

Observational Study

Adalimumab efficacy in enteropathic spondyloarthritis: A 12-mo observational multidisciplinary study

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Abstract

AIM

To report adalimumab (Ada) efficacy on articular-gastrointestinal disease and health-related quality of life (HRQoL) in patients with enteropathic spondyloarthritis (ES).

METHODS

A cohort of 52 patients with ES was evaluated in the departments of gastroenterology and internal medicine. At baseline, all patients underwent assessment by an integrated gastro-rheumatologic evaluation of articular and gastrointestinal activity, as well patient reported outcomes (PROs) of the HRQoL questionnaires. After this integrated evaluation and following a specific working flowchart, the Ada anti-tumor necrosis factor (TNF)-inhibitor was assigned to a cohort of 30 patients and its clinical efficacy was evaluated at baseline and

after 6-mo and 12-mo treatment by the following tests: (1) Ankylosing Spondylitis Disease Activity Score-C-Reactive Protein (ASDAS-CRP); Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), Bath Ankylosing Spondylitis Functional Index (BASFI) and Bath Ankylosing Spondylitis Metrology Index (BASMI) for articular activity; (2) Inflammatory Bowel Disease Questionnaire (IBDQ), Crohn's Disease Activity Index (CDAI) and partial Mayo (pMayo) score for gastrointestinal symptoms and activity; and (3) Health Assessment Questionnaire (HAQ), Patient Global Assessment (PGA) and Short Form-36 health survey (SF-36) questionnaires for PROs of the HRQoL.

RESULTS

Integrated evaluation and management of the patients affected by ES, carried out simultaneously by a gastroenterologist and a rheumatologist, allowed clinicians to choose the optimal therapeutic strategy. In a cohort of 30 ES patients affected by active articular and gastrointestinal disease, or axial active articular inflammation, Ada led to fast and sustained improvement of both articular and gastrointestinal disease activities. In fact, all the clinimetric evaluation tests exploring articular or gastrointestinal activity, as well as all the HRQoL scores, showed a significant improvement having been achieved at the earliest (6-mo) assessment. This important clinical improvement was maintained at the 12-mo follow-up. Importantly, global and gastrointestinal quality of life significantly correlated with articular disease activity, providing evidence to support that the integrated evaluation is the best option to manage patients with ES.

CONCLUSION

Ada treatment, upon multidisciplinary (gastro-rheumatologic) evaluation, significantly improves both articular and gastrointestinal inflammation, thereby improving the HRQoL in patients affected by ES.

Key words: Clinimetric assessment; Patient reported outcomes; Inflammatory bowel diseases; Enteropathic spondyloarthritis; Tumor necrosis factor-inhibitors; Multidisciplinary evaluation

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Core tip: Enteropathic spondyloarthritis (ES) is characterized by articular inflammation in patients with inflammatory bowel diseases, such as Crohn's disease or ulcerative colitis. Correct management, especially covering both of the two clinical manifestations (gastro-rheumatologic), remains a challenge. In this study, we demonstrated that the integrated gastroenterological and rheumatologic evaluation of ES patients achieved the best therapeutic approach. In particular, we demonstrated that in a real-life cohort of ES patients, the tumor necrosis factor-inhibitor, adalimumab, led to fast and sustained improvement of articular and

gastrointestinal inflammation, with a consequent improvement in the global and gastrointestinal quality of life.

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INTRODUCTION

Enteropathic spondyloarthritis (ES) is a seronegative spondyloarthropathy (SpA) characterized by the presence of articular inflammation in patients affected by inflammatory bowel diseases (IBDs), such as Crohn's disease (CD) or ulcerative colitis (UC)^[1,2]. Arthritis is the most frequent extra-intestinal manifestation in patients with IBDs^[1] and it may primarily involve the axial joints, presenting with definite ankylosing spondylitis (AS) and/or isolated sacroiliitis, or peripheral joints and/or peri-articular structures, such as tendons and entheses^[3]. The articular manifestations significantly affect health-related quality of life (HRQoL) of ES patients^[4].

Although a link between inflammation of the joints and gut has been demonstrated^[5,6], only half of ES patients are actually evaluated by a rheumatologist for proper diagnosis and, thus, for an integrated therapeutic approach through a coordinated action with the treating gastroenterologist^[7]. Thus, an integrated clinical evaluation and therapeutic approach encompassing both the intestinal and articular features in ES patients, will likely be beneficial, particularly for the clinical outcomes. It has been demonstrated by recent studies that tumor necrosis factor (TNF)-alpha inhibitors could be effective therapeutic agents against ES^[8], but few to date have reported on their real-life efficacy in this disease.

Herein, we have investigated the role of a gastro-rheumatologic multidisciplinary management and therapeutic approach in ES patients through evaluation of the efficacy of the TNF-alpha inhibitor adalimumab (Ada), assessing the efficacy on both gastrointestinal and rheumatologic disease activities and on the patient-reported HRQoL.

MATERIALS AND METHODS

Patients and study design

This study was carried out in a cohort of 52 patients with ES, including 31 affected by CD (59.6%) and 21 by UC (40.3%), collectively representing 23.6% of the 220 overall patient population with IBD in the

