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Original Article

How to Manage Inflammatory Bowel Disease Patients When They Withdraw Anti-Tumour Necrosis Factor [Anti-TNF] Due to Severe Anti-TNF-Induced Skin Lesions? A Multicentre Cohort Study

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Abstract

Background and Aims: Optimal management of patients with inflammatory bowel disease [IBD] after anti-tumour necrosis factor [TNF] discontinuation due to severe induced skin lesions is unclear. Our study aimed to describe dermatological and IBD evolution after anti-TNF discontinuation for this side effect.

Methods: We conducted a multicentre retrospective study including consecutive IBD patients who discontinued anti-TNF due to severe induced skin lesions. Our objectives were to determine factors associated with dermatological remission [complete disappearance of skin lesions] and with IBD relapse in patients with inactive disease at inclusion, notably the impact of an early switch to another biological agent within 3 months of anti-TNF discontinuation.

Results: Among the 181 patients [134 women, 160 Crohn's disease] included in the 13 participating centres, dermatological remission occurred in 110 [62%] patients with a median [interquartile range, IQR] interval of 8.0 [6.8–11.0] months. Scalp location was independently associated with less remission of skin lesions (hazard ratio [HR] = 0.64 [95% CI 0.43–0.94], $p = 0.02$) while early switch was independently associated with a higher probability of remission of skin lesions (HR = 1.64 [95% CI 1.1–2.5], $p = 0.02$). Among the 148 patients with inactive IBD at inclusion, disease relapse occurred in 75 [51%] patients with a median [IQR] interval of 26.0 [23.0–39.1] months. Survival rates without IBD relapse at 1 year were 85.8% [95% CI 77.5–94.9] in the early switch group and 59.3% [95% CI 48.9–71.9] in the other group [$p < 0.01$].

Conclusions: Early switch to a new biological is associated with a higher probability of healing of anti-TNF-induced skin lesions and significantly reduces the risk of IBD relapse.

Key Words: Inflammatory bowel disease; anti-TNF; skin lesions

1. Introduction

Anti-tumour necrosis factor [TNF] therapies have dramatically modified the management of inflammatory bowel disease [IBD]. Although three anti-TNF agents—infliximab, adalimumab and golimumab—have proven to be effective in IBD and generally well tolerated,[1,2] their use is associated with a wide range of side effects. Dermatological side effects are among the most common, affecting ~20% of patients treated

with anti-TNF agents,[3] including infections, cancers and anti-TNF-induced skin lesions, so-called paradoxical reactions.[3–7] Anti-TNF-induced psoriasis, which can manifest *de novo* or as an exacerbation of a pre-existing psoriasis, is the most frequent induced skin reaction while other lesions, such as eczematiform lesions, vasculitis or granulomatous skin reactions, occur less frequently.[4,6,8] These anti-TNF-induced skin lesions may be severe, having a major impact on the patient's quality of life. In the most severe cases, corresponding to 10–34% of patients depending on series,[3,5,7,9,10] the anti-TNF agent is discontinued even if effective for controlling IBD in the majority of patients.[3,4,9]

The objectives of the management of IBD patients after anti-TNF discontinuation in case of severe induced skin lesions are to maintain IBD in remission and to achieve remission of skin lesions. The first option is to switch to another anti-TNF agent. However, the recurrence rate of skin lesions is elevated—~60% of patients according to several retrospective series.[3,11] Another option is to start a drug with a different mode of action, such as vedolizumab or ustekinumab. The latter is a monoclonal antibody targeting the common subunit p40 of interleukins 12 and 23 that has already demonstrated its efficacy in both psoriasis and IBD. Thus, ustekinumab is an attractive option for managing IBD patients with severe anti-TNF-induced skin lesions. Indeed, a few studies with a small number of patients reported healing of anti-TNF-induced skin lesions with ustekinumab as well as with vedolizumab.[9,12,13] However, these studies could not determine whether this healing was related to anti-TNF discontinuation or to the new medication started. Overall, there is a lack of data available to guide the management of patients who withdraw anti-TNF due to severe induced skin lesions, especially when IBD is in remission. The aims of the present study were to assess the evolution of anti-TNF-induced skin lesions and course of IBD in patients with severe skin lesions leading to anti-TNF discontinuation.

2. Patients and Methods

2.1. Study design and patients

We conducted a retrospective multicentre observational study in 11 French and two Belgian tertiary IBD centres, including consecutive patients with IBD who had stopped anti-TNF from December 2005 to December 2020 because of severe anti-TNF-induced skin lesions. Patients were retrieved within databases from each participating centre. They were eligible if they were more than 15 years old, had an IBD diagnosis according to usual criteria[14] and had developed severe anti-TNF-induced skin lesions requiring drug discontinuation. Anti-TNF-induced skin lesions were defined by new-onset or worsening skin lesions, usually psoriasiform or eczematiform, in patients receiving anti-TNF therapy when drug imputability was confirmed by a visit to a dermatologist.[15]

Inclusion date corresponded to the last administration of anti-TNF. Patients were informed by written notice of their participation. The French Data Protection Agency [Commission Nationale de l'Informatique et des Libertés, registration number 2210131] and the investigational review board of each centre approved the study.

2.2. Data collection

Patient medical records were retrospectively reviewed and the following data concerning patients and IBD at inclusion were collected through a standardized form: age, gender, smoking status, body mass index, disease type (Crohn's disease [CD] or ulcerative colitis [UC]), IBD location and phenotype according to the Montreal classification,[16] disease duration, previous intestinal surgery, extra-intestinal manifestation, type and duration of the anti-TNF agent discontinued at inclusion, prior or concomitant immunosuppressive therapies [thiopurines, methotrexate], prior other biological agent [other anti-TNF agent, vedolizumab, ustekinumab], and disease activity based on the physician's global assessment [active or inactive].

The following data related to anti-TNF-induced skin lesions were also collected at inclusion: personal and familial [first-degree relatives] history of dermatological diseases [atopic dermatitis, psoriasis, immune-mediated diseases or other skin disease], date of onset of skin lesions, topography of skin lesions [palmoplantar, face, scalp, trunk, skin folds, genitals, limbs], subtype of skin lesions [psoriasiform lesions including palmoplantar pustulosis, eczematiform lesions, xerosis, vasculitis or other], dermatological management of skin lesions before anti-TNF discontinuation [no medication, topical medication, systemic medication including cyclosporine, methotrexate, retinoid, phototherapy or other], and skin biopsy realization.

2.3. Follow-up

Dermatological follow-up corresponded to the interval from inclusion to dermatological remission [defined as a complete resolution of anti-TNF-induced skin lesions], or date of last news or end of the follow-up period.

Digestive follow-up corresponded to the interval from inclusion to IBD relapse [defined as a recurrence of disease symptoms with a need for introduction or optimization of systemic treatment, hospitalization, or surgery] for those who were in digestive remission at inclusion, or date of last reporting or end of the follow-up period.

The follow-up period endpoint was April 2021.

During the follow-up period, the following events and their dates were collected: introduction of any biological agent [other anti-TNF, ustekinumab, vedolizumab], continuation or introduction of tofacitinib or investigational drug and immunosuppressive therapies [thiopurines, methotrexate, cyclosporine], dermatological remission and IBD relapse.

Patients were divided into two subgroups according to introduction of a new biological agent within 3 months of inclusion: the early switch group and the non-early switch group. We arbitrarily chose a cut off of 3 months after anti-TNF discontinuation to define early switch of a new biological agent, considering that in current practice, it was most often during this pivotal period that the decision to introduce a new biological agent was made.

2.4. Objectives

The study objectives were to determine [i] factors associated with remission of anti-TNF-induced skin lesions and [ii] factors associated with IBD relapse in patients who were inactive at inclusion. For both study objectives, the impacts of the early switch to a new biological agent and IBD subtype were specifically assessed.

2.5. Statistical analysis

Categorical variables were described as frequencies [%] and compared using a chi-square test or a Fischer's exact test depending on the expected numbers in each category.

Continuous variables were described as median and interquartile range [IQR] and compared using a Wilcoxon rank sum test.

Kaplan–Meier curves were plotted for time to inclusion to remission of induced skin lesions in the overall population, and according to early switch or not; and for time to inclusion to IBD relapse in patients with inactive IBD at inclusion, according to early introduction or not of a new biological agent and IBD subtype. Log rank tests were used to compare the survival curves.

A univariate Cox regression model was conducted in the overall population for eligible predictive factors of remission of induced skin lesions. Results are presented as the hazard ratio [HR] with confidence intervals [95% CI]. Factors with $p < 0.15$ in univariate regression were included in the full multivariate Cox regression model. One enforced covariate was introduced in the model despite a p-value of >0.15 in univariate regression: systemic medication for skin lesions. Manual stepwise elimination was performed to find the best suitable model of factors predicting remission of induced skin lesions. The univariate Cox regression model was also conducted for eligible predictive factors of IBD relapse in CD patients with inactive disease at inclusion. Factors with $p < 0.20$ in univariate regression were included in the full model of the multivariate Cox regression. Manual stepwise elimination was performed to find the best suitable model of factors predicting digestive relapse. Predictive factors of IBD relapse were not investigated in UC patients due to the small number of patients.

Two-sided statistical tests were used for all analyses. A p-value of <0.05 was considered significant.

Statistical analyses were performed using R version 3.5.1 [R Development Core Team].

3. Results

3.1. Patient characteristics at anti-TNF discontinuation

A total of 181 patients were included in the present study. Their main characteristics at anti-TNF discontinuation are presented in Table 1. To summarize, 134 [74%] were women, median age was 29 [IQR: 24–41] years, median body mass index was 22.5 [20.6–26.6] kg/m² and 74 [41%] were active smokers. Median duration of IBD was 7 [3–12] years. Regarding IBD subtypes, CD was found in 160 [88%] patients and UC in 21 [12%]. Ninety-six [53%] received adalimumab, 82 [45%] infliximab, two [1%] golimumab and one patient [1%] had certolizumab indicated for concomitant ankylosing spondylitis. The median duration of the anti-TNF agent was 22 [8.0–44.0] months and 33 [18%] patients were also treated with a conventional immunosuppressant [thiopurine in 23 patients and methotrexate in ten]. At anti-TNF discontinuation, 148 patients [82%] had inactive IBD.

Dermatological characteristics at anti-TNF discontinuation are displayed in Table 2. Thirty-four [19%] patients had a personal history of dermatological diseases and nine [6%] patients had a familial history. Median interval from start of anti-TNF to onset of induced skin lesions was 8.9 [2.0–26.1] months; it was 6.0 [1.9–14.0] months from onset of skin lesions to anti-TNF discontinuation. The main types of lesions were psoriasiform lesions [58%], eczematiform lesions [21%] and other type of lesions [16%] corresponding mainly to cutaneous infections.

