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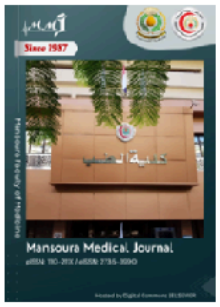

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Assessment of response of Enteropathic Spondyloarthritis to different types of biological therapy; an Egyptian single center study

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ORIGINAL STUDY

Assessment of Response of Enteropathic Spondyloarthritis to Different Types of Biological Therapy: An Egyptian Single-center Study

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Abstract

Introduction: **Arthropathy is one of the most prevalent extraintestinal symptoms of inflammatory bowel disease (IBD). It may be either peripheral or axial spondyloarthropathy. Biological treatments such as anti-tumor necrosis factor alpha (TNFα) or anti-interleukin 12/23 have shown efficacy in controlling gut inflammation and reducing joint manifestation. Our aim of the study was to assess the different aspects of response (laboratory, endoscopically, and radiologically) of axial arthropathy associated with IBD patients after receiving biological drugs, including anti-TNF (infliximab and adalimumab) and anti-interleukin 12/23 (ustekinumab).**

Patients and methods: **A single-center observational study was conducted over 1 year duration from June 2022 to June 2023. Out of 650 patients with IBD, who attended the IBD Clinic at Mansoura Specialized Medical Hospital, 122 patients had arthritis as one of the extraintestinal manifestations of IBD. A group of 25 patients with enteropathic axial arthropathy were selected according to inclusion criteria, and their data were analyzed.**

Results: **The prevalence of arthritis in IBD represents 18.8%. Axial arthropathy prevalence among IBD cases was 3.38%, and among IBD patients with arthritis was 18%. While ankylosing spondylitis prevalence was 0.46% among IBD cases and 2.45% among IBD cases with arthritis. Fourteen (56%) patients started biological treatment, while the rest were on conventional therapy. We found significant improvement as regards hemoglobin, serum albumin, C-reactive protein, and fecal calprotectin under biological treatment ($P<0.05$). There was significant improvement in terms of endoscopic score (Mayo for ulcerative colitis $P = 0.006$ and Crohn's disease activity index for Crohn's disease $P = 0.034$) prebiological and postbiological. There was a significant decline as regards the grade of inflammation at the axial sacroiliac joint by MRI after receiving biological treatment ($P = 0.0001$).**

Conclusion: **Biological therapy should be considered early in axial arthropathy associated with IBD. Anti-TNF should be considered as the first line of therapy in these cases.**

Keywords: Axial arthropathy, Biological treatment, Inflammatory bowel disease

1. Introduction

Inflammatory bowel disease (IBD) is an idiopathic autoimmune disease. It includes Crohn's disease (CD) and ulcerative colitis (UC) and is characterized by recurrent episodes of intestinal inflammation (Federici et al., 2022). It is believed that IBD is caused by an abnormal and ongoing immune response to gut microbiota, which is triggered by an individual's genetic susceptibility. IBD is a complicated combination of immune responses and genetic, environmental, or microbial factors, even though its exact cause is still unknown (Zhang and Li, 2014).

One of the extraintestinal manifestations of IBD is joint affection. Forty percent of patients diagnosed with IBD may experience joint symptoms affecting both the axial and peripheral joints. One kind of seronegative spondyloarthropathy (SpA) is thought to be IBD-associated arthropathy. Dominant axial symptoms of axial spondyloarthritis include morning stiffness of the spine and back pain. Conversely,

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upper and lower limb symptoms are present in peripheral arthritis (Vavricka et al., 2011).

The correlations observed between SpA and IBD suggest a shared inflammatory pathway. Shared loci linked to the chance of developing both SpA and IBD have been found through genome-wide association studies. These loci include association signals in or close to the interleukin (IL12/23) gene pathway (Parkes et al., 2013; Gracey et al., 2019). Sacroiliitis and ankylosing spondylitis are associated with NOD2/CARD15 and IL23R (Rogler et al., 2021). Ankylosing spondylitis and IBD have the strongest genetic correlations (Hedin et al., 2019).