Table 1 Enteropathic spondyloarthritis patient features

	ES-AN, <i>n</i> = 52	ES-AN/Ada, <i>n</i> = 30
Crohn's disease:Ulcerative colitis	31 (60):21 (40)	19 (63):11 (37)
Males:Females	22 (42):30 (58)	17 (57):13 (43)
Age in years	47.2 ± 14.2	46.2 ± 14.4
Disease duration of IBD in years	11.3 ± 10.1	8.8 ± 7.9
Smokers:Ex-smokers	9 (17):20 (38)	
HLA-B27 positivity	5 (10)	4 (13)
Prior surgical intervention for IBD	13 (25)	5 (17)
Previous extra-intestinal disease	6 (11)	5 (17)
Eritema nodosum	2	1
Uveitis	3	3
Pioderma gangrenosum	1	1
Crohn's disease activity by CDAI		
Inactive	14 (45)	7 (37)
Moderate	10 (32)	8 (42)
Moderate-to-Severe	7 (23)	4 (21)
Ulcerative colitis activity by partial Mayo		
Mild	18 (86)	8 (73)
Moderate	3 (14)	3 (27)
Severe	0	0
Current medication at baseline		
Non-steroids anti-inflammatory drugs	3	0
Sulfasalazine	3	2
Mesalazine	25	12
Cyclosporine	1	1
Azathioprine	9	5
Oral steroids	12	7
Topical steroids	3	2
Metotrexate	2	1
Infliximab	6	4
Adalimumab	2	0
Spondyloarthritis features		
Ankylosing spondylitis according to Modified New York Criteria	16 (31)	10 (33)
Non-radiographic Axial-Spondyloarthritis by ASAS Criteria	13 (25)	10 (33)
Peripheral- Spondyloarthritis	23 (44)	10 (33)
Type of axial involvement	<i>n</i> = 29	<i>n</i> = 20
Syndesmophytosis	8 (28)	6 (30)
Bamboo spine	2 (7)	2 (10)
Sacroiliitis by MRI and/or X-ray	29 (100)	20 (100)
Type of articular involvement in Crohn's disease	<i>n</i> = 31	<i>n</i> = 19
Axial	16 (52)	11 (58)
Axial and peripheral	4	3
Peripheral only	15 (48)	8 (42)
Enthesitis	9 (29)	5 (26)
Type of articular involvement in ulcerative colitis	<i>n</i> = 21	<i>n</i> = 11
Axial	13 (62)	9 (82)
Axial and peripheral	9	5
Peripheral only	8 (38)	2 (18)
Enthesitis	4 (19)	2 (18)

Data are presented as *n*, *n* (%) or mean ± SD. CDAI: Crohn's Disease Activity Index; ES-AN: Patient cohort with enteropathic spondyloarthritis from the SPIB Program, Ancona, Italy; ES-AN/Ada: Patients of the ES-AN cohort treated with adalimumab; IBD: Inflammatory bowel disease; NSAID: Non-steroidal anti-inflammatory drug.

Spondyloarthritis in IBD Project (commonly referred to as SPIB), described elsewhere^[9]. The patients' clinical and laboratory data are shown in Table 1, and the patient group is henceforth defined as the "ES-AN" cohort (Enteropathic spondyloarthritis from Ancona, Italy).

At each clinical observation, both the rheumatologist and the gastroenterologist collaborated in a shared session to develop the therapeutic strategy by applying a specifically designed algorithm (Figure 1) that was mainly based upon gastrointestinal-articular

disease activity and the site of articular involvement at diagnosis (axial or peripheral arthritis). Briefly, the ES-AN patients were primarily separated into the following two groups for comparative analysis:

Group I (biological drugs-naïve group): This group encompassed three treatment subgroups. In the axial-ES-AN (Ax-ES-AN) subgroup, patients were administered Ada as first-line therapy, due to the absolute contraindication for a long-course treatment with nonsteroidal anti-inflammatory drugs (NSAIDs)

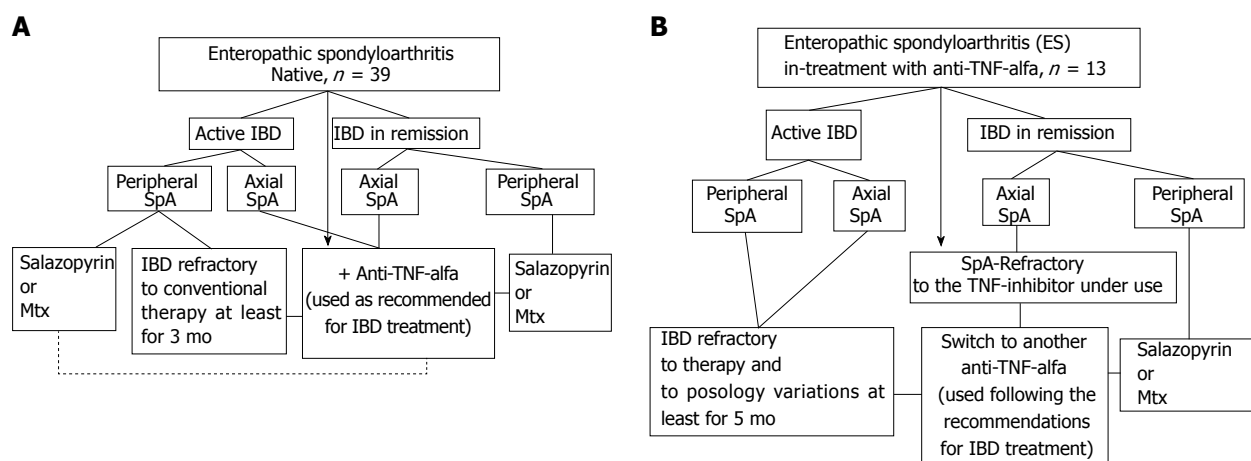


Figure 1 Therapeutic algorithm of the ES-AN patient cohort at the time of entry into the study. A: ES patients biological drugs-naïve were treated depending on IBD activity and site of the articular involvement, as follows: a) Ax-ES-AN with Ada as the TNF-inhibitor in first-line therapy, due to the absolute contraindication for a long-course treatment with NSAIDs in cases of IBDs; b) Per-ES-AN in cases of active IBD and in those patients who were non-responders to short-course corticosteroid treatment (not > 3 mo) or NSAIDs (not > 2 wk), with DMARD (methotrexate or sulfasalazine), or in cases of ESR > 30 mm/h and/or CRP > 0.5 mg/dL, and polyarticular inflammatory involvement with Ada; c) Per-ES-AN in inactive IBD, with steroids or DMARDs, depending on the number of inflamed joints and systemic inflammation (evaluated by ESR and/or CRP); B: ES patients already in treatment with infliximab for the IBD. In the ES-AN patients already treated with IFX: a) Per-ES-AN with active IBD were switched to Ada; b) Per-ES-AN with IBD in remission received a DMARD in addition to the IFX already in use; c) Ax-ES-AN were switched to Ada, regardless of IBD activity. Dashed line: Patients refractory to therapy. Therapeutic doses: DMARDs were prescribed at the standard dose regimens (salazopyrine 2 gr bid; methotrexate 10-20 mg once a week); Ada was used following the therapeutic dosage and indications for IBDs (160 mg at d 1 and 80 mg after 2 wk, followed by 40 mg every 2 wk). Ada: Adalimumab; AX-ES-AN: Patients with axial spondyloarthritis in the ES-AN cohort; CRP: C-reactive protein; ES: Enteropathic spondyloarthritis; ES-AN: Patients affected by ES in the Ancona's cohort; ESR: Erythrocyte sedimentation rate; DMARD: Disease modifying anti-rheumatic drug; IBD: Inflammatory bowel disease; NSAID: Non-steroidal anti-inflammatory drug; Per-ES-AN: Patients with peripheral spondyloarthritis in the ES-AN cohort.