Table 1. Baseline characteristics of the 181 patients with inflammatory bowel disease [IBD] who discontinued anti-TNF due to severe anti-TNF-induced skin lesions

Characteristic	*n* = 181
Median age, years [IQR]	29.0 [24.0–41.0]
Female gender, *n* [%]	134 [74]
IBD subtype, *n* [%]	
Crohn's disease	160 [88]
Ulcerative colitis	21 [12]
UC disease location,[16] *n* [%]	
E1	2 [9.5]
E2	8 [38]
E3	11 [52]
CD disease location,[16] *n* [%]	
L1	53 [33]
L2	21 [13]
L3	84 [52]
L4	2 [1.2]
CD behaviour*,[16] *n* [%]	
B1	85 [53]
B2	40 [25]
B3	34 [21]
Perianal disease, *n* [%]	55 [34]
Previous intestinal surgery, *n* [%]	48 [27]
Extra intestinal manifestation, *n*[b] [%]	46 [25]
Active disease at inclusion,[a] *n* [%]	33 [18]
Median IBD duration, years [IQR]	7.0 [3.0–12.0]
Median body mass index, kg/m² [IQR]	22.5 [20.6–26.6]
Body mass index range**, *n* [%]	
<25 kg/m²	113 [67]
≥25 kg/m²	55 [33]
Smoking status***, *n* [%]	
Never smoker	83 [47]
Smoker	74 [42]
Former smoker	20 [11]
Anti-TNF agent discontinued, *n* [%]	
Infliximab	82 [45]
Adalimumab	96 [53]
Golimumab	2 [1.1]
Certolizumab	1 [0.6]
Median interval from start of anti-TNF to discontinuation, months [IQR]	22.0 [8.0–44.0]
Concomitant immunosuppressive therapy, *n* [%]	
Thiopurines	23 [13]
Methotrexate	10 [5.6]
Previous lines of biological therapy, *n* [%]	
None	128 [71]
One	50 [28]
Two	2 [1.1]
Four	1 [0.6]

[a]Based on the physician's global assessment[16]: according to the Montreal classification, IQR: interquartile range, IBD: inflammatory bowel disease, UC: ulcerative colitis, CD: Crohn's disease,*one missing data;**13 missing data; ***four missing data.
[b]Including 18 axial spondyloarthropathies, 13 peripheral arthritis, six erythema nodosum, two pyoderma gangrenosum, two glomerulonephritis, two uveitis, one episcleritis, one oral aphthous ulcers and one purpura.

Table 2. Dermatological characteristics of the study population at inclusion

Characteristic	*n* = 181
Personal history of dermatological diseases, *n* [%]	
None	147 [81]
Psoriasis	11 [6.1]
Atopy	10 [5.5]
Immune-mediated diseases	1 [0.6]
Others	12 [6.6]
Familial history of dermatological diseases*, *n* [%]	
None	153 [94]
Psoriasis	6 [3.7]
Atopic dermatitis	3 [1.9]
Median interval from start of anti-TNF to onset of skin lesions, months [IQR]	8.9 [2.0–26.1]
Median interval from onset of skin lesions to anti-TNF discontinuation, months [IQR]	6.0 [1.9–14]
Location of skin lesions, *n* [%]	
Palmoplantar	61 [34]
Face	47 [26]
Scalp	84 [46]
Trunk	71 [39]
Skin folds	58 [32]
Genitals	30 [17]
Limbs	70 [39]
Type of skin lesions, *n* [%]	
Psoriasiform**	105 [58]
Eczematiform	38 [21]
Xerosis	15 [8.3]
Vasculitis	6 [3.3]
Others[a]	29 [16]
Prior management of skin lesions, *n* [%]	
None	16 [8.8]
Topical medication only	122 [67]
Systemic medication only	12 [6.6]
Both topical and systemic medications	31 [17]
Skin biopsy, *n* [%]	36 [20]

*Nineteen missing data; **including palmoplantar pustulosis.
[a]Including 12 cutaneous infections, three alopecia areata, three urticaria, two Sweet's syndrome, one pseudo-bullous dermatosis, one hidradenitis suppurativa, one sarcoidosis, one pyoderma gangrenosum, one erythroderma, four unknown.

The most commonly involved areas were the scalp [46%], trunk [39%], limbs [39%], palmoplantar region [34%] and skin folds [32%]. Dermatological management of induced skin lesions before anti-TNF discontinuation included no medication in 16 [9%] patients, topical medication only in 122 [67%] patients, systemic medication only in 12 [7%] patients, and both topical and systemic medications in 31 [17%] patients. A skin biopsy was performed in 36 [20%] patients.

Compared to patients with inactive IBD at inclusion, patients with active IBD were less naive to biological treatment [49% vs. 76%; $p = 0.01$], more often had a familial history of dermatological diseases [17% vs. 3%; $p = 0.01$], had a shorter interval between onset of lesions and anti-TNF discontinuation (2 [0.9–10.0] months vs. 6.5 [2.0-15.1] months; $p = 0.01$) and had more psoriasiform lesion subtype [79% vs. 53%; $p = 0.01$]. There was no other significant difference between the two groups.

3.2. Follow-up period

The median dermatological follow-up period was 30.0 [11.9–50.9] months and the median digestive follow-up period was 19.1 [8.5–35.5] months. Among the population as a whole, 131 patients started a biological agent during follow-up with a median interval between anti-TNF discontinuation and start of a new biological agent of 6 [3–13] weeks, including 99 [55%] patients who started a new agent within the first 3 months. In this subgroup, the new agent was ustekinumab in 74 [75%] patients, another anti-TNF agent in 13 [13%] [four infliximab, nine adalimumab], vedolizumab in ten [10%], tofacitinib in one [1%] and an investigational drug in one [1%].

3.3. Dermatological outcome

3.3.1. Remission of induced skin lesions in the overall population

Remission of severe anti-TNF-induced skin lesions occurred in 110/178 [62%—three missing data] patients with a median time from inclusion to remission of 8.0 [IQR: 6.8–11.0] months. The cumulative probability of remission of induced skin lesions at 1, 2 and 3 years was respectively 61.6, 67.8 and 73.1%.

3.3.2. Remission of induced skin lesions according to early introduction of biological agent

Among the 110 patients who achieved remission of anti-TNF-induced skin lesions, 60 [55%] were switched early to a new biological agent. The median time from anti-TNF discontinuation to remission was 7.0 [6.0–11.0] months in the early switch group and 9.0 [7.7–27.7] months in the other group. The cumulative probability of remission of anti-TNF-induced skin lesions at 1, 2 and 3 years was respectively 65.4, 75.0 and 81.7% in the early switch group and 57.9, 61.1 and 66.2% in the other group [$p = 0.11$] [Figure 1].