The recent shift in the therapeutic goal for IBD has been from symptom control to achieving clinical remission and endoscopic mucosal healing in order to prevent disease progression, damage to axial and peripheral joints, and disability (Talley et al., 2011). Biotechnology is used to produce biological drugs in living organisms. The only thing that unites the medications is their manufacturing process; neither a shared mechanism of action nor a shared target organ does. Monoclonal antibodies or antibody fragments that bind to immunological mediators and receptors are the primary ingredients in biological drugs (Cote-Daigneault et al., 2015).

Anti-tumor necrosis factor alpha (TNFα), particularly infliximab and adalimumab, have demonstrated efficacy in treating extraintestinal manifestations, such as axial or peripheral arthropathy, as well as intestinal inflammation (de Vos et al., 2000). Anti-IL12/23 (ustekinumab) has also demonstrated effectiveness in controlling gut inflammation and joint manifestation (Sandborn et al., 2008) and may be particularly beneficial in patients who are not responding well to infliximab (Louis et al., 2012). However, when it comes to managing axial SpA in IBD, no randomized controlled trial has assessed the effectiveness of any of the biologics (Gordon et al., 2024). Furthermore, there is currently a deficiency in the literature comparing the ways in which patients with enteropathic arthropathy respond to various biological drug modalities.

Our aim of the study was to assess the different aspects of response (clinically, laboratory, endoscopically, and radiologically) of axial arthropathy associated with IBD patients after receiving biological drugs including: anti-TNF (infliximab and adalimumab) and anti-IL12/23 (ustekinumab).

Abbreviations

5′ASA	5 aminosalicylates
ASAS	the Assessment of SpondyloArthritis Society
AZA	azathioprine
CD	Crohn's disease
CDAI	Crohn's disease activity index
CRP	C-reactive protein
FC	fecal calprotectin
IBD	inflammatory bowel disease
IL12/23	interleukin 12/23
SpA	spondyloarthropathy
TNF	tumor necrosis factor
UC	ulcerative colitis

2. Patients and methods

A single-center observational study was conducted over 1 year duration from June 2022 to June 2023. Out of 650 patients with IBD, who visited the IBD Clinic at Mansoura Specialized Medical Hospital, 122 patients had arthritis as one of the extraintestinal manifestations of IBD. A group of 25 patients with enteropathic axial arthropathy were selected according to inclusion criteria, and their data were analyzed.

Enteropathic arthropathy case is defined as a type of seronegative SpA that coexists with IBD, either CD or UC. IBD-related arthritis can be of two types: either axial with characteristic sacroiliitis and/or spondylitis or peripheral (type I; pauciarticular and type II; polyarticular) arthritis (Peluso et al., 2013).

Patients included were diagnosed as UC or CD, aged more than 18 years old, and developed axial with/without peripheral arthritis. Patients should be fit for endoscopy and maybe treated naive or on conventional treatment in the form of 5 aminosalicylates (5′ASA) (oral or topical), azathioprine (AZA), and corticosteroids. Patients who fulfilled "the new Assessment of SpondyloArthritis Society (ASAS) classification criteria for axial SpA" where an MRI clearly shows sacroiliac inflammation as sufficient proof of sacroiliitis were chosen (Rudwaleit et al., 2009).

Assessment of spondylarthritis International Society Classification Criteria for axial spondylarthritis (SpA) (Rudwaleit et al., 2009)

In patients with back pain more than 3 months and age at onset <45 years
Sacroiliitis by imaging* HLA-B27
Plus
>1SpA features** >2 other SpA features

*Sacroiliitis by imaging: Acute and active inflammation on MRI strongly suggests the presence of SpA associated with sacroiliitis. Defined by the modified New York criteria as definitive radiographic sacroiliitis.

**SpA features: Inflammatory back pain, arthritis, enthesitis [heel], uveitis, dactylitis, psoriasis, IBD, showing response to NSAIDs, with family history of SpA, HLA-B27, or elevated C-reactive protein.

