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Alimentary Tract

Outcome in ulcerative colitis after switch from adalimumab/golimumab to infliximab: A multicenter retrospective study

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ABSTRACT

Background: Anti-TNF therapies infliximab (IFX), adalimumab (ADA), and golimumab (GOL) are approved for treating moderate to severe ulcerative colitis (UC). In UC, only the switch from IFX to ADA has been investigated, reaching no more than 10–43% remission rates at 12 months.
Aim: Of the present study was to investigate disease outcome after a switch from subcutaneous (SC) agents to the intravenous (IV) agent (IFX).
Methods: In this retrospective multicentre study, we analysed the charts of UC patients unresponsive/intolerant or with secondary loss of response (LOR) to ADA or GOL who were switched to IFX. We evaluated clinical response and remission together with adverse events at 3, 6, and 12 months follow-up.
Results: Seventy-six patients were included; 38 patients started ADA and 38 started GOL for a mean therapy duration of 6 ± 6 months. Indications for switch were adverse events in 3%, primary failure in 79%, and LOR in 18% of patients. Clinical remission was reached by 47%, 50%, and 77% of patients, respectively. Patients that switched for LOR did numerically, but not statistically, better than patients who switched for primary failure.
Conclusions: Our data show a superior remission rate in SC to IV anti-TNF switch in UC compared to the IV to SC switch reported in literature.

1. Introduction

The introduction of biological therapies has revolutionized therapeutic strategies in inflammatory bowel diseases (IBD) leading to induction and maintenance of remission, mucosal healing and improvement of quality of life. TNF-alfa blockers are monoclonal antibodies with potent anti-inflammatory effects that block the proinflammatory cascade which triggers the activation and proliferation of T lymphocytes in the bowel. Anti-TNF agents have shown efficacy in both Crohn's disease (CD) and ulcerative colitis (UC), refractory to conventional treatments. Infliximab (IFX), a chimeric IgG1 monoclonal antibody administered intravenously (IV) with weight-based dosing, is effective in inducing and maintaining remission in patients with moderate-to-severe UC [1]. The

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immunogenicity of IFX can lead to the development of antibodies and, consequently, loss of response (LOR) or intolerance [2]. Adalimumab (ADA) and, more recently, golimumab (GOL), are subcutaneous (SC) and fully human monoclonal antibodies that do not have cross-immunogenicity with IFX and are effective and safe in inducing and maintaining remission in UC patients [3]. However, one-third of patients receiving anti-TNFs do not respond to treatment (primary failure), show loss of response (secondary failure) or intolerance. In UC refractory to standard medications treatment choice among available biologic agents may be challenging and switching from a formulation to another is possible. While efficacy and safety of a second anti-TNF after primary/secondary failure or intolerance to a first anti-TNF drug in CD has been reported [4], in UC only the switch from IFX to ADA has been investigated [5–12]. The aim of the present study was to investigate clinical characteristics and disease outcome in UC patients who started with SC anti-TNF (ADA or GOL) and subsequently switched to IV anti-TNF (IFX).

2. Materials and methods

In this retrospective multicentre study (8 referral centres in Italy), we analysed retrospectively the charts of UC patients unresponsive (primary failure, PF) or intolerant or with secondary LOR to ADA or GOL who were switched to IFX. The following data were collected: age and gender, smoker status (current, never, and ex-smokers), age at diagnosis and disease duration from diagnosis to first anti-TNF, extension of disease according to the Montreal classification and severity of disease according to the endoscopic Mayo subscore before the first anti-TNF and during follow-up after switch. In addition, data on previous SC biologic therapy (ADA or GOL) were collected including indication for biologic therapy, treatment duration, concomitant immunomodulators (IMM) and reason of withdrawal of the first anti-TNF and switch to IFX. Dose escalation of ADA after LOR was defined as a decrease in the interval of administration from every other week (EOW) to every week. A similar dose escalation of GOL is not permitted by the national Medicines Agency (AIFA) in Italy. Dose escalation of IFX was defined either as an increase in IFX dosing or a shortening of IFX infusion interval.

LOR was defined as worsening of patient's symptoms together with serologic evidence of inflammation and/or endoscopic findings. Clinical remission was defined as partial Mayo score ≤ 1 without additional steroids and normalized CRP. Clinical response was defined as a decrease in the Mayo score of 3 or more points from baseline, along with a reduction of the rectal bleeding subscore of at least 1 point, but without achieving remission. Mucosal healing was defined as Mayo endoscopic subscore ≤ 1. In the follow-up period, we evaluated clinical response and remission together with adverse events at 3, 6, and 12 months follow-up. We also collected data on endoscopy after switch where available, and possible therapy optimization by adding IMM. The study was approved by the Ethics Committee of the coordinating centre (Messina; prot. n. 34/18) and, subsequently, in all the participating centres.

2.1. Statistics

Data were collected anonymously in a validated eCRF. Mean values ± SD (median and range) were calculated for continuous variables and comparison was carried out with the t-test for unpaired data. Percentages were calculated on the total of patients who completed follow-up at the different time points, excluding patients that were colectomized or lost to follow-up. Categorical variables were expressed as percentages, and comparison was carried out on the number of patients reaching the time-points 3, 6, and 12 months, with the chi-square test when appropriate. Multiple logistic regression models were employed to identify factors associated with remission at 12 months after switch.

Table 1
Patients' baseline characteristics and anti-TNF treatment details.

Gender	
Male; n (%)	47 (61)
Female; n (%)	29 (39)
Smoking history	
Active; n (%)	1 (2)
Ex-smokers; n (%)	17 (22)
Never smokers; n (%)	58 (76)
Age at diagnosis; median (range)	31 (10–76)
Age at first SC biologic; median (range)	39.5 (16–76)
Duration of disease from diagnosis to IFX; months, median (range)	36 (1–408)
Extension (Montreal Classification)	
E1; n (%)	2 (3)
E2; n (%)	33 (43)
E3; n (%)	41 (54)
First anti-TNF	
Adalimumab; n (%)	38 (50)
Golimumab; n (%)	38 (50)
Duration of first anti-TNF; months	
Adalimumab; median (range)	6 (1–36)
Golimumab; median (range)	5 (1–13)
Optimization of first anti-TNF	
Interval shortening; n (%)	19 (25)
Concomitant immunosuppressors; n (%)	16 (21)
Reason for discontinuation of SC anti-TNF	
Adverse events; n (%)	2 (3)
Primary failure; n (%)	60 (79)
Loss of response; n (%)	14 (18)
Second anti-TNF	
Infliximab originator; n (%)	20 (26)
Infliximab biosimilar (CTP-13); n (%)	56 (74)
Optimization of second anti-TNF	
Total; n (%)	27 (34)
Interval shortening; n (%)	11 (41)
Dose increase; n (%)	5 (18)
Interval shortening + dose increase; n (%)	10 (37)
Adding immunosuppressors; n (%)	1 (4)

3. Results

Seventy-six patients were identified and included in the study (males 47, mean age 46 yrs ± 16). Patient baseