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Alimentary Tract

Psoriasis induced by antiTNF therapy in inflammatory bowel disease: Therapeutic management and evolution of both diseases in a nationwide cohort study

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ABSTRACT

Background: some patients with inflammatory bowel disease (IBD) treated with antiTNF develop drug-induced psoriasis (antiTNF-IP). Several therapeutic strategies are possible.
Aims: to assess the management of antiTNF-IP in IBD, and its impact in both diseases.
Methods: patients with antiTNF-IP from ENEIDA registry were included. Therapeutic strategy was classified as continuing the same antiTNF, stopping antiTNF, switch to another antiTNF or swap to a non-antiTNF biologic. IP severity and IBD activity were assessed at baseline and 16, 32 and 54 weeks.
Results: 234 patients were included. At baseline, antiTNF-IP was moderate-severe in 60 % of them, and IBD was in remission in 80 %. Therapeutic strategy was associated to antiTNF-IP severity ($p < 0.001$). AntiTNF-IP improved at week 54 with all strategies, but continuing with the same antiTNF showed the worst results ($p = 0.042$). Among patients with IBD in remission, relapse was higher in those who stopped antiTNF ($p = 0.025$). In multivariate analysis, stopping antiTNF, trunk and palms and soles location were associated with antiTNF-IP remission; female sex and previous surgery in Crohnś disease with IBD relapse.
Conclusion: skin lesions severity and IBD activity seem to determine antiTNF-IP management. Continuing antiTNF in mild antiTNF-IP, and swap to ustekinumab or switch to another antiTNF in moderate-severe cases, are suitable strategies.

1. Introduction

Inflammatory bowel disease (IBD) is a chronic inflammatory condition of the gastrointestinal tract, which comprises Crohn's disease (CD) and ulcerative colitis (UC). Its etiology is complex and not well known, but the dysregulation of the immune response in the gastrointestinal mucosae, environmental and genetic factors play a key role in the pathogenesis [1,2]. Psoriasis is a chronic immune skin disease, characterized by a significant proliferation and abnormal differentiation of keratinocytes, and an imbalance of inflammatory cytokines [3].

Both entities share tumor necrosis factor alpha (TNF-α) as one of the cytokines involved in their pathogenesis, being antiTNF treatment effective in both diseases. However, some patients treated with antiTNF develop psoriasis as an adverse event, named antiTNF-induced psoriasis (IP). This adverse event has been observed in 2–5 % of these patients [4], being considered as a class adverse event rather than a reaction to a specific drug [5].

The mechanisms by which these paradoxical lesions appear are poorly understood. There are several theories, the most accepted is that the TNF-α inhibitor leads to uncontrolled production of interferon-alpha (IFN-α) by plasmacytoid dendritic cells. This results in the release of the inflammatory cytokines IL-23, TNF-α and IL-12, which activate T helper cells and stimulate further inflammatory cytokine release, resulting in unregulated keratinocytes [6].

Most patients will be treated using a conventional approach (topical treatment, phototherapy, etc.) while continuing the antiTNF therapy, according to severity skin lesions. However, change to another antiTNF or discontinue antiTNF therapy is often considered in severe cases, even when the intestinal disease is well controlled, which represents a therapeutic challenge because of the risk of aggravating the underlying IBD [7].

The appearance of ustekinumab, an interleukin 12/23 antagonist, which is effective and safe in moderate to severe psoriasis [8,9], as well as in moderate-severe CD and UC, could be a good alternative [10–13]. Nevertheless, IBD is very complex, and this change could reactivate IBD, previously controlled by the antiTNF. However, to date, antiTNF-IP treatment is variable according to the center's experience, and evidence-based guidelines to manage these lesions are lacking due to insufficient data [14–16]. The main aim of the present study was to assess antiTNF-IP and IBD evolution with different therapeutic strategies motivated by the appearance of antiTNF-IP.

2. Methods

2.1. Study protocol

This is an observational, multicenter study, carried out using data from the ENEIDA registry (Estudio Nacional en Enfermedad Inflamatoria Intestinal sobre Determinantes genéticos y Ambientales) [17], a large prospective Spanish database promoted by the Spanish Working Group in Crohn's and Colitis (GETECCU), which in 2022 included over 75,000 patients, and more than 31,500 antiTNF treatments.

The aim of the study was to assess the therapeutic management of antiTNF-IP in IBD, and the impact of that decision in the evolution of both diseases. The main outcomes of our study were IBD activity and antiTNF-IP response regarding the therapeutic strategy, assessed at baseline and weeks 16, 32 and 54 (Fig. 1).

Patients in the ENEIDA registry with IBD and antiTNF-IP, with a follow up of at least 16 weeks, were included. We excluded patients treated with antiTNF for an indication other than IBD, or if diagnosis of psoriasis was made before starting antiTNF treatment.

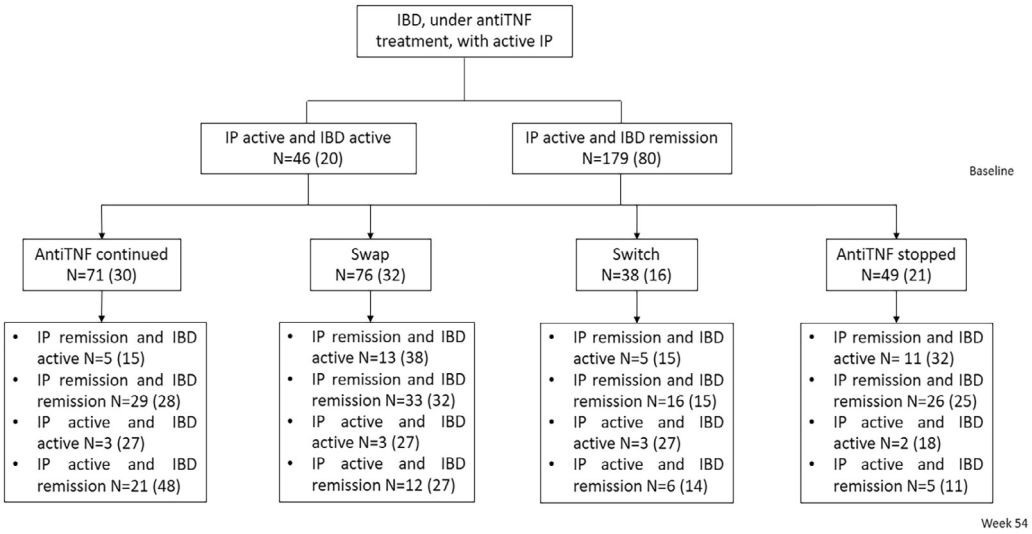

Fig. 1. Flow chart of patients. At baseline, all patients had active antiTNF-IP, while IBD may be in remission or active. At week 54, there could be 4 different settings: a) IBD active + IP active b) IBD remission + IP active c) IBD active + IP remission d) IBD remission + IP remission.

We consider and compare 4 strategy groups regarding biological therapy: 1) to stop antiTNF treatment (without starting a new biologic therapy); 2) to continue the same antiTNF; 3) to switch to another antiTNF or 4) to swap to another biologic with different mechanism of action.

2.2. Data collection

The ENEIDA registry is a large prospectively maintained IBD database that includes data of immunomodulators and biological therapies. ENEIDA captures several variables including IBD type, age at diagnosis, sex, disease extent and behavior, extraintestinal manifestations, perianal disease, smoking status, comorbidity, body mass index (BMI), surgical and medical treatments.

Additional data needed for this study and not included in the ENEIDA database were requested to the treating practitioners. This review included information about IBD, as well as antiTNF-IP: confirmation by a dermatologist, biopsy, phenotype and location of skin lesions, family history of psoriasis, treatment related to psoriasis and its clinical management and evolution.

Study data were collected and managed using REDCap electronic data capture tools [18] hosted at Asociación Española de Gastroenterología (www.redcap.aegastro.es) with technical support by AEGASTRO [19].

2.3. Definitions

2.3.1. IBD activity

IBD clinical activity was assessed with Harvey-Bradshaw Index (HBI) in CD and Partial Mayo Score (pMS) in UC [20,21]. Active IBD was defined as a HBI≥5 or a pMS≥2; remission as a HBI≤4 or pMS<2, and clinical response as a drop of ≥3 points in HBI or ≥2 points in pMS over baseline. IBD activity was evaluated at baseline, 16, 32 and 54 weeks. Fecal calprotectin (FCP) and C-reactive protein (CRP) were assessed when available (a value of FCP<250 mg/kg and CRP<0,5 mg/dl was considered normal).