We excluded any patient who was unable/refused to undergo endoscopy or incapable of providing informed consent. Patients with malignant conditions like colorectal cancer, surgical local causes of bleeding per rectum (piles, fissures, sinuses, etc.), or other associated autoimmune diseases, for example, reactive arthropathy, were also excluded. Any patient with no evidence of sacroiliitis, spondylitis, or synovitis on imaging was not enrolled.

All patients were subjected – after thorough history – to a full examination of any affected joints for evidence of synovitis or enthesitis. Tests of pelvic compression, Gaenslen's test, and Patrick's test were done for sacroiliitis. Occiput-to-wall test, chest expansion, and modified Schober test were done for spondylitis (Buchanan et al., 2021).

Laboratory investigations were done before biological treatment, especially complete blood count (CBC), using an automated hematology analyzer Cell - dyn 1700, Abbott, USA. Hemoglobin (g/dl), white blood cell count (10^3/cmm), platelet count (10^3/cmm), C-reactive protein (CRP) by Cobas C311m, Roche, Germany, fecal calprotectin (FC): through stool sample using enzyme-linked immunosorbent assays, then measured as mcg/g (<50 was considered normal, between 100 and 250 is in definitive, and >250 IBD is a likely diagnosis). Liver function tests: by auto-analyzer Roche Cobas Integra-800, Germany including serum albumin (g/dl), serum total, direct and indirect bilirubin (mg/dl), aspartate aminotransferase (U/l), alanine aminotransferase (U/l). Virology markers including HIV, HBV surface Ag, and HCV testing by enzyme-linked immunosorbent assays. Tuberculin test was done to exclude tuberculosis. CBC, liver function tests, CRP, and FC were repeated after biological treatment (after 4–6 months).

Sigmoidoscopy and/or ileo-colonoscopy were performed at the endoscopy unit of Mansoura University Hospital by colonoscopy (type Pentax PK 100 video scope, Japan). Preparation before colonoscopy was done by 2–4 l of hypertonic polyethylene glycol 24 h. Propofol intravenously was used for sedation at the patient's request.

It was repeated before shifting the biologic treatment or within 4–6 months of starting biologic. Four biopsies were taken – for diagnosis – from the area where any lesion was suspected (ulcer, pseudo polyp, or stricture). Biopsies were fixed in 10% formalin solution and embedded in paraffin for subsequent analyses. Then, they were stained with hematoxylin and eosin. A pathologist examined all biopsies.

Additionally, imaging of axial arthritis by plain radiography for detection of structural changes and/or MRI for detecting active inflammation in the spine and sacroiliac joints.

IBD activity scores were measured. Mayo score for assessment of UC (Schroeder et al., 1987) and Crohn's disease activity index (CDAI) for CD (Best, 2006). Mayo score of more than or equal to 1 and CDAI more than or equal to 150 mean active disease in patients. Conversely, Mayo less than 1 and CDAI less than 150 indicate inactive disease.

Types of biological drugs used:

(1) Anti-TNF (infliximab, adalimumab) is highly effective for IBD patients who are steroid-dependent or resistant to traditional therapy.
(2) Ustikenumab is clinically effective in treating IBD gut inflammation, it is a fully human monoclonal immunoglobulin (IgG1) against the IL12/23 shared P40 subunit may be especially helpful for patients who are not responding well to infliximab.
   (a) Clinical response was defined through the change in IBD clinical score from active to be in remission.
   (b) Laboratory response was shown in terms of improvement in CBC, CRP, and FC.
   (c) The endoscopic response was detected in terms of improvement of the picture of ulceration and extension of IBD by endoscopy.
   (d) Radiologic response was reported in terms of any improvement of inflammation or decrease of edema of affected joints by MRI.
   (e) Short-term response: when a patient shows a response within 12–16 weeks.
   (f) Long-term response: when the patient showed a response within 6 months.

After educating them about the study's procedures, the patients or their family members who were taking part provided written informed consent. The Faculty of Medicine's Ethical Committee gave its approval to the study, Mansoura University code (R.21.11.1529).