When performing a sensitivity analysis in the early switch group considering only the 74 patients treated with ustekinumab compared to the patients without early switch, the difference between the two groups in terms of cumulative probability of dermatological remission was not significant [$p = 0.06$].

3.3.3. Factors associated with remission of induced skin lesions in univariate and multivariate analysis

In univariate analysis, remission of anti-TNF-induced skin lesions was associated with scalp location (HR 0.57 [95% CI 0.39–0.84], $p < 0.01$), and the non-psoriasiform non-eczematiform lesion subtype (HR 2.28 [95% CI 1.44–3.61], $p < 0.01$; Table 3). Age, gender, smoking status, body mass index [BMI], type of IBD, disease activity, type of anti-TNF and early switch to another biological agent were not associated with remission of induced skin lesions. In multivariate analysis, scalp location (HR 0.64 [95% CI 0.43–0.94], $p = 0.02$), non-psoriasiform non-eczematiform lesion subtype

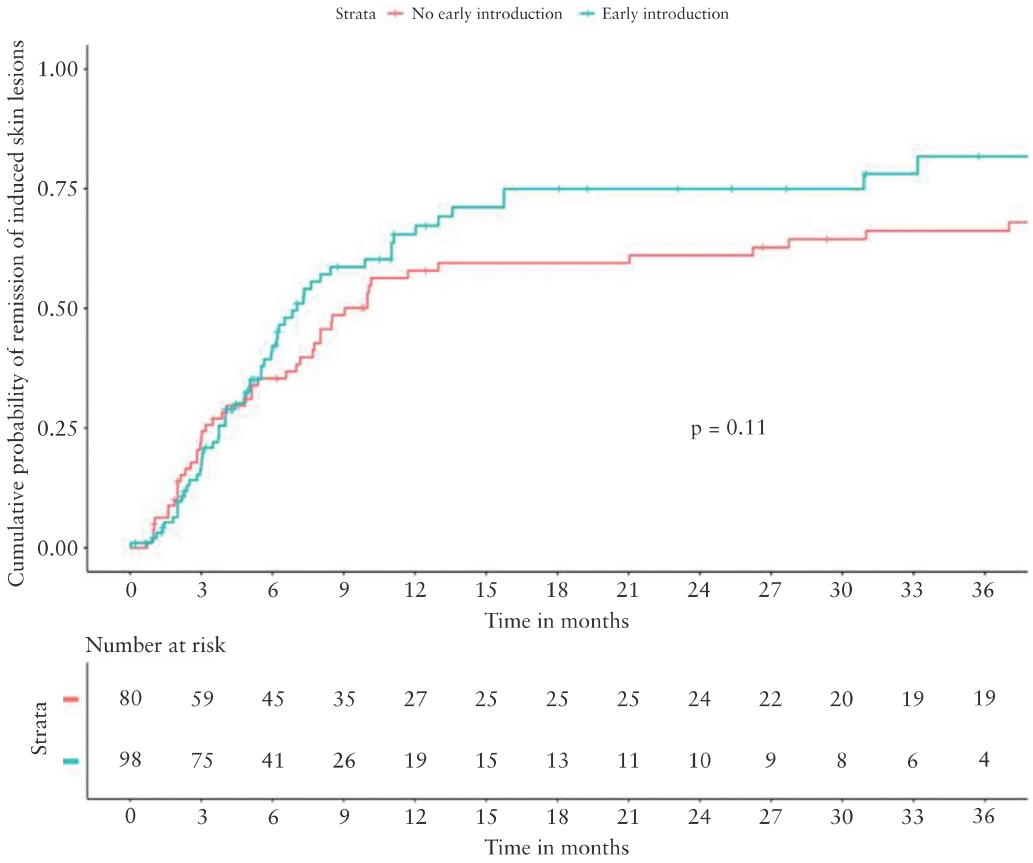

Figure 1. Cumulative probability of remission of anti-TNF-induced skin lesions in patients who started early with a new biological agent or not [*n* = 178].

Table 3. Factors associated with dermatological remission in the overall population [*n* = 178]

	Univariate analysis		Multivariate analysis	
	HR [95% CI]	*p*-value	HR [95% CI]	*p*-value
Female gender	—	0.4	—	—
Age ≥ 29 years	—	0.073	—	0.063
BMI ≥ 25 kg/m^2	—	0.6	—	—
Crohn's disease	—	0.3	—	—
Smoking status	—	0.3	—	—
Anti-TNF ADA or GOL	—	0.084	—	0.3
Median interval from start of anti-TNF to onset of lesions ≥ 9 months	—	0.2	—	—
Median interval from onset of lesions to anti-TNF discontinuation ≥ 6 months	—	0.10	—	—
Active IBD	—	0.5	—	—
Personal history of dermatological disease	—	0.2	—	—
Familial history of dermatological disease	0.19 [0.03–1.39]	0.028	—	—
Scalp location	0.57 [0.39–0.84]	0.004	0.64 [0.43–0.94]	0.022
Other type of lesions	2.28 [1.44–3.61]	0.001	2.26 [1.41–3.61]	<0.001
Systemic medication use before anti-TNF discontinuation	—	0.4	—	—
Early introduction of biological agent	—	0.11	1.64 [1.10–2.45]	0.016

BMI: body mass index, ADA: adalimumab, GOL: golimumab, IBD: inflammatory bowel disease, HR: hazard ratio, 95% CI: 95% confidence interval.