2.3.2. AntiTNF-induced psoriasis severity

At baseline, antiTNF-IP severity was classified as mild, moderate, or severe (determined by body surface area covered and intensity of symptoms) by the dermatologist. If it was not available, a subjective gastroenterologist assessment was included (determined by psoriasis extent and symptoms). AntiTNF-IP response after therapeutic decision was classified as remission (complete resolution), response (improvement without complete resolution), and no response (absence of improvement). All items were evaluated at baseline and 16, 32 and 54 weeks.

2.3.3. Statistical analysis

A descriptive analysis was carried out, showing categorical variables as frequencies and continuous ones as mean and standard deviation or median and interquartile range according to distribution using SPSS 28.0 software. The Kolmogorov-Smirnov test was used to evaluate normality in continuous variables.

A comparative analysis was performed by means of a McNemar test for qualitative variables, and repeated measures ANOVA for quantitative variables. Bonferroni post-hoc analysis was used in case the null hypothesis was rejected. Variables were compared using chi-square test or a Fisher-Freeman-Halton test if frequencies were less than 5 and no null value.

Logistic regression model was used to evaluate predictive factors of IBD relapse and psoriasis evolution. The variables were included in this analysis if p value <0.1 in the univariate analysis. Statistical differences were considered as significant with $p < 0.05$.

2.3.4. Ethics

ENEIDA project was approved by Research Ethic Committees in all participating centers. Written informed consent was obtained from all patients. This study has been evaluated and approved by the Clinical Research Ethics Committee of Aragon (CEICA) and ENEIDA Committee. All co-authors had reviewed and approved the final manuscript.

3. Results

3.1. Baseline characteristics

234 patients with antiTNF-IP were included from 38 referral centers. 185 (79 %) patients had CD, 46 (20 %) UC, and 3 (1 %) unclassified IBD. Baseline characteristics are shown in Table 1.

At baseline, all patients had active antiTNF-IP, whose diagnosis was confirmed by a dermatologist in 216 patients (92 %), 60 of them with skin biopsy (26 %). The mean time since antiTNF treatment initiation was 23.4 months (range 0–163). Only 10 patients had previously received a potential trigger drug (beta blockers, lithium, NSAIDs…). Psoriatic lesions were classified as mild,

Table 1
Characteristics of patients with IBD and psoriasis induced by antiTNF.