The computer was fed by data, and IBM SPSS software package, version 25.0 Armonk, NY, USA. IBM Corp. was used for analysis. Utilizing percentages and numbers, the qualitative data was described. The Kolmogrov–Smirnov test was used to verify the normality of the quantitative data before describing it using the mean and SD for parametric variables and the median (minimum and maximum) for nonparametric variables. The significance of the results obtained was assessed at the 5% level. All tests were 2-tailed. The Student *t* test was

Table 1. Sociodemographic characters of the selected cases of axial spondyloarthropathy associated with inflammatory bowel disease (N = 25).

Variables	Cases (percent)
Sex	
Male	11 (44)
Female	14 (56)
Smoking	
EX-smoker	1 (4)
Current	3 (12)
Never	21 (84)
Diabetes mellitus	2 (8)
Hypertension	2 (8)
	Mean ± SD
	Minimum–maximum
Age in years	37.6 ± 10.9
	27–50
Height in cm	165 ± 10.5
	150–178
Weight in kg	70.1 ± 15.2
	50–96
BMI	27.8 ± 5.6
	17–35

used to compare continuous data, and the χ^2 test was used for the comparison of categorical data. Wilcoxon test was used to compare two groups of nonparametric data. Correlations between variables were done by the Spearman correlation coefficient. P values of less than 0.05 were reflected as statistically significant. To determine the sample size, we assumed a confidence level of 80%, a margin error of 5%, and a z score of 1.28.

Table 2. Number of cases in relation to different lines of treatment.

	Axial arthropathy + peripheral artheritis	Ankylosing spondylitis	Total
Conventional treatment	10	1	11
Anti-TNF	10	2	12
Anti-TNF and anti-IL12/23	2	0	2
Total	22	3	25

IL, interleukin; TNF, tumor necrosis factor.

3. Results

Fourteen (56%) patients were females. Twenty-one (84%) patients were nonsmokers. The mean ± SD age 37.6 ± 10.9 years, BMI was 27.8 ± 5.6. Their mean height 165 ± 5.5 cm and weight 70.1 ± 15.2 kg.

Seventeen patients were diagnosed with UC, while eight patients were diagnosed with CD. Extension of inflammation in UC patients was reported as seven patients had proctosigmoiditis, five had left-sided colitis, and five had pancolitis. Fifteen patients were Mayo 2–3 by the endoscopic score of activity before starting biologics. The phenotype of CD patients was four patients with inflammation at the terminal ileum; two patients had ileal stricture and another two had fistulizing CD. Seven patients were with CDAI more than 150.

Table 2 shows 11 (44%) patients received conventional therapy in the form of 5-ASA, AZA, and small dose steroid 5–10 mg. Fourteen (56%) patients received biological treatment. Twelve patients stared anti-TNF, and two patients shifted between anti-TNF to anti-IL12/23.

Eleven patients received anti-TNF treatment and shifted within the same class from infliximab to adalimumab, two patients shifted from anti-TNF to anti-IL12/23 (ustekinumab), last patient had a double shift (within anti-TNF class and then to anti-IL12/23).

Table 3 shows significant improvement in patients as regard hemoglobin, serum albumin, CRP, and FC before and after biological treatment (P<0.05).

There was a significant improvement in terms of endoscopic score (Mayo for UC by $P = 0.006$ and CDAI for CD by $P = 0.034$) before and after

Table 3. Relation of different laboratory variables between cases (N = 14) prebiological and postbiological treatment.

Variables	Prebiological (mean ± SD)	Postbiological (mean ± SD)	P value (paired t test)
Hb (g/dl)	9.2 ± 1.9	11.1 ± 1.2	0.04[a]
Platelets 10^3/cmm	350 ± 83.3	277 ± 91.1	0.31
Albumin (g/dl)	2.5 ± 0.8	3.5 ± 0.6	0.04[a]
Bilirubin (mg/dl)	0.9 ± 0.4	0.8 ± 0.3	0.78
	Prebiological [median (minimum–maximum)	Postbiological [median (minimum–maximum)	P value (Wilcoxon test)
WBCs 10^3/cmm	9 (4–14)	7 (3–8)	0.72
AST (U/l)	55 (33–68)	34 (23–50)	0.25
ALT (U/l)	50 (30–59)	31 (20–60)	0.06
CRP	34 (20–160)	2 (0–8)	0.02[a]
FC (mg/kg)	450 (300–1220)	250 (150–1000)	0.05[a]

ALT, alanine aminotransferase; AST, aspartate aminotransferase; CRP, C-reactive protein; FC, fecal calprotectin; Hb, hemoglobin; WBC, white blood cells.