in case of IBD. In the peripheral-ES-AN (Per-ES-AN) subgroup, patients with active IBD or who were non-responders to a short course of corticosteroids (not more than 3 mo) or NSAIDs (not more than 2 wk) were administered either a disease-modifying anti-rheumatic drug (DMARD), such as either methotrexate (MTX) or sulfasalazine (SSZ), or Ada if erythrocyte sedimentation rate (ESR) was > 30 mm/h and/or C-reactive protein (CRP) concentration was > 0.5 mg/dL and/or in the presence of polyarticular inflammatory involvement. In the Per-ES-AN in inactive IBDs subgroup, patients were administered steroids or DMARDs, depending on count number of inflamed joints and systemic inflammation (evaluated by ESR and/or CRP).

Group II (TNF inhibitor-treated group): This group also encompassed three treatment subgroups. For the first, the Per-ES-AN consisting of patients with still active IBD were switched to another TNF-inhibitor (Ada). For the second, the Per-ES-AN consisting of patients with IBD in remission were administered a DMARD in addition to the TNF-inhibitor already in use. For the third, the Ax-ES-AN patients were switched to Ada, regardless of IBD activity.

In all patients, the TNF-inhibitor Ada was used as recommended for IBD treatment: 160 mg in the first week, 80 mg for the next 2 wk, and thereafter 40 mg

once every 2 wk.

Study measures and evaluation

All patients of the ES-AN cohort were assessed for clinical disease activity and HRQoL (Table 2). Briefly, articular (SpA) disease activity was assessed by the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI)^[10] and the Ankylosing Spondylitis Disease Activity Score-C-Reactive Protein (ASDAS-CRP) calculation^[11]; gastrointestinal (IBD) disease activity was assessed with the Crohn's Disease Activity Index (CDAI) for CD^[12] and the partial Mayo (pMAYO) score for UC^[13].

Patient-reported outcomes (PROs) were assessed with tests specific for articular-related symptoms [i.e. the Bath Ankylosing Spondylitis Functional Index (BASFI)]^[14] and gastrointestinal-related symptoms [i.e. the Inflammatory Bowel Disease Questionnaire (IBDQ)]^[15]. Global wellness was assessed by use of the Health Assessment Questionnaire (HAQ), Patient Global Assessment (PtGA), and the Short Form-36 health survey (SF-36)^[16].

Statistical analysis

Endpoints of this study were the disease activity indexes at baseline and at 6-mo and 12-mo follow-ups. Variables are presented as mean ± standard deviation. Comparisons between groups at baseline

Table 2 Clinimetric test for articular-gastrointestinal activity and patient reported outcomes of health-related quality of life

Test	Items and interpretation
Bath Ankylosing Spondylitis Disease Index ^[10]	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-C-Reactive Protein ^[11]	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 = moderate 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 ^[12]	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 ^[13]	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 ^[14]	10 questions designed to determine the degree of functional limitation; Final score ranges from 0 to 10, with lower score indicating less functional limitation.
Inflammatory Bowel Disease Questionnaire ^[15]	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 ^[16]	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).

and between baseline and subsequent assessments were performed, respectively, with unpaired and paired Student's *t*-tests. Correlations between variables were assessed using Pearson's correlation coefficient. Data were analyzed using the SPSS software (v22.0; IBM SPSS Statistics for Windows, Armonk, NY, United States).

RESULTS

Baseline assessment of the patients

In the ES-AN cohort, 29 (57.6%) patients were affected by predominant axial SpA (Ax-ES-AN) and 23 (42.3%) by peripheral SpA (Per-ES-AN) (Table 1). Only 5 patients showed positivity for human leukocyte antigen-B27 (9.6%), including 4 affected by Ax-ES-AN and 1 by Per-ES-AN. Sacroiliitis was found in all the Ax-ES-AN patients, but 17 (55%) patients fulfilled the Modified New York Criteria for AS, whereas 13 (45%) were affected by non-radiographic axial-SpA^[2]. Syndesmophytosis was found in 8 (27.6%) of the Ax-ES-AN patients at different levels, but only 2 (6.9%) presented a bamboo spine radiologic feature at baseline. Concurrent peripheral arthritis and enthesitis were present in about half of the Ax-ES-AN patients (44.8%).

According to the established criteria, IBD was

active in 63.2% of the CD patients and in 98% of the UC patients, although the degrees of activity varied. At baseline, no differences were observed between the axial and peripheral spondyloarthritis patients and between the CD and UC patients for the articular disease activity (BASDAI, ASDAS-CRP) and the PROs [IBDQ, BASFI, PtGA, HAQ, SF-36 Physical Component Score (PCS) and Mental Component Score (MCS)] (data not shown). Following findings from the integrated evaluation and according to the algorithm presented in Figure 1, the criteria employed in our study to guide the therapeutic choice were (1) the presence and/or absence of active IBD (evaluated by both the gastroenterologist and by the results of the gastrointestinal tests and PROs); and (2) the site of articular involvement (axial or peripheral joints). Thus, Ada was assigned to a cohort of 30 patients, henceforth defined as the ES-AN/Ada cohort. Among this cohort, 4 were switched from infliximab for inefficacy, and the total was comprised of 20 patients with Ax-ES-AN and 10 patients with Per-ES-AN (Table 1).