Variable (n,%)[1]	Total $n = 234$	Continue antiTNF $n = 71$	SWITCH $n = 38$	SWAP $n = 76$	Stop antiTNF $n = 49$	p
Type IBD						0.068[2]
CD	185 (79)	56 (30)	26 (14)	67 (36)	36 (19)	
UC	46 (20)	13 (28)	12 (26)	9 (20)	12 (26)	
IC	3 (1)	2 (67)	0	0	1 (33)	
Sex, n (%)						0.016[1]
Female	158 (68)	38 (24)	27 (17)	59 (37)	34 (22)	
Male	76 (33)	33 (43)	11 (14)	17 (22)	15 (20)	
BMI (Body Mass Index)						0.8712[2]
Underweight (≤18.5)	13 (7)	3 (23)	4 (31)	4 (31)	2 (15)	
Normal weight (18.5–24.9)	94 (53)	32 (34)	15 (16)	31 (33)	16 (17)	
Overweight (25–29.9)	43 (24)	13 (30)	5 (12)	17 (40)	8 (19)	
Obesity (>≥30)	28 (16)	10 (36)	2 (7)	11 (39)	5 (18)	
Smoking status n (%)						0.313[1]
Nonsmoker	90 (39)	26 (29)	14 (16)	31 (34)	19 (21)	
Former smoker	91 (39)	27 (30)	20 (22)	29 (32)	15 (16)	
Smoker	53 (23)	18 (34)	4 (8)	15 (28)	15 (28)	
Age at diagnosis n (%)						0.3262[2]
A1 (< 17)	21 (9)	4 (19)	5 (24)	8 (38)	4 (19)	
A2 (17–40)	140 (60)	40 (29)	18 (13)	53 (38)	29 (21)	
A3 (>40)	24 (10)	12 (50)	3 (13)	6 (25)	3 (13)	
Location CD n (%)						0.373[2]
L1 ileal	81 (44)	23 (28)	10 (12)	35 (43)	13 (16)	
L2 colic	16 (9)	4 (25)	4 (25)	3 (19)	5 (31)	
L3 ileocolic	90 (49)	29 (32)	14 (16)	26 (29)	18 (20)	
+L4 upper GI tract	14 (8)	-	-	-	-	
Behaviour, n (%)						0.724[2]
B1 inflammatory	105 (57)	34 (32)	17 (16)	33 (31)	21 (20)	
B2 stricturing	44 (24)	15 (34)	5 (11)	16 (36)	8 (18)	
B3 penetrating	31 (17)	7 (23)	3 (10)	14 (45)	7 (23)	
B2+B3	3 (2)	-	1 (33)	2 (67)	-	
Extent						0.463[2]
E1 proctitis	8 (17)	1 (8)	3 (23)	1 (11)	3 (25)	
E2 left sided	16 (34)	6 (46)	6 (46)	2 (22)	2 (17)	
E3 extensive	23 (49)	6 (46)	4 (31)	6 (67)	7 (58)	
Perianal disease n (%)	88 (38)	25 (28)	15 (17)	28 (32)	20 (23)	0.928[1]
EIM, n (%)	88 (38)	32 (36)	14 (16)	28 (32)	14 (16)	0.337[1]
Musculoskeletal	60 (26)	24 (40)	9 (15)	19 (32)	8 (13)	0.188[1]
Ocular	12 (5)	4 (33)	2 (17)	4 (33)	2 (17)	1[2]
Cutaneous	31 (13)	12 (39)	8 (26)	7 (23)	4 (13)	0.037[2]
Hepatobiliary	1 (0.4)	-	1 (100)	-	-	NA
Oral aphthous lesions	7 (3)	-	5 (71)	2 (29)	-	NA
Thromboembolism	5 (2)	1 (20)	3 (60)	1 (20)	-	NA
Previous surgery, n (%)	98 (42)	28 (39)	11 (29)	36 (47)	23 (47)	0.239[1]
Resection/Strictureplasty	72 (31)	18 (25)	9 (24)	30 (40)	15 (31)	0.210[1]
Perianal	39 (17)	14 (20)	7 (18)	10 (13)	8 (16)	0.752[1]
Pouch	4 (2)	2 (3)	-	1 (1)	1 (2)	0.836[2]
Comorbidity, n (%)	46 (20)	19 (41)	8 (17)	13 (28)	6 (13)	0.234[1]
Arterial hypertension	24 (52)	9 (38)	6 (25)	6 (25)	3 (16)	0.394[1]
Dyslipidemia	39 (85)	11 (28)	4 (10)	4 (10)	2 (5)	0.091[2]
Diabetes mellitus	9 (19)	4 (44)	1 (11)	3 (33)	1 (11)	0.876[2]
Baseline IBD activity						0.065[1]
Remission	179 (80)	58 (32)	26 (15)	56 (31)	39 (22)	
Active	46 (20)	10 (22)	11 (24)	20 (43)	5 (11)	
Unknown	9					
AntiTNF-IP severity						**<0.001**[1]
Mild	93 (40)	52 (56)	10 (11)	19 (20)	12 (13)	
Moderate	108 (46)	17 (16)	21 (19)	46 (43)	24 (22)	
Severe	33 (14)	2 (6)	7 (21)	11 (33)	13 (39)	

[1] Pearson's chi-square test; 2: Fisher-Freeman-Halton test; 3: one-way ANOVA.

moderate, and severe in 93 (40 %), 108 (46 %) and 33 (14 %) patients respectively. Palms and soles, and scalps, were the most frequent locations, being limited to one area in 103 patients (44 %), and two or more in 131 (56 %). Plaque and pustulosis were the most developed phenotype (Table 2).

IBD was in clinical remission in 179 (80 %) patients, while 46 (20 %) had active disease, with an average score of 6.8 and 3.5 on HBI and pMS respectively. Baseline IBD activity was not registered in 9 patients. AntiTNF therapy in the full cohort at the diagnosis of antiTNF-IP was: 128 (55 %) infliximab, 102 (44 %) adalimumab, 2 (0.9 %) certolizumab and 2 (0.9 %) golimumab, being 48 of them (24 %) biosimilar agents. 190 (81 %) patients had received one antiTNF agent, and 44 (19 %) two or more. 73 (32 %) patients were on concomitant immunosuppressive therapy (thiopurines, methotrexate), and 159 (68 %) had previously been exposed to them.

3.2. Clinical management

Within the entire cohort, therapeutic strategy chosen was: swap in 76 patients (33 %), 69 of them to ustekinumab; continuing the same antiTNF in 71 (30 %), 69 of them with the same dose and 2 with lower dose; stopping antiTNF (without starting a new biologic treatment) in 49 (21 %), and switch to another antiTNF in 38

Table 2
Diagnosis and characteristics of psoriasis induced by antiTNF.