[a] Statistically significant.

Table 4. Relation of the endoscopic score and radiological axial MRI between cases (N = 14) prebiological and postbiological treatment.

	Prebiological	Postbiological	P value
Endoscopic Mayo score of UC (N = 9) [median (IQR)]	3 (2–3)	1 (0–2)	Z = −2.724 P = 0.006[a]
Endoscopic CDAI score of CD (N = 5) [median (IQR)]	350 (150–400)	250 (150–300)	Z = −2.121 P = 0.034[a]
MRI on axial joints (N = 14) [median (IQR)]	3 (2–4)	0 (0–1)	Z = −3.494 P 0 .0001[a]

CD, Crohn's disease; CDAI, Crohn's disease activity index; IQR, interquartile range; UC, ulcerative colitis; Z, Wilcoxon signed ranks test.
[a] Statistically significant.

biological treatment (Table 4). There was also a significant decline in the grade of inflammation at the axial sacroiliac joint by MRI after receiving biological treatment ($P = 0.0001$).

4. Discussion

IBD, can present with various extraintestinal symptoms. Arthropathy is among the most typical symptoms. Peripheral and axial SpA are two examples of arthropathy's clinical symptoms. The onset of symptoms may precede or follow an IBD diagnosis (Fragoulis et al., 2019; Proft and Poddubnyy, 2018). Based on clinical presentation, the ASAS criteria differentiate between axial and peripheral spondyloarthritis. It acknowledges the notable occurrence of IBD in SpA, with a reported 4–14% lifetime risk for IBD. ASAS now lists IBD as a classification criterion (Rudwaleit et al., 2009; Stolwijk et al., 2015; de Winter et al., 2016). Axial involvement is seen more commonly in patients with CD than in UC and is more often associated with HLA-B 27 (Gionchetti et al., 2015).

Out of 650 patients with IBD, who visited the IBD Clinic at Mansoura Specialized Medical Hospital through 1 year duration from June 2022 to June 2023, 122 patients had arthritis as one of the extra-intestinal manifestations of IBD. It was found that the prevalence of arthritis in IBD reached 18.8%. A group of 25 patients with enteropathic axial arthropathy were selected according to inclusion criteria, and their data were analyzed. Axial arthropathy was documented in 22 patients, making its prevalence among IBD cases (3.38%) and among patients with arthritis as extraintestinal manifestation (18%). While there were three patients diagnosed with ankylosing spondylitis with prevalence among IBD cases (0.46%) and among patients with arthritis as extraintestinal manifestation (2.45%). Both axial arthropathy and ankylosing spondylitis are collectively known as axial SpA.

The most frequent symptom of SpA in IBD, according to a systematic review, was peripheral arthritis, representing 13%, which was followed by sacroiliitis of 10% and ankylosing spondylitis at about 3% (Karreman et al., 2017). A pooled prevalence of 21% was found in another systematic review addressing radiological diagnoses of sacroiliitis in IBD (Evans et al., 2021).

In a Norwegian cohort of IBD patients (Ossum et al., 2020), 36% fulfilled the ASAS criteria specific for SpA, of whom 8% were diagnosed with axial SpA and 28% were diagnosed with peripheral SpA. This wide variation might be attributed to IBD treatment with anti-TNFα, which can help improve the spinal symptoms.