Evaluation of articular and gastrointestinal disease activity

In most of the ES-AN/Ada patients, articular disease activity, as assessed by ASDAS-CRP and BASDAI, was significantly improved at 6-mo compared to baseline

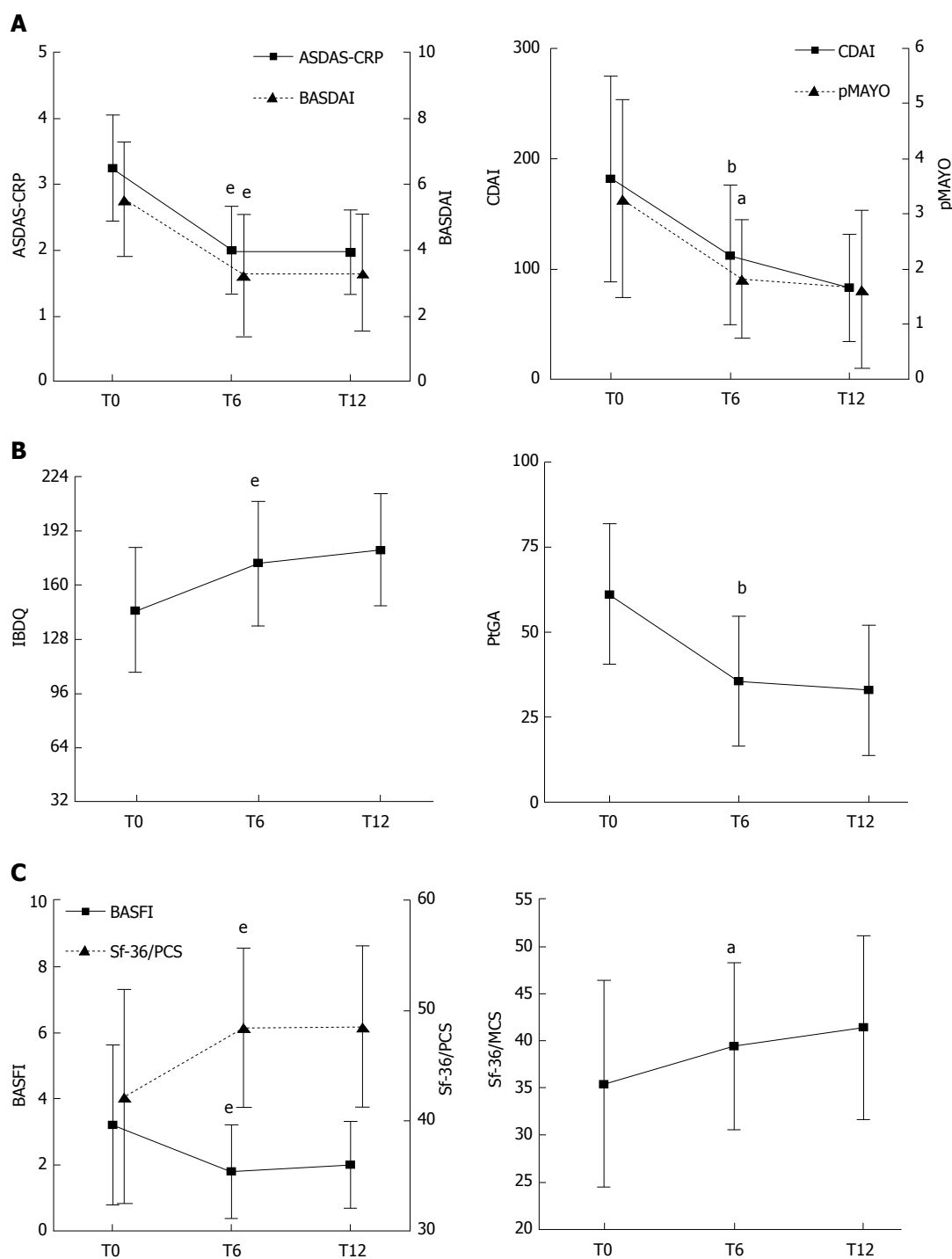


Figure 2 Evaluation of articular-gastrointestinal disease activity and HRQoL in the ES-AN patient cohort at baseline and after adalimumab therapy. All data of the ES-AN patients were collected at baseline (T0), and after 6 mo (T6) and 12 mo (T12) of therapy. A: Evaluation of the articular disease activity with BASDAI or ASDAS-CRP (Left), and of the gastrointestinal disease activity by CDAI for CD and pMAYO for UC (Right); B: Evaluation of PROs of gastrointestinal disease activity by IBDQ (Left), and of global wellness by the PtGA (Right). ^a $P < 0.05$, ^b $P < 0.01$, ^e $P < 0.001$. ASDAS-CRP: Ankylosing Spondylitis Disease Activity Score/C-Reactive Protein; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; CDAI: Crohn's Disease Activity Index; ES: Enteropathic spondyloarthritis; ES-AN: Patients affected by ES in the Ancona's cohort; HRQoL: Health-Related Quality of Life; IBDQ: Inflammatory Bowel Disease Questionnaire; pMAYO: Partial Mayo score; PROs: Patient reported outcomes.

(ASDAS-CRP: 3.2 ± 0.8 vs 1.9 ± 0.6 , $P < 0.001$; BASDAI: 5.5 ± 1.7 vs 3.2 ± 1.8 , $P < 0.001$). A major clinical improvement (ASDAS change of ≥ 2) occurred in 21% and an important clinical improvement (ASDAS change of ≥ 1.1) occurred in 52% (Figure 2A). The improvement of articular disease was significant in both

the axial and the peripheral subgroups of patients ($P < 0.001$ for both comparisons). The clinical improvement at the articular level was maintained at the 12-mo examination (Figure 2A).