Confirmation by dermatologist's evaluation	216 (92)
Skin biopsy	60 (26)
Phenotype	
Plaque	142 (61)
Pustulosis	75 (32)
Scalp	45 (19)
Inverse	22 (9)
Guttate	13 (6)
Erythrodermic	12 (5)
Nails	4 (2)
Location	
Palms and soles	114 (49)
Scalp	94 (40)
Limbs	90 (39)
Trunk	67 (29)
Folds	41 (18)
Facial and/or retro auricular	32 (14)
Genitals	21 (9)
Others	4 (2)
Adjuvant treatment	**182 (78)**
Phototherapy	**21 (12)**
PUVA	16 (9)
RePUVA	0 (0)
UVB-NB	3 (2)
Not available	2 (1)
Topical	**174 (96)**
Corticosteroids	146 (80)
Emollients	66 (36)
Vitamine D analog	23 (13)
Calcineurin inhibitors	10 (5)
Others	22 (12)
Systemic	**26 (14)**
Methotrexate	23 (13)
Acitretin	3 (2)
Dimethyl fumarate	0 (0)
Others	**17 (9)**

PUVA: Psolaren-UVA (Ultraviolet A); RePUVA: Retinoid-PUVA; UVB-NB: Ultraviolet B-Narrow band.

patients (16 %), adalimumab in 25 (11 %), infliximab in 6 (3 %) and another in 7 patients (3 %).

The choice of therapeutic strategy was associated to antiTNF-IP severity ($p < 0.001$). In moderate and severe cases, swap and stopping antiTNF were the most used strategies (43 % and 39 % respectively), while in patients with mild antiTNF-IP, continuing the same antiTNF was the preferred option (56 %). However, continuing the same antiTNF was only chosen in 2/33 patients with severe psoriasis. Most patients (78 %) received adjuvant treatment, being topical agents ($n = 182$, 96 %) with corticosteroids ($n = 146$, 80 %) the most used. Systemic treatment was used in 26 patients (14 %) (Table 2).

Regarding IBD activity, in patients with active IBD, a tendency to choose swap strategy (43 %), followed by switch to another antiTNF (24 %), was observed ($p = 0.065$). Continuing the same antiTNF (32 %) and swap (31 %) were the most used strategies when IBD was in clinical remission.

3.3. AntiTNF-induced psoriasis evolution

Skin lesions showed a significant improvement from baseline in terms of remission rate within the entire cohort of patients: from 40.3 % (93/231) at week 16 to 59.2 % (126/213) at week 32 ($p < 0.001$), and 72.1 % (147/204) at week 54 ($p < 0.001$). These rates were better in stopping antiTNF group (from 46.9 % at week 16 to 84.8 % at week 54, $p = 0.002$), swap group (from 42.1 % at week 16 to 75.8 % at week 54, $p = 0.012$) and in switch group (from to 40.5 % at week 16 to 72.7 % at week 54, $p = 0.017$). Continuing the same antiTNF strategy showed the worst results ($p = 0.042$), although patients still showed improvement during follow-up: remission rate increased from 33.3 % at week 16 to 58.7 % at week 54 ($p = 0.045$) (Fig. 2). No significant differences in antiTNF-IP remission between swap, switch and antiTNF stopped groups were found at week 54 ($p = 0.251$). Swap group included 6 patients treated with vedolizumab, achieving the remission in all cases.

Regarding factors associated with antiTNF-IP evolution, in multivariate analysis, stopping antiTNF treatment strategy [OR: 3.010; IC 95 %: (1.110–8.159), $p = 0.030$] and trunk [OR: 2.777; IC 95 %: (1.120–6.889), $p = 0.028$] as well as palms and soles location [OR: 2.091; IC 95 %: (1.018–4.294), $p = 0.044$], were independently associated with remission of antiTNF-IP (Supplementary Table 1).

3.4. Inflammatory bowel disease evolution

The evolution of IBD could be evaluated in 225/234 patients, 179 (80 %) of them were in clinical remission. In patients whose antiTNF treatment was stopped (without starting a new biologic therapy), CD activity worsened during follow-up: remission rate decreased from 93.5 % at baseline to 79.4 % ($p = 0.046$), 78.8 % ($p = 0.046$) and 71.9 % ($p = 0.014$), at week 16, 32 and 54 respectively. In addition, 2 patients required surgical management during follow-up (perianal fistula and small bowel obstruction). No significant differences were found in UC ($p = 0.705$).