Sociodemographic data was shown in Table 1 of 25 participants of axial SpA. Fourteen patients were females, with the percentage of 56%. Twenty-one (84%) patients were nonsmokers. They were middle-aged of mean ± SD age of 37.6 ± 10.9 and mean ± SD BMI of 27.8 ± 5.6. Two patients had diabetes and another two patients took anti-hypertensive medication.

Twelve (48%) patients were diagnosed over 5-year duration, while only two patients were diagnosed in less than 1 year as in Fig. 1. Disease duration and active inflammation of gut mucosa also increase the risk of SpA onset, although they may also occur irrespective of gut inflammation (Karreman et al., 2017).

Various pharmacotherapies were used for the treatment of arthtropathy associated with IBD, ranging from steroids to biologics that targeted disease-related pathways. These therapeutic approaches were extrapolated based on research in other SpA studies (Rogler et al., 2021). Table 2; there

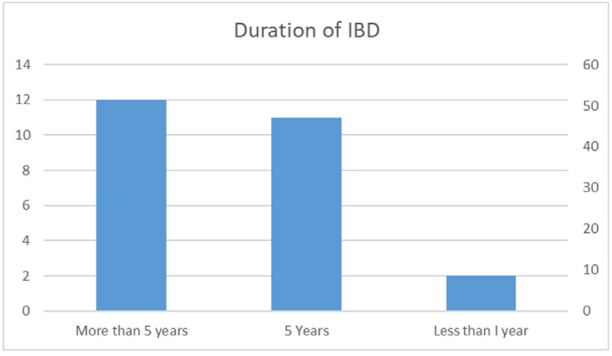

Fig. 1. Duration of disease in IBD cases. IBD, inflammatory bowel disease.

were 11 (44%) patients continued on conventional therapy in the form of 5-ASA (3 g/day), AZA (100 mg/day), and small dose corticosteroid (5–10 mg/day), while 14 (56%) patients started biological treatment. In Fig. 2 11 patients took anti-TNF, two patients shifted from anti-TNF to anti-IL12/23 (ustekinumab), last patient had a double shift (within anti-TNF class and then to anti-IL12/23). Anti-IL12/23(ustekinumab) was never used as first-line therapy in any of these patients.

According to response, 11 (78.6%) cases out of 14 showed a response. The response was reported by improvement clinically, laboratory, and endoscopic parameters for the gastrointestinal tract manifestations. As for the rheumatologic manifestation, the response was detected clinically and radiologically. Short-term efficacy was reported in seven (63.6%) cases, while long-term efficacy was reported in four (36.4%) cases (Fig. 3).

In terms of laboratory response (Table 3), there was significant improvement as regards hemoglobin and serum albumin. Also, regarding phase reactants of CRP and FC, they showed significant improvement before and after biological treatment (P<0.05).

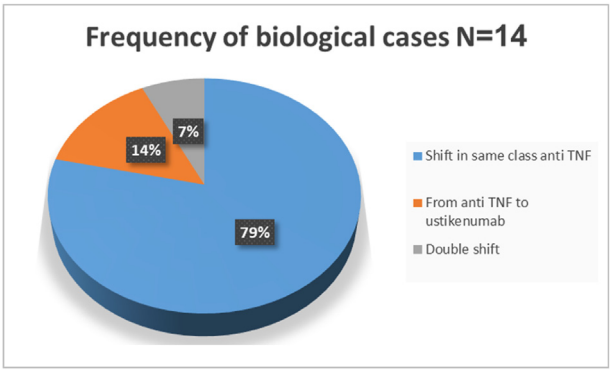

Fig. 2. Frequency of axial SpA cases associated with IBD who received biological treatment. IBD, inflammatory bowel disease; SpA, spondyloarthropathy.

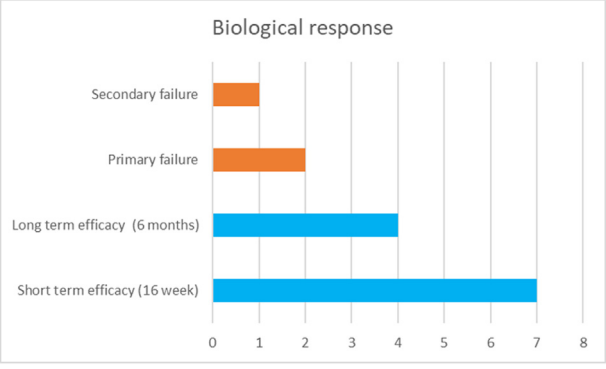

Fig. 3. Response of cases to biological treatment.