Regarding the gastrointestinal disease activity, in the CD patients the treatment led to a fast, consistent

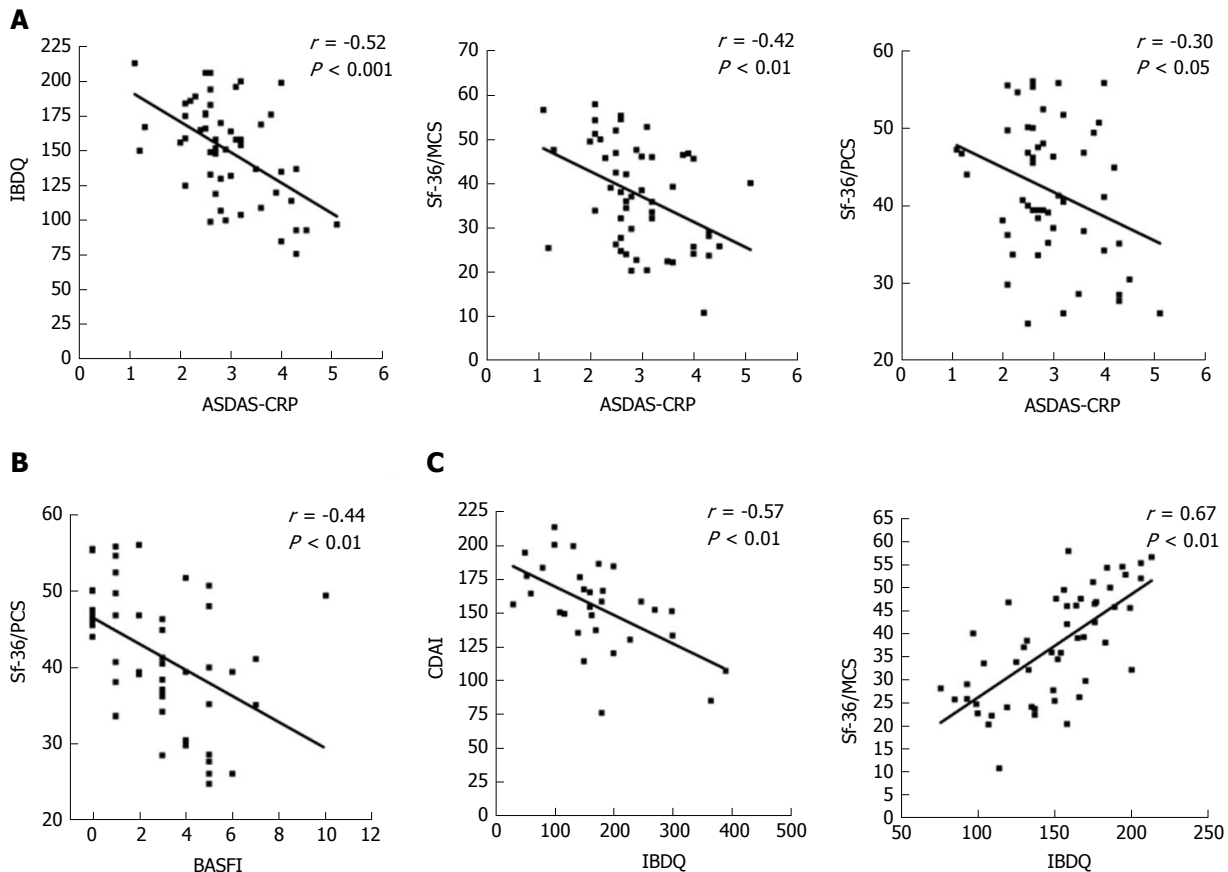


Figure 3 Correlations between articular and gastrointestinal disease activity and HRQoL scores in the ES-AN patient cohort at baseline. A: Correlation between the PROs of gastrointestinal disease activity (assessed by IBDQ) scores and SF-36 summary scores (assessed by PCS and MCS) with articular activity scores (assessed by ASDAS-CRP); B: Correlation of the articular function (assessed by BASFI with SF-36/PCS); C: Correlation of the IBDQ with crohn's disease gastrointestinal disease activity (assessed by CDAI) and the SF-36/MCS. ASDAS-CRP: Ankylosing Spondylitis Disease Activity Score-C-Reactive Protein; CDAI: Crohn's Disease Activity Index; ES: Enteropathic spondyloarthritis; ES-AN: Patients affected by ES in the ancona's cohort; HRQoL: Health-Related Quality of Life; IBDQ: Inflammatory Bowel Disease Questionnaire; PROs: Patient reported outcomes; SF-36/MCS: Summary of "Mental Component Score" of the Short Form-36 health survey; SF-36/PCS: Summary of "Physical Component Score" of the Short Form-36 health survey.

and significant improvement of the gastrointestinal symptoms at 6 mo, as assessed by the CDAI score (181.3 ± 93.2 vs 112.3 ± 63.0 , $P < 0.01$; Figure 2A), and maintained at 12 mo, when the clinical remission was observed in almost all patients (Figure 2A). In parallel, a significant clinical improvement was observed also in the UC patients, as shown by the decrease of the pMAYO score at the 6-mo and 12-mo examinations (Figure 2A). All the values and comparisons are detailed in Table 3.

Evaluation of the HRQoL

ES-AN/Ada patients reported significant improvement, from baseline to 6 mo, in the IBDQ (145.3 ± 36.8 vs 172.8 ± 36.7 , $P < 0.01$), PtGA (61.1 ± 20.6 vs 35.6 ± 19.1 , $P < 0.01$; Figure 2B) and HAQ (4.8 ± 7.9 vs 2.0 ± 4.2 , $P < 0.05$) scores, and this improvement was maintained at 12 mo. Moreover, regarding the PROs impacting articular function and global health wellness, significant improvements were observed from baseline to 6 mo in the BASFI (3.2 ± 2.4 vs 1.8 ± 1.4 , $P < 0.01$), SF-36/PCS (42.2 ± 9.7 vs 48.4 ± 7.3 , $P < 0.01$) and SF-36/MCS scores (35.4 ± 10.9 vs 39.4 ± 8.8 , $P < 0.05$;

Figure 2C); again, the improvements were maintained at 12 mo. The improvement of all the scores for PROs was similar in both the Ax-ES-AN/Ada and Per-ES-AN/Ada subgroups at each follow-up observation. All the values and comparisons are detailed in Table 3.