(HR 2.26 [95% CI 1.41–3.61], $p < 0.01$) and early switch to another biological agent (HR 1.64 [95% CI 1.10–2.45], $p = 0.02$) were independently associated with remission of anti-TNF-induced skin lesions.

3.4. IBD relapse in patients with inactive disease at anti-TNF discontinuation

Among the 181 patients included, 148 [82%] had inactive IBD at inclusion. Seventy-five [51%] started a new IBD treatment

within the 3 months following anti-TNF discontinuation, with a median interval of 1.2 [0.6–1.9] months: ustekinumab in 61 [82%], another anti-TNF in seven [9%] [two infliximab, five adalimumab], vedolizumab in six [8%] and tofacitinib in one [1%]. Among the 73 [49%] patients who did not switch early to a new biological agent, 26 [36%] patients started a drug afterward [11 ustekinumab, nine infliximab, three adalimumab, one vedolizumab and two others] and 47 did not take another biological until the end of the follow-up period. Concerning immunosuppressants, 32 [22%] had immunosuppressive therapies [17 thiopurine, 13 methotrexate, two cyclosporine], 15 of which had been introduced within 3 months of inclusion with a median time of 0.8 [0.2–1.6] months.

There was no significant difference in the baseline characteristics between the early switch group and the other group, except for a greater proportion of limb location of induced skin lesions [51% vs. 27%; $p < 0.01$] [Supplementary Table 1].

Among the 148 patients with inactive IBD at inclusion, IBD relapse occurred in 75/147 [51%; one missing data] patients with a median time from anti-TNF discontinuation to IBD relapse of 26.0 [IQR: 22.8–39.1] months. Rates of IBD relapse-free survival at 1, 2 and 3 years were respectively 71.5, 52.0 and 40.5%.

3.4.1. IBD relapse according to early introduction of biological agent

Among the 75 patients who relapsed, 24 [32%] were switched early to a new biological agent. The median time from anti-TNF discontinuation to IBD relapse was 39.1 (31.2 to not applicable [NA]) months in the early switch group and 18.0 [11.7–25.0] months in the other group. Rates of survival without IBD relapse at 1, 2 and 3 years were significantly lower in patients switched early: 85.8, 71.0 and 52.7% vs. 59.3, 37.4 and 30.0% in the other group [$p = 0.02$] [Figure 2].

3.4.2. IBD relapse according to IBD subtype

The median time from inclusion to IBD relapse was 29.5 [23.11–40.9] months in CD patients and 14.9 [5.03–NA] months in UC patients [$p = 0.01$]. Rates of survival without IBD relapse at 1 and 2 years were respectively 72.9 and 55.8% in CD patients and 61.4 and 12.3% in UC patients [$p = 0.01$] [Supplementary Figure 1].

3.4.3. Factors associated with IBD relapse in CD patients with inactive IBD at inclusion in univariate and multivariate analysis

In univariate analysis, absence of IBD relapse in CD patients with inactive disease at inclusion was associated with early switch to a new biological agent (HR 0.49 [95% CI 0.29–0.83], $p = 0.01$; Table 4). Age, gender, smoking status, BMI and type of anti-TNF were not associated with IBD relapse. In multivariate analysis, early switch (HR 0.51 [95% CI 0.29–0.90], $p = 0.017$) and female gender (HR 2.24 [95% CI 1.08–4.65], $p = 0.019$) were independently associated with absence of IBD relapse.

3.5. Remission of induced skin lesions with maintenance of IBD remission

At the end of the follow-up, 51/181 [28%] patients achieved remission of severe anti-TNF-induced skin lesions without

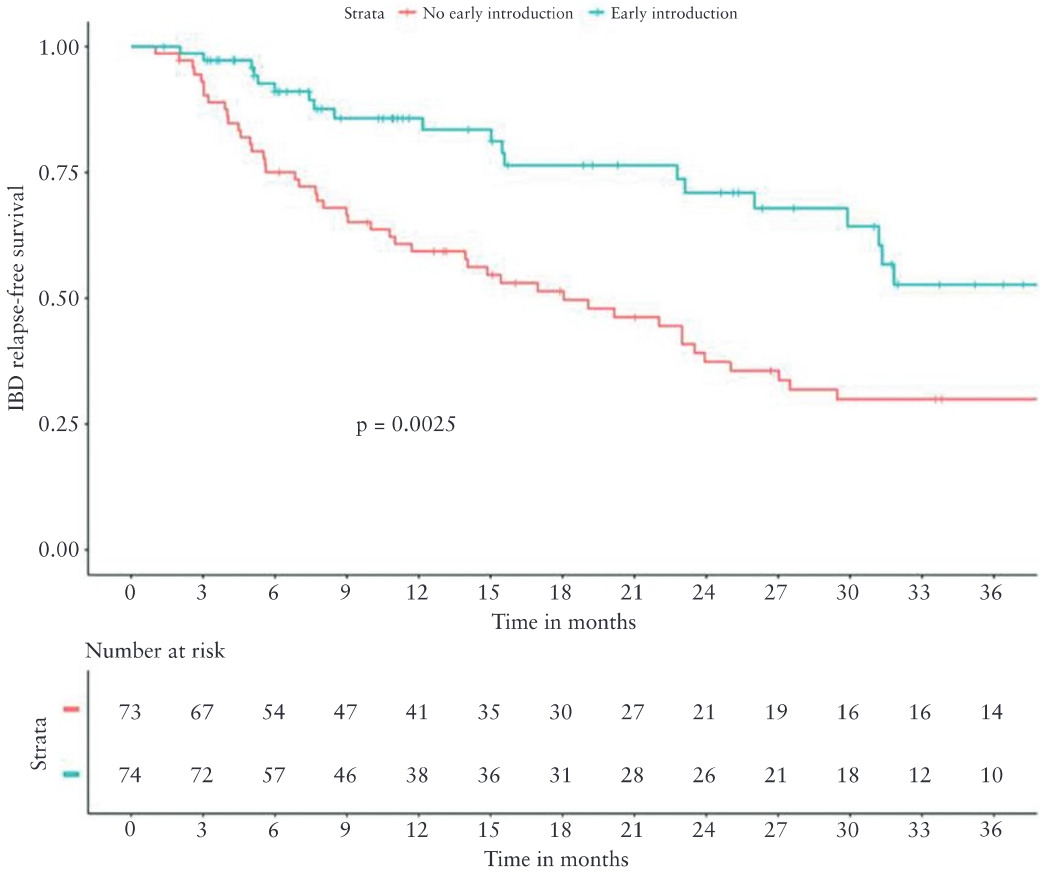

Figure 2. Survival without inflammatory bowel disease relapse in patients who started early with a new biological agent or not [$n = 147$].