In switch, swap and antiTNF maintained groups, no significant differences in CD clinical activity were found, and the number of patients with UC was too low to draw conclusions. FCP value increased at week 16 ($p = 0.043$), and a later decrease at week 54 ($p = 0.012$) was found in swap group. There were no differences in CRP or FCP levels in the other groups during follow-up.

The risk of IBD relapse was analyzed within the group of 179 patients with IBD in remission at baseline. Among those patients, antiTNF was maintained in 58 (32 %), swap strategy in 56 (31 %), antiTNF was stopped in 39 (22 %), and switched to another antiTNF in 26 (15 %) patients. Among these 179 patients, IBD relapse occurred in 18 patients at week 54, being rates of IBD relapse-free survival at 16, 32 and 54 weeks of 92 % (157/170), 89 % (139/157) and 88 % (135/153) respectively. According to the chosen strategy, IBD relapse-free rates at week 54 were 95 % (21/22) in switch group, 94 % (47/50) in antiTNF maintained group, 83 % (40/48) in swap group, and 82 % (27/33) in antiTNF stopped group (Fig. 3). No significant association between the strategy and IBD relapse was found ($p = 0.171$). However, in patients with antiTNF treatment (antiTNF continued and switch groups) and IBD remission at baseline, IBD remission rate at week 54 was significantly higher compared to those who did not continue antiTNF (antiTNF stopped and swap groups) (94.4% vs 82.7 %, $p = 0.025$).

In multivariate analysis, male gender was associated with lower risk of IBD relapse [OR 0.180 (95 %CI 0.038–0.847), $p = 0.03$] while previous surgery in CD, was associated with higher risk [OR 3.472 (95 %CI 1.019–11.833), $p = 0.047$] (Supplementary Table 2).

3.5. AntiTNF-Induced psoriasis and IBD evolution within the same patient

At baseline, all patients had active antiTNF-IP, but their IBD could be in remission (80 %) or active (20 %). These define two different baseline scenarios, from which patients could evolve to 4 possible others during follow-up by week 54: 1) IP remission and IBD remission (57 %, 104/183); 2) IP active and IBD remission (24 %, 44/183); 3) IP remission and IBD active (13 %, 24/183) and 4) IP active and IBD active (6 %, 11/183). Swap strategy achieved the remission of both entities in 32 % of these patients, followed by those who continued antiTNF (28 %).

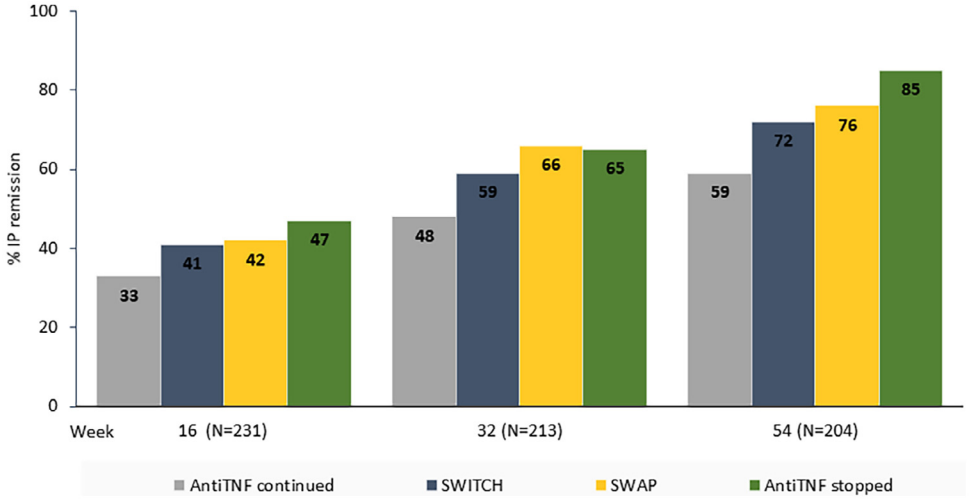

Fig. 2. IP remission rate regarding the therapeutic strategy. *NOTE: At baseline, all patients had active IP.*