Correlations between variables

At baseline, it is noteworthy that a consistent significant correlation was observed between the IBDQ test (specific for the evaluation of the PROs related to the gastrointestinal disease activity) and the clinimetric scores of articular activity, as assessed by ASDAS-CRP (Figure 3A), BASDAI, and with most of the PROs of the HRQoL, as assessed by SF-36/MCS and CDAI (Table 4). Moreover, articular disease activity at baseline was significantly correlated with worse results in the HRQoL tests, as shown by the SF-36/PCS and SF-36/MCS scores (Table 4). After 12 mo of Ada treatment, improvement of the articular activity (ASDAS-CRP) correlated significantly with decrease in the gastrointestinal disease activity scores, as assessed by CDAI in the CD patients (Figure 4A) and IBDQ in all of the patients, and with most of the PROs of the HRQoL, as

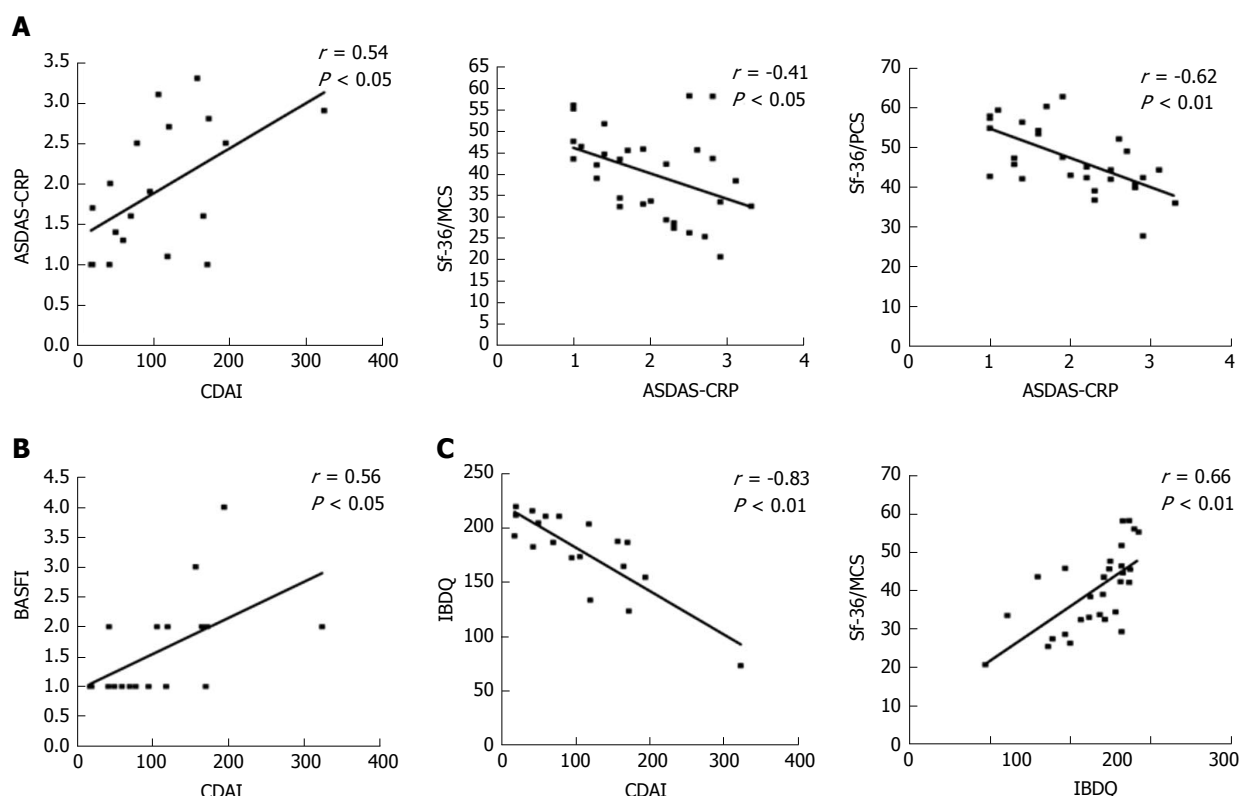


Figure 4 Correlations between articular and gastrointestinal disease activity and HRQoL scores in the ES-AN patient cohort after adalimumab therapy. A: Evaluation data collected for the 30 ES-AN/Ada patients after 12 mo of therapy, showing correlation between gastrointestinal and articular disease activity in Crohn's disease patients (assessed by CDAI) and ASDAS-CRP respectively, and between ASDAS-CRP and SF-36 summary scores (PCS and MCS); B: Correlation between CDAI and articular function (assessed by BASFI); C: Correlation between the gastrointestinal quality of life (assessed by IBDQ) and CDAI and SF-36/MCS. ASDAS-CRP: Ankylosing Spondylitis Disease Activity Score-C-Reactive Protein; CDAI: Crohn's Disease Activity Index; ES-AN: Patients affected by ES in the Ancona's cohort; ES-AN/Ada: Patients of the ES-AN cohort treated with adalimumab; HRQoL: Health-Related Quality of Life; IBDQ: Inflammatory Bowel Disease Questionnaire; SF-36/MCS: Summary of "Mental Component Score" of the Short Form-36 health survey; SF-36/PCS: Summary of "Physical Component Score" of the short form-36 health survey; PROs: Patient reported outcomes.

Table 3 Scores of the clinimetric test for articular-gastrointestinal activity and patient reported outcomes of health-related quality of life

	Baseline	T6	T12
CDAI, <i>n</i> = 19	181.3 ± 93.2	112.3 ± 63.0 ^b	82.7 ± 48.7 ^b
pMAYO, <i>n</i> = 11	3.27 ± 1.79	1.81 ± 1.07 ^a	1.63 ± 1.43 ^a
IBDQ	145.3 ± 36.8	172.8 ± 36.7 ^e	180.7 ± 33.0 ^e
BASDAI	5.5 ± 1.7	3.2 ± 1.8 ^e	3.3 ± 1.7 ^e
BASFI	3.2 ± 2.4	1.8 ± 1.4 ^e	2.0 ± 1.3 ^a
ASDAS-CRP	3.2 ± 0.8	1.9 ± 0.6 ^e	1.9 ± 0.6 ^e
PtGA	61.1 ± 20.6	35.6 ± 19.1 ^b	33.0 ± 19.1 ^b
HAQ	4.7 ± 8.5	2.0 ± 4.2 ^a	1.6 ± 3.5 ^a
Sf-36/PCS	42.2 ± 9.7	48.4 ± 7.2 ^e	48.5 ± 7.3 ^b
Sf-36/MCS	35.4 ± 10.9	39.4 ± 8.8 ^a	41.4 ± 9.7 ^a
CRP in mg/dL	2.7 ± 3.7	0.8 ± 1.2 ^a	0.5 ± 0.6 ^a