Table 4. Factors associated with IBD relapse in patients with inactive Crohn's disease at inclusion [*n* = 130]

	Univariate analysis		Multivariate analysis	
	HR[95% CI]	*p*-value	HR[95% CI]	*p*-value
Female gender	—	0.067	2.24 [1.08–4.65]	0.019
Age ≥ 29 years	—	0.13	—	—
BMI ≥25 kg/m^2	—	0.2	—	0.3
Previous surgery	—	0.2	—	0.058
Ileal location	—	0.089	—	0.2
Perianal disease	—	0.2	—	0.3
Extra intestinal manifestation	—	0.8	—	—
Never or former smokers	—	0.3	—	—
Disease duration ≥7 years	—	0.9	—	—
No previous biological agent	—	0.3	—	—
Anti-TNF duration ≥22 months	—	0.6	—	—
Anti-TNF ADA or GOL	—	>0.9	—	—
Early introduction of biological agent	0.49 [0.29–0.83]	0.007	0.51 [0.29–0.90]	0.017

BMI: body mass index, ADA: adalimumab, GOL: golimumab, HR: hazard ratio, 95% CI: 95% confidence interval.

IBD relapse, including 34 [67%] who switched early to a new biological agent. Among the 51 patients achieving remission of induced skin lesions without IBD relapse, 29 [57%] received ustekinumab, six [12%] received an anti-TNF agent [one infliximab, five adalimumab], two [4%] received vedolizumab and 14 [27%] received no new biological agent during the follow-up period.

4. Discussion

In the largest cohort to date having investigated dermatological and digestive outcomes after anti-TNF discontinuation due to severe induced skin lesions in patients with IBD, approximately two-thirds of patients achieved remission of induced skin lesions within the year following anti-TNF discontinuation. In patients who switched early to a new biological agent after anti-TNF discontinuation, the cumulative probability of dermatological healing was higher and IBD relapse was less frequent.

The present study population displays characteristics consistent with those previously observed in the literature. Severe anti-TNF-induced skin lesions were more frequent in women,[3,8,9] patients with CD,[4,7,9,17] and active or former smokers.[9,10] Moreover, at anti-TNF discontinuation, IBD was inactive in 82% of patients, which highlights that development of severe anti-TNF-induced skin lesions is not correlated with intestinal activity, as observed in the Nancy cohort.[3] We also observed that the median time between the start of anti-TNF and onset of induced skin lesions was 8.9 [IQR: 2.0–26.1] months. This wide range illustrates that the development of skin lesions is unpredictable, and may appear as soon as at induction or after several months of treatment.[4,18] Regarding severe anti-TNF-induced skin lesions, psoriasiform and eczematiform were the most frequent, which is consistent with other IBD cohorts.[4,5,9,12,19,20] IBD patients are more prone to develop severe psoriasiform lesions with predominant scalp involvement than those having other inflammatory disorders.[20,21]

Early switch to a new biological agent, especially ustekinumab [which has demonstrated its efficacy in psoriasis], was considered to be helpful for managing patients with severe anti-TNF-induced skin lesions.[9,11,12,22] In the present cohort, in contrast to the study of Rahier et al.,[4] remission of anti-TNF-induced skin lesions was achieved in only two-thirds of patients within the year following anti-TNF withdrawal, suggesting autonomization of this phenomenon despite removing the causative agent. However, we observed an independent beneficial impact of an early switch to a new biological therapy, especially ustekinumab, on healing of skin lesions as compared to anti-TNF discontinuation alone. The benefit of switching early was more visible in the Kaplan–Meier curve after 6 months and in multivariate analysis.

Concerning IBD course among patients with inactive disease at inclusion, we observed an overall IBD relapse rate of 51% after anti-TNF discontinuation that was comparable with reports from other studies.[23–25] Importantly, survival without IBD relapse was significantly higher when a new biological agent was started early. This finding supports early switch especially in patients with a high risk of relapse. In our study, we only identified female gender as a predictive factor of CD relapse. Other risk factors of disease relapse in this subset of patients have been identified in previous studies[26,27] such as younger age at diagnosis, treatment with adalimumab, stricturing CD, perianal disease, long disease duration and absence of concomitant immunosuppressants. These predictors could be useful to target those patients who might benefit the most from the early introduction of a biological agent after anti-TNF discontinuation.

Our results also demonstrate that anti-TNF discontinuation because of severe induced skin lesions represents a poor event for IBD patients. Indeed, at the end of the follow-up, less than one-third of patients achieved dermatological remission without IBD relapse. This poor outcome suggests that these patients should be managed closely by a multidisciplinary team of gastroenterologists and specialized dermatologists, including psychological support if needed.