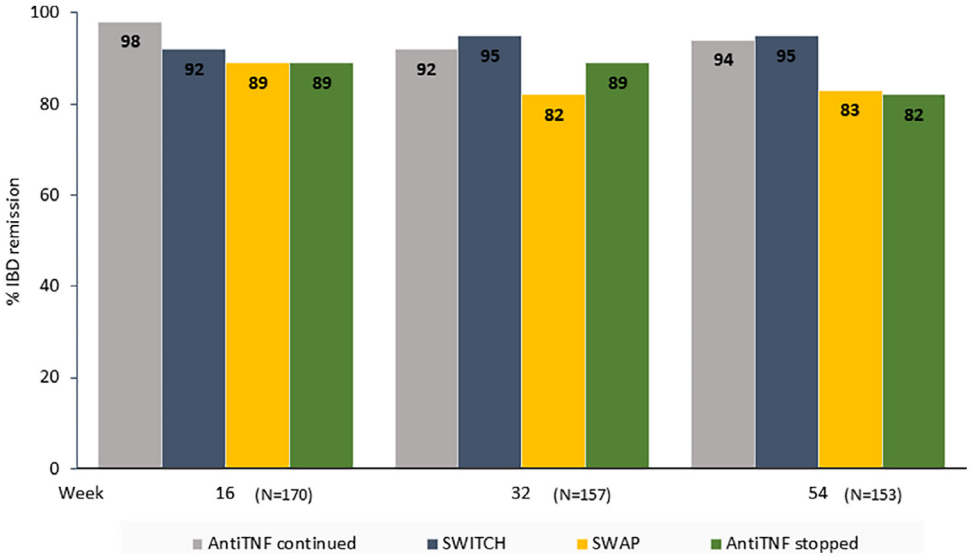

Fig. 3. IBD remission rate regarding the therapeutic strategy in patients with IBD remission at baseline.

In patients with IBD remission at baseline, no significant differences were found between continuing or not antiTNF treatment to achieve remission of both entities at week 54 (59.2 % and 60.2 % respectively). However, the number of patients with active antiTNF-IP and IBD remission at week 54 was significantly higher in those under antiTNF treatment than those who stopped it ($p = 0.022$).

4. Discussion

In this study, antiTNF-IP management was conditioned by its baseline severity and also IBD activity. Swap to ustekinumab or switch to another antiTNF were good options in cases with moderate or severe skin lesions, even when IBD was in remission. To the best of our knowledge, this is the first study analyzing the characteristics and management of antiTNF-IP in patients with IBD, taking into account the evolution of both diseases with different strategies.

AntiTNF-IP was initially described as isolated case reports in patients treated with antiTNF agents in rheumatic diseases, psoriasis and IBD [22–24]. With the increasing usage of antiTNF agents, large series cases have been increasingly recognized[25], as well as other immune conditions [26,27].

Several aspects provided evidence for the idea that it is a side effect of antiTNF agents: the temporal relationship between antiTNF treatment and IP appearance, the clinical improvement observed after its discontinuation, or the absence of commonly identified risk factors for idiopathic psoriasis (family history, BMI, etc.) [28–31].

Predictor factors of antiTNF-IP onset are largely unknown. In our study, it was more frequent in women, CD, and most of them had received infliximab. This could be partially explained by the earlier approval and longer use of infliximab, as well as the latter approval for infliximab and adalimumab for the treatment of UC, compared with CD. Plaque and pustulosis phenotype, and palms and soles, as well as scalp location, were the most frequently observed. Similar findings were reported in other studies [32–37].

Differential diagnosis with other skin lesions is an important issue and a challenge due to the different clinical management which could affect IBD activity [38,39]. The different management reflects that dermatologist's evaluation should be considered in all cases, to avoid unnecessary treatment changes, as well as to opti-

mize standard adjuvant treatment. In our study, most of the skin lesions (92 %) had been confirmed by a dermatologist.

There is no consensus yet on the need to discontinue antiTNF[40]. The therapeutic goal is to achieve long-term IBD remission, but also achieving the control of skin lesions. The therapeutic strategy should take into account IBD activity and severity of skin lesions. Regarding biologic therapy, there are four possible strategies: 1) to stop antiTNF treatment, 2) to continue the same antiTNF, 3) to switch to another antiTNF or 4) to swap to a biologic with different mechanism of action.

In our study, the decision to continue or not antiTNF treatment was related with antiTNF-IP severity: continue antiTNF was the most used strategy in mild IP, swap to ustekinumab in moderate cases, and stop antiTNF in severe ones. Baseline IBD activity was not significantly associated with the therapeutic approach ($p = 0.065$), but a tendency to choose swap strategy and to continue antiTNF was observed in active IBD.

