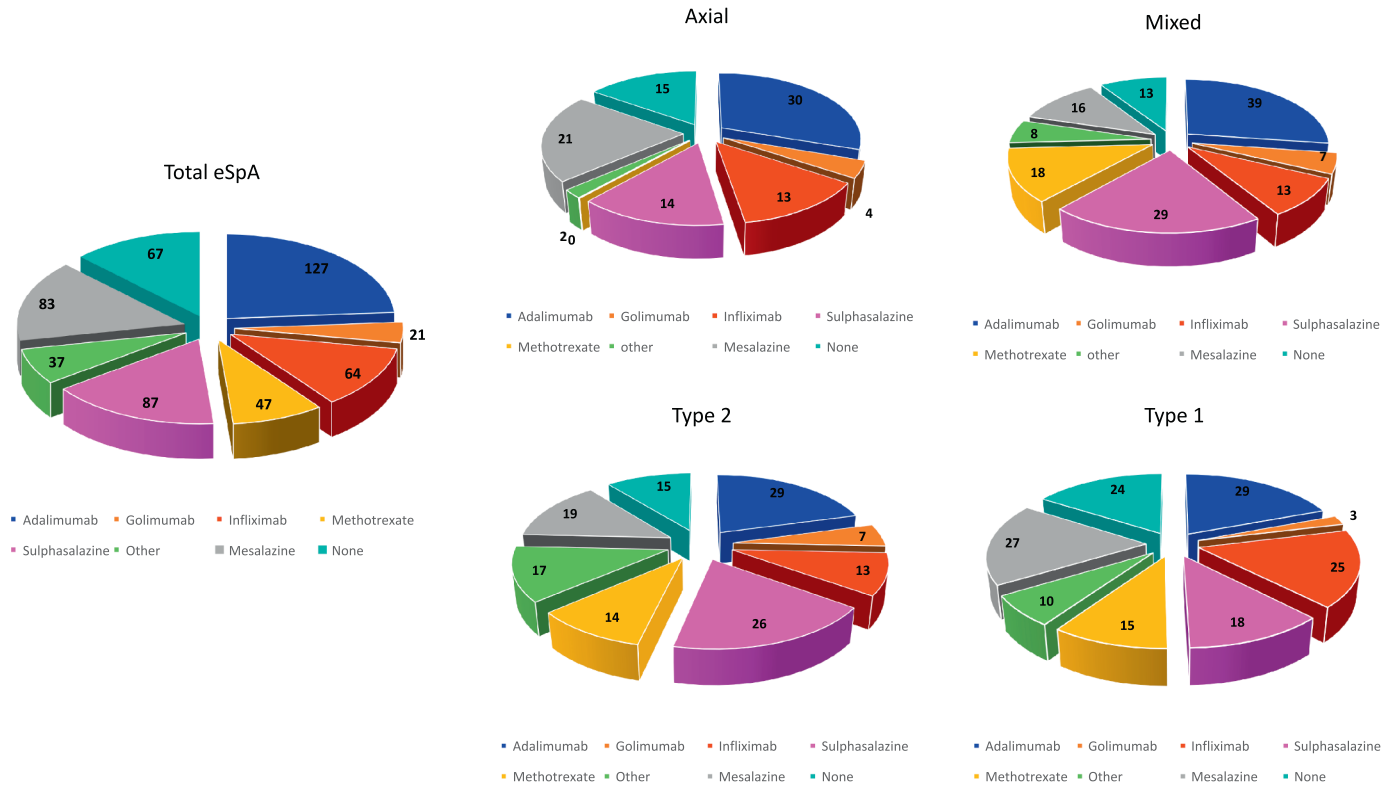

Fig. 2. Number of patients receiving the different therapeutic agents in the total eSpA and in the axial, mixed, type 1 and type 2 eSpA.

represented than UC [[7,8,36,40–44]]. Concerning disease localization, pancolitis was the most frequent form of UC, whereas the ileal and ileo-colic involvement was the most frequent localization of CD with a non-stricturing and non-penetrating behavior.

Interestingly, our cohort of eSpA patients presented an overall good control of both IBD and SpA activity. Axial eSpA patients, indeed, were active in less than half of the patients and only a minority of patients with peripheral eSpA had > 4 active joints; moreover, most of the patients with IBD were in clinical remission. UC activity was higher in the axial and mixed form than in the peripheral eSpA whereas CD activity was similar among the different eSpA groups.

(Fig. 1).

The overall low disease activity observed in this cohort of eSpA patients, could be explained by the fact that all the centers participating in this study have a IBD/SpA integrated outpatient unit that can allow a combined management and a tight and tailored follow up of eSpA patients. This observation seems further supported by the significant percentage of patients who were free from therapy at the time of the enrollment, however the cross-sectional design of this data collection can't allow to draw conclusive statements and require a prospective evaluation.

Although not mandatory, imaging data were obtained in a relevant

subgroup of patients. In particular US has been documented in 76% and 50% of type 2 and type 1 peripheral eSpA respectively, showing an overall high sensitivity in confirming joints involvement (97%). On the other hand, MRI has been reported in about half of total axial/mixed eSpA and showed axial involvement in 90% of patients.

bDMARDS have been administered in 61% of eSpA patients, of which 70% alone and 30% in combination with csDMARDs. SSA was the most frequently used csDMARD and ADA was the most frequently adopted bDMARD. These therapeutic choices could be related to specific challenges in the management of eSpA patients. For example, MTX is not so frequently adopted by gastroenterologist as by rheumatologist and is indicated only in CD [45], whereas GOL is indicated only in UC [46,47] that represented a minority of IBD in our cohort. In line with the ASAS recommendations [48], csDMARDs were less frequently used in the axial than in the other form of eSpA, whereas bDMARDs were most frequently adopted in the mixed and type 1 eSpA (Fig. 2).

5. Conclusions

To the best of our knowledge, this Italian multicenter study represents the first web-based integrated rheumatologic and gastroenterologic interface specifically created for patients with eSpA.

This web-based platform allows to obtain consistent data in large cohort of eSpA patients, potentially improving and facilitating a multidisciplinary approach to these diseases in a real-life scenario.

Ethics approval and consent to participate

The study was conducted according to the ethical principles of the Declaration of Helsinki and was consistent with the guidelines for good clinical practice. Written informed consent was obtained from patients and the ethics committee approved the study (prot 2546/CE Lazio1).

Availability of data and material

The datasets used and/or analysed during the current study are available from SIGR on reasonable request.

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Authors contributions

APD, BL, RL, RP and MSC designed the study; APD and RL coordinated the study; APD wrote the manuscript; RP critically revised the manuscript; MSC, PC, CC, MML and DB acquired data from > 40 patients; the authors on behalf of SIGR, acquired data from 10 to 20 patients. All authors read and approved the final manuscript.

Declaration of Competing Interest

The authors declare no conflict of interest related to the manuscript.

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