We acknowledge several limitations of the present study. Due to its retrospective design, some misclassification of anti-TNF-induced skin lesions may have occurred, given the wide variability in their description. Moreover, dermatological and

digestive evaluations were mainly based on physician clinical assessment, and not on clinical scores, which are more reproducible. To overcome this limitation, we chose robust endpoints such as remission of induced skin lesions and IBD relapse defined by any significant event reflecting disease activity [new systemic treatment, hospitalization or surgery]. Finally, given the limited number of patients treated with each biological agent and the multiple approaches reflecting the difficult management of patients who have to stop anti-TNF due to severe induced skin lesions, we could not compare all treatment strategies. Our study also has several strengths. This was a multicentre study, including patients from 13 participating tertiary centres with a long duration of the follow-up period, allowing better observation of long-term dermatological and digestive outcomes after anti-TNF discontinuation.

In conclusion, early switch to a new biological agent seems to have a beneficial impact on the healing of severe anti-TNF-induced skin lesions and significantly reduces the risk of IBD relapse. Given the poor outcomes of these patients, management of IBD patients after anti-TNF discontinuation for induced skin lesions should be multidisciplinary, proactive and closely monitored.

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Conflicts of Interest

CC, CR, LV and OD declare no conflict of interest. XT declares consulting fees from Abbvie, Janssen, Tillotts, Pfizer, Takeda, Gilead as well as lecture fees and travel accommodations from Abbvie, Janssen, Ferring, Pfizer, Ferring, Tillotts, Takeda and MSD. XT received advisory board fees from Janssen, Takeda and Abbvie. RA declares lecture fees and consultancy fees from Abbvie, MSD, Janssen, Takeda and Pfizer. AA declares consulting fees from Abbvie, Hospira, Janssen, Tillotts, Pfizer, Takeda, Gilead and Biocodex as well as lecture fees and travel accommodations from Abbvie, Janssen, Biocodex, Hospira, Ferring, Pfizer, Ferring, Tillotts, Grifols, Takeda and MSD. AA also received advisory board fees from Gilead, Takeda and Abbvie. MF declares lecture fees and consultancy fees from Abbvie, Ferring, MSD, Janssen, Takeda, Gilead, Celgene, Boehringer, Amgen, Biogen, Sandoz, Celltrion, Galapagos, Lilly, Arena, Pfizer and Tillots. LPB declares personal fees from AbbVie, Janssen, Genentech, Ferring, Tillots, Pharmacosmos, Celltrion, Takeda, Boerhinger Ingelheim, Pfizer, Index Pharmaceuticals, Sandoz, Celgene, Biogen, Samsung Bioepis, Alma, Sterna, Nestle, Enterome, Allergan, MSD, Roche, Arena, Gilead, Hikma, Amgen, BMS, Vifor, Norgine; Mylan, Lilly, Fresenius Kabi, Oppilan Pharma, Sublimity Therapeutics, Applied Molecular Transport, OSE Immunotherapeutics, Enthera and Theravance; grants from Abbvie, MSD and Takeda; stock options: CTMA. GB declares conflicts of interest with Abbvie, Amgen, Biogen, Ferring, Janssen, MSD, Mylan, Pfizer, Sandoz, Takeda, Tillots, Fresinius Kabi and Celtrion. SN declares lecture fees and consultancy fees with Abbvie, Takeda, Pfizer, Novartis, Janssen, Tillots, Mylan, MSD, Amgen, Biogen and HAC Pharma. LC declares conflicts of interest with Abbvie, Amgen, Janssen, Pfizer, Takeda, Tillots and Celtrion. XR declares lecture fees and consultancy fees from Abbvie, Takeda, Pfizer, Gilead, Janssen, Tillots, Sandoz, MSD, Amgen, Biogen and Theradiag. MBB declares lecture fees from Abbvie, Janssen and Takeda. PR declares counselling fees from Amgen and Janssen. DL declares counselling, board, transport or personal fees from Abbvie, Biogaran, Biogen, Celgene, Celltrion, Ferring, Galapagos, HAC-pharma, Janssen, MSD, Novartis, Pfizer, Prometheus, Roche, Takeda, Theradiag and Tillots.

Author Contributions

CC, DL: conception, design, acquisition, analysis and interpretation of data, drafting. PR: analysis and interpretation of data, drafting. XT, CR, AA, MF, LV, LPB, GB, OD, SN, LC, XR and MBB: acquisition of data, critical revision of the manuscript for important intellectual content. All: final approval of the version to be submitted.

Data Availability

The data underlying this article are available in the article and in its online supplementary material.

Supplementary Data

Supplementary data are available online at *ECCO-JCC* online.

References

1. Fidder H, Schnitzler F, Ferrante M, *et al*. Long-term safety of infliximab for the treatment of inflammatory bowel disease: a single-centre cohort study. *Gut* 2009;**58**:501–8.
2. Peyrin–Biroulet L, Deltenre P, de Suray N, *et al*. Efficacy and safety of tumor necrosis factor antagonists in Crohn's disease: meta-analysis of placebo-controlled trials. *Clin Gastroenterol Hepatol* 2008;**6**:644–53.
3. Fréling E, Baumann C, Cuny JF, *et al*. Cumulative incidence of, risk factors for, and outcome of dermatological complications of anti-TNF therapy in inflammatory bowel disease: a 14-year experience. *Am J Gastroenterol* 2015;**110**:1186–96.
4. Rahier J, Buche S, Peyrin-Biroulet L *et al*. Severe skin lesions cause patients with inflammatory bowel disease to discontinue anti-tumor necrosis factor therapy. *Clin Gastroenterol Hepatol* 2010;**8**:1048–1055.
5. Cleynen I, Van Moerkercke W, Billiet T, *et al*. Characteristics of skin lesions associated with anti-tumor necrosis factor therapy in patients with inflammatory bowel disease: a cohort study. *Ann Intern Med* 2016;**164**:10–22.
6. Cleynen I, Vermeire S. Paradoxical inflammation induced by anti-TNF agents in patients with IBD. *Nat Rev Gastroenterol Hepatol* 2012;**9**:496–503.
7. Cullen G, Kroshinsky D, Cheifetz AS, Korzenik JR. Psoriasis associated with anti-tumour necrosis factor therapy in inflammatory bowel disease: a new series and a review of 120 cases from the literature. *Aliment Pharmacol Ther* 2011;**34**:1318–27.
8. Torres J, Buche S, Delaporte E, Colombel JF. Skin side effects of inflammatory bowel disease therapy. *Inflamm Bowel Dis* 2013;**19**:1086–98.
9. Tillack C, Ehmann LM, Friedrich M, *et al*. Anti-TNF antibody-induced psoriasiform skin lesions in patients with inflammatory bowel disease are characterised by interferon-γ-expressing Th1 cells and IL-17A/IL-22-expressing Th17 cells and respond to anti-IL-12/IL-23 antibody treatment. *Gut* 2014;**63**:567–77.
10. Andrade P, Lopes S, Gaspar R, Nunes A, Magina S, Macedo G. Anti-tumor necrosis factor-α-induced dermatological complications in a large cohort of inflammatory bowel disease patients. *Dig Dis Sci* 2018;**63**:746–54.