Moreover, it was found that there was significant improvement in terms of endoscopic score (Mayo for UC $P = 0.006$ and CDAI for CD $P = 0.034$) before and after biological treatment. There was a significant decline concerning the grade of inflammation at the axial sacroiliac joint by MRI after receiving biological treatment ($P = 0.0001$) (Table 4). This goes with STRIDE II and the importance of achieving treatment targets over short, intermediate, and long duration. Symptomatic improvement has been determined as an immediate goal. Serum and fecal biomarkers are considered intermediate medium-term. Long-term treatment targets are endoscopic healing of mucosa, restoration of quality of life, and absence of disability (Turner et al., 2021).

Among the biologics used to treat axial SpA in IBD, no randomized controlled trial has assessed the biologics' effectiveness. To determine whether anti-TNFα is effective in treating IBD, four open-label trials involving a total of 100 patients were conducted (Barreiro-de-Acosta et al., 2012; Generini et al., 2004). They concluded that the first choice of treatment in such cases should be anti-TNFα. However, it is not advised to use anti-integrin (vedolizumab) or anti-IL12/23 (ustekinumab). These studies had a range of outcomes and different time frames (Gordon et al., 2024).

In our study, there was failure of response reported in three (21.4%) cases. Two cases showed primary mechanistic failure: one was shifted to ustekinumab with a quite control of gastrointestinal tract symptoms, and the second one, after failure and decision to shift to ustekinumab, was not able to complete the course due to financial issues.

There have not been many studies on ustekinumab's efficacy in axial SpA. Forty-three of patients receiving ustekinumab treatment (for both axial and peripheral arthritis) demonstrated a clinical response in an open-label study (Macaluso et al., 2020). However, a quite large retrospective cohort study revealed that the arthropathy already present worsened by percentage (34.9 and 22.5%) for patients with intestinal IBD receiving vedolizumab and ustekinumab, respectively. Additionally, a few patients also experienced the onset of a new joint disease (De Galan et al., 2022). Additionally, ustekinumab was not found to show efficacy in treating axial spondyloarthritis in a systematic review involving 254 patients (Guillo et al., 2021).

The third case of failure in this study had been shifted between infliximab to adalimumab with rheumatological control over 1 year then new activity of CD started and was shifted to ustekinumab. Unfortunately she showed activity of sacroileitis. This raises the issue of shifting to a new biologic as

Janus A kinase inhibitors, which has shown high efficacy in the management of ankylosing spondylitis (van der Heijde et al., 2022), so it can be considered in such cases. Also, the idea of dual biologics has become agitated. However, the safety and financial issues will always be considered as obstacles.

Management of patients with IBD-related SpA has shown some encounters: complete lack of evidence in studies concerning the efficacy of those treatments for the combined disease. Moreover, some of those drugs occasionally have adverse effects on either disease aspect. Another important point is the dosage that may vary between rheumatological and gastroenterological needs, with IBD generally requiring higher dosing.

Limitations of this study were a quite small number of patients included, and their follow-up was through limited time. Also, we did not depend on any clinical score for the assessment of joint manifestations. We tried to focus on cases of axial arthropathy associated with IBD, mainly those under biological treatment. Besides, we depended on objective rather than subjective parameters for their follow-up, despite its short duration.

In conclusion, biological therapy should be considered early in axial arthropathy associated with IBD, with response reaching 78.6%. Anti-TNF should be considered as the initial line of therapy. In cases of coexisting rheumatological conditions, a multidisciplinary team should be present involving a gastroenterologist and a rheumatologist for the best choice of immunosuppressive therapy, that should be tailored for each patient.

Conflict of interest

The authors declare that there was nothing to announce as conflict of interest.

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