^a*P* < 0.05, ^b*P* < 0.01, ^c*P* < 0.001. ASDAS-CRP: Ankylosing Spondylitis Disease Activity Score-C-Reactive Protein; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; BASFI: Bath Ankylosing Spondylitis Functional Index; CDAI: Crohn's Disease Activity Index; CRP: C-Reactive Protein; pMAYO: partial Mayo score; HAQ: Health Assessment Questionnaire; IBDQ: Inflammatory Bowel Disease Questionnaire; PtGA: Patient Global Assessment; SF-36/MCS: Summary of "Mental Component Score" of the Short Form-36 health survey; SF-36/PCS: Summary of "Physical Component Score" of the Short Form-36 health survey; T6 and T12: Results of the evaluation after 6 mo and 12 mo of treatment with adalimumab respectively.

shown by the Sf-36/PCS (*r* = -0.30, *P* < 0.05) and Sf-36/MCS (*r* = -0.41, *P* < 0.01) scores (Figure 2C), as well as the BASFI (*r* = 0.57, *P* < 0.001), PtGA (*r* = 0.37, *P* < 0.01) and HAQ (*r* = 0.28, *P* < 0.05) scores. All the correlations for the values at 12-mo examination are detailed in Table 4.

Tolerability

Ada was well tolerated throughout the follow-up period. Side effects reported included recurrent upper respiratory tract infections (*n* = 2), bothersome hair loss (*n* = 1), and widespread itch (*n* = 2); but none necessitated suspension of the treatment. One patient suffered from a serious infection (axillary suppurative hidradenitis) that required prolonged antibiotic treatment. The other minor side effects reported were headache and fatigue.

DISCUSSION

The association between SpAs and IBDs has been known since the beginning of the last century^[17]. However, gastroenterologists and rheumatologists continue to carry out their clinical evaluations and

Table 4 Correlations between the scores of clinimetric tests for articular-gastrointestinal activity and patient reported outcomes of health-related quality of life scores

	CDAI	pMAYO	IBDQ	BASDAI	BASFI	ASDAS-CRP	PtGA	HAQ	Sf-36/PCS	Sf-36/MCS	CRP
At baseline											
CDAI	1	1	-0.57 ^b	0.19	0.29	0.21	0.14	0.12	-0.24	-0.33	0.35
pMAYO	1	1	-0.48 ^a	0.34	0.38	0.37	0.15	0.18	-0.14	-0.11	0.28
IBDQ	-0.57 ^b	-0.48 ^a	1	-0.38 ^b	-0.34 ^a	-0.52 ^b	-0.26	-0.19	0.27	0.67 ^b	-0.26
BASDAI	0.19	0.34	-0.38 ^b	1	0.64 ^b	0.69 ^b	0.24	0.26	-0.22	-0.31 ^a	0.00
BASFI	0.29	0.38	-0.34 ^a	0.64 ^b	1	0.57 ^b	0.37 ^b	0.36 ^b	-0.44 ^b	-0.15	0.37 ^b
ASDAS-CRP	0.21	0.37	-0.52 ^b	0.69 ^b	0.57 ^b	1	0.37 ^b	0.36 ^b	-0.30 ^a	-0.41 ^b	0.32 ^a
PtGA	0.14	0.15	-0.26	0.24	0.37 ^b	0.37 ^b	1	0.22	-0.14	-0.22	0.14
HAQ	0.12	0.18	-0.19	0.26	0.36 ^b	0.36 ^b	0.22	1	-0.46 ^b	-0.03	0.07
Sf-36/PCS	-0.24	-0.14	0.27	-0.22	-0.44 ^e	-0.30 ^a	-0.14	-0.46 ^b	1	0.05	-0.13
Sf-36/MCS	-0.33	-0.11	0.67 ^b	-0.31 ^a	-0.15	-0.41 ^b	-0.22	-0.03	0.05	1	-0.08
After 12 mo of therapy with adalimumab (ES-AN/Ada cohort)											
CDAI	1	1	-0.83 ^b	0.16	0.56 ^a	0.54 ^a	0.53 ^a	0.53 ^a	-0.71 ^b	-0.67 ^b	0.75 ^b
pMAYO	1	1	-0.51	0.18	0.49	0.17	0.56	-0.29	-0.14	-0.25	0.6
IBDQ	-0.83 ^b	-0.51	1	-0.23	-0.56 ^b	-0.55 ^b	-0.61 ^b	-0.36 ^a	0.53 ^b	0.66 ^b	-0.52 ^b
BASDAI	0.16	0.18	-0.23	1	0.58 ^b	0.68 ^b	0.51 ^b	0.39 ^a	-0.52 ^b	-0.11	-0.14
BASFI	0.56 ^a	0.49	-0.56 ^b	0.58 ^b	1	0.56 ^b	0.64 ^b	0.54 ^b	-0.52 ^b	-0.45 ^a	0.16
ASDAS-CRP	0.54 ^a	0.17	-0.55 ^b	0.68 ^b	0.56 ^b	1	0.67 ^b	0.38 ^a	-0.62 ^b	-0.41 ^a	0.31
PtGA	0.53 ^a	0.56	-0.61 ^b	0.51 ^b	0.64 ^b	0.67 ^b	1	0.51 ^b	-0.37 ^a	-0.59 ^b	0.26
HAQ	0.53 ^a	-0.29	-0.36 ^a	0.39 ^a	0.54 ^b	0.38 ^a	0.51 ^b	1	-0.47 ^b	-0.40 ^a	0.10
Sf-36/PCS	1	1	-0.83 ^b	0.16	0.56 ^a	0.54 ^a	0.53 ^a	0.53 ^a	-0.71 ^b	-0.67 ^b	0.75 ^b
Sf-36/MCS	1	1	-0.51	0.18	0.49	0.17	0.56	-0.29	-0.14	-0.25	0.60
CRP	-0.83 ^b	-0.51	1	-0.23	-0.56 ^b	-0.55 ^b	-0.61 ^b	-0.36 ^a	0.53 ^b	0.66 ^b	-0.52 ^b

Correlations between variables were assessed in the 30 patients with enteropathic spondyloarthritis from Ancona, Italy, at baseline and after 6 mo (data not shown) and 12 mo of therapy with adalimumab (ES-AN/Ada), using Pearson's correlation coefficient; ^a $P < 0.05$, ^b $P < 0.01$. ASDAS-CRP: Ankylosing Spondylitis Disease Activity Score-C-Reactive Protein; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; BASFI: Bath Ankylosing Spondylitis Functional Index; CDAI: Crohn's Disease Activity Index; CRP: C-Reactive Protein; HAQ: Health Assessment Questionnaire; IBDQ: Inflammatory Bowel Disease Questionnaire; pMAYO: partial Mayo score; PtGA: Patient Global Assessment; SF-36/MCS: Summary of "Mental Component Score" of the Short Form-36 health survey; SF-36/PCS: Summary of "Physical Component Score" of the Short Form-36 health survey.

the therapeutic management of these diseases, now known collectively as ES, independently. In this regard, the different clinical guidelines employed by the two medical specialists may lead to different therapeutic decisions for the same clinical scenario, ultimately harboring potential for different clinical outcomes of the disease. A critical issue in the clinical management of ES is the correct therapeutic choice, and an important role has emerged recently for the TNF- α inhibitors in this regard. Infliximab was the first TNF- α inhibitor used in ES^[18], but Ada has recently been applied to ES patients affected by CD and has achieved rates of clinical remission up to 50%^[19].

To our knowledge, this is the first study demonstrating the efficacy of the integrated gastroenterologic approach for evaluation and therapeutic management of ES patients, with efficacy evidenced through assessments of disease activity and HRQoL over a 12-mo period. As dictated by our operative algorithm, both the gastroenterologist and the rheumatologist evaluated each of the patients in the study cohort, with both of the specialists collaborating to choose the optimal therapy. This integrated multidisciplinary approach, therefore, considered the gastrointestinal and articular disease activities simultaneously and, most importantly in the latter case, the site of articular inflammation (axial or peripheral). Thus, for example, in the case of axial spondyloarthritis, the therapy with

anti-TNF- α inhibitors was mandatory, following the latest rheumatologic indications^[20].

Since only few studies in the literature have so far evaluated the efficacy and safety of anti-TNF- α in ES, we employed the up and coming Ada treatment in our study. The results indicated that in ES patients, regardless of IBD type and/or site of articular involvement, Ada significantly improves the inflammation states of both the joints (assessed by ASDAS-CRP and BASDAI) and gut (assessed by CDAI or pMAYO score), as well as the HRQoL. Moreover, the benefits were already observable at 6 mo and the improvements were maintained at 12 mo. Ada also consistently improved not only the physical function in almost all ES patients (assessed by PtGA, BASFI, HAQ and Sf-36/PCS) but also their psychological function (assessed by Sf-36/MCS and IBDQ), from baseline to 6 mo.

It is noteworthy that in our study the strong linear relationship between articular-gastrointestinal disease activity and the PROs confirms the strong link between gut and joint inflammations. In fact, the IBDQ (specific for the gastrointestinal-related quality of life) strongly correlated with results of the clinimetric tests of articular activity (ASDAS-CRP, BASDAI and BASFI); additionally, the articular disease activity (assessed by ASDAS-CRP) strongly correlated with all of the PROs studied, even those specific for IBDs. To

the contrary, however, at baseline the gastrointestinal disease activity scores (except for those of the IBDQ) did not correlate well with the other variables, but at 12 mo of therapy the CDAI correlated with most of the articular and PROs of HRQoL. This latter finding may be consequent to the different degrees of disease activities reported by the patients at baseline, which, after the treatment, tend to be globally ameliorated both at the gastrointestinal and articular levels.

Thus, since only the ASDAS-CRP test proved to be the most reliable in all patients in our study, we think that it should be necessary to develop composite scores and HRQoL questionnaires specific and suitable for ES patients at diagnosis, similar to those developed for other multidisciplinary diseases, such as psoriatic arthritis^[21]. In conclusion, in our work that was carried out in a real-life cohort of a significant number of ES patients, we demonstrated that Ada produced a fast and significant improvement of both the gastrointestinal and articular scores of disease activity and, moreover, of the HRQoL. This clinical result was achieved by employing an integrated outpatient clinic specific for ES patients, as recently endorsed, particularly with regard to early diagnosis^[22,23]. The integrated approach provided the optimal management of both the multidisciplinary clinical evaluation and the therapy of these patients. Further studies are certainly warranted to assess the long-term outcomes, and tolerability, of Ada and other TNF-alpha inhibitors in patients affected by ES.

COMMENTS

Background

Enteropathic spondyloarthritis (ES) is characterized by articular inflammation in patients with inflammatory bowel diseases (IBDs), such as Crohn's disease or ulcerative colitis. Arthritis is the most frequent extra-intestinal manifestation found in IBD patients, yet only half of the ES patients are actually evaluated by a rheumatologist for a proper diagnosis and, thereafter, for receipt of an integrated therapeutic approach through a coordinated action between the two specialists.

Research frontiers

Considering the multidisciplinary intrinsic "face" of IBDs and the novel therapeutic opportunities that comprise the biological drugs, as in the case of anti-tumor necrosis factor (TNF)-alpha inhibitors, an integrated approach and evaluation of all ES patients should be routinely employed and strongly encouraged to obtain the best therapeutic efficacy on all the clinical manifestations of this disease.

Innovations and breakthroughs

In this work, the authors have demonstrated that the integrated (simultaneous) evaluation of patients affected by ES, through the coordinated efforts of a gastroenterologist and rheumatologist, led to the best therapeutic approach, thereby allowing the patients to achieve a consistent clinical remission of both the articular and gastrointestinal inflammations.

Applications

Through this study authors have been able to generate a simple working flowchart of the multidisciplinary clinical care process applied during the patients' integrated assessment. They suggest that in patients with ES and in consideration of the therapeutic choice, particular attention should be

paid to the presence of active intestinal disease, presence of active articular (arthritis) and/or periarticular (enthesitis) disease and localization of the joints' inflammation (peripheral or axial, as in the case of sacroiliitis).

Terminology

ES belongs to the group of seronegative spondyloarthritis (SpA) and, as such, is characterized by the presence of arthritis in patients affected by IBDs; it is also known as SpA-IBD.

Peer-review

This is an interesting and well-conducted work.

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