11. Guerra I, Pérez-Jeldres T, Iborra M, *et al.*; Spanish GETECCU group (ENEIDA project). Incidence, clinical characteristics, and management of psoriasis induced by anti-TNF therapy in patients with inflammatory bowel disease: a nationwide cohort study. *Inflamm Bowel Dis* 2016;**22**:894–901.
12. Ezzedine K, Visseaux L, Cadiot G, Brixi H, Bernard P, Reguiai Z. Ustekinumab for skin reactions associated with anti-tumor necrosis factor-α agents in patients with inflammatory bowel diseases: a single-center retrospective study. *J Dermatol* 2019;**46**:322–7.
13. Pijls PA, Gilissen LP. Vedolizumab is an effective alternative in inflammatory bowel disease patients with anti-TNF-alpha therapy-induced dermatological side effects. *Dig Liver Dis* 2016;**48**:1391–3.
14. Maaser C, Sturm A, Vavricka SR, *et al.*; European Crohn's and Colitis Organisation [ECCO] and the European Society of Gastrointestinal and Abdominal Radiology [ESGAR]. ECCO-ESGAR guideline for diagnostic assessment in IBD part 1: initial diagnosis, monitoring of known IBD, detection of complications. *J Crohns Colitis* 2019;**13**:144–64.
15. Harbord M, Annese V, Vavricka SR, *et al.*; European Crohn's and Colitis Organisation. The First European evidence-based consensus on extra-intestinal manifestations in inflammatory bowel disease. *J Crohns Colitis* 2016;**10**:239–54.
16. Satsangi J, Silverberg MS, Vermeire S, Colombel JF. The Montreal classification of inflammatory bowel disease: controversies, consensus, and implications. *Gut* 2006;**55**:749–53.
17. Afzali A, Wheat CL, Hu JK, Olerud JE, Lee SD. The association of psoriasiform rash with anti-tumor necrosis factor [anti-TNF] therapy in inflammatory bowel disease: a single academic centre case series. *J Crohns Colitis* 2014;**8**:480–8.
18. Collamer AN, Battafarano DF. Psoriatic skin lesions induced by tumor necrosis factor antagonist therapy: clinical features and possible immunopathogenesis. *Semin Arthritis Rheum* 2010;**40**:233–40.
19. Lee HH, Song IH, Friedrich M, *et al.* Cutaneous side-effects in patients with rheumatic diseases during application of tumour necrosis factor-alpha antagonists. *Br J Dermatol* 2007;**156**:486–91.
20. Pugliese D, Guidi L, Ferraro PM, *et al.* Paradoxical psoriasis in a large cohort of patients with inflammatory bowel disease receiving treatment with anti-TNF alpha: 5-year follow-up study. *Aliment Pharmacol Ther* 2015;**42**:880–8.
21. Darrigade AS, Milpied B, Truchetet ME, *et al.* Pattern and severity of psoriasiform eruptions in patients with inflammatory bowel diseases, arthritis or skin inflammatory disorders treated with TNF-alpha inhibitors. *Acta Derm Venereol* 2017;**97**:731–4.
22. Pugliese D, Daperno M, Fiorino G, *et al.* Real-life effectiveness of ustekinumab in inflammatory bowel disease patients with concomitant psoriasis or psoriatic arthritis: an IG-IBD study. *Dig Liver Dis* 2019;**51**:972–7.
23. Bots SJ, Kuin S, Ponsioen CY, *et al.* Relapse rates and predictors for relapse in a real-life cohort of IBD patients after discontinuation of anti-TNF therapy. *Scand J Gastroenterol* 2019;**54**:281–8.
24. Gisbert JP, Marín AC, Chaparro M. The risk of relapse after anti-TNF discontinuation in inflammatory bowel disease: systematic review and meta-analysis. *Am J Gastroenterol* 2016;**111**:632–47.
25. Casanova MJ, Chaparro M, Nantes Ó, *et al.*; EVODIS Study Group. Clinical outcome after anti-tumour necrosis factor therapy discontinuation in 1000 patients with inflammatory bowel disease: the EVODIS long-term study. *Aliment Pharmacol Ther* 2021;**53**:1277–88.
26. Gisbert JP, Marín AC, Chaparro M. Systematic review: factors associated with relapse of inflammatory bowel disease after discontinuation of anti-TNF therapy. *Aliment Pharmacol Ther* 2015;**42**:391–405.
27. Pauwels RWM, van der Woude CJ, Nieboer D, *et al.* Prediction of relapse after anti-tumor necrosis factor cessation in Crohn's disease: individual participant data meta-analysis of 1317 patients from 14 studies. *Clin Gastroenterol Hepatol* 2021. Doi: 10.1016/j.cgh.2021.03.037