During follow-up, all therapeutic groups showed significant improvement of antiTNF-IP, which could be partially explained by the high frequency (77.4 %) of adjuvant treatment. Topical treatment with corticosteroids was the most used. Trunk and palms and soles location, and especially, stopping antiTNF strategy, were associated with skin lesions remission. Severity antiTNF-IP at baseline determined therapeutic strategy chosen, so it was not included in multivariate analysis.

As well as in our work, previous studies have shown that discontinuing antiTNF therapy results in higher response rates of skin lesions [41,42]. Our data confirms that maintain the same antiTNF showed the worst results, with no differences between antiTNF stopped, swap and switch groups in week 54. Therefore, swap and switch could be suitable alternatives, maybe needed when IBD is active. However, antiTNF-IP severity in patients within swap strategy was higher than those within switch group, so probably this strategy could be better in the control of the skin lesions.

In our study, 80 % of patients were at IBD clinical remission at baseline. IBD relapse was identified in 12 % of those patients by week 54, although this value could be affected by loss of follow-up, changing therapeutic strategy, or recent patient recruitment. AntiTNF strategies (continue the same antiTNF and switch groups) achieved higher IBD remission rate than the other strategies at week 54 ($p = 0.025$). Stopping antiTNF treatment (without starting a new biologic treatment), compared with antiTNF strategies, showed higher rates of IBD relapse, but slightly lower than other studies [43–46].

Given the efficacy of anti-IL12/IL23 therapy in IBD and psoriasis [47,48], ustekinumab may be a suitable alternative. In our study, it was the most used option in patients with moderate-severe antiTNF-IP and active IBD, achieving the remission of 76 % of skin lesions and 83 % of IBD at week 54. Alternative biological therapy such as vedolizumab has also been described. Our results showed the remission of all cases of antiTNF-IP at week 54 after starting vedolizumab, but the number of these patients was small and available data in the literature is still lacking.

Female sex was the strongest risk factor of IBD relapse, whereas features previously associated with disease evolution (IBD characteristics, smoking status, etc.), with the exception of previous surgery in CD patients, were not associated with worse outcomes in our cohort [49,50]. However, these features could be useful to identify patients at higher risk of relapse, and therefore, needing a closer monitoring.

Assessing the IBD clinical activity and antiTNF-IP response to the therapeutic approach as a whole in the patient, 104 of them (57 %) were on remission of both entities at week 54, while only 11 patients (6 %) have active psoriasis and IBD. Swap strategy achieved the remission of both entities in most patients, followed by those who continued antiTNF, but no significant differences were found between both strategies in this group of patients, probably because they are effective (and approved) treatments for both entities.

The strengths of our study are its large sample size and multicenter design, which enhance the generalizability of our results to real-world clinical settings, as well as evaluating and comparing alternative therapies (switch and swap) not previously assessed in antiTNF-IP. Our cohort is the largest one analyzing them in patients with IBD. In addition, assessment of IBD evolution with different therapeutic strategies, confirms that changing the baseline treatment must be carefully considered.

However, our study has some limitations, such as its retrospective design and the large time ranges, which were used for data collection that influenced in each strategy prevalence. Regarding the date when ustekinumab was approved in our country to treat CD (August 2017), swap strategy to ustekinumab was made in 15 (4 %) against 59 (25 %) patients before and after its approval, respectively. Secondly, as ours was a real-world study, objective scores of skin lesions, such as Psoriasis Area Severity Index (PASI) or Body Surface Area (BSA), were not registered in most patients, as well as biochemical parameters or endoscopic assessment of IBD. It reflects what happens in clinical practice, even though, most skin lesions were initially evaluated by a dermatologist.

In conclusion, evaluating antiTNF-IP severity and IBD activity is mandatory previous IBD treatment modification. In all patients, skin lesions may benefit from conventional management. In cases of mild antiTNF-IP, continuing antiTNF treatment may be the best option if IBD is in remission. In patients with moderate or severe antiTNF-IP, a new treatment strategy must be considered, being swap to ustekinumab or switch to another antiTNF, appropriate ones. The decision of changing a biologic drug because of antiTNF-IP when IBD is in remission, must be cautiously taken, especially in those patients with an aggressive IBD. Nevertheless, prospective cohort studies would help to establish guidelines for optimize its diagnosis and better characterize the effectiveness and safety of each approach, above all in patients with severe psoriasis and aggressive IBD course.

Conflict of interest

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.dld.2024.05.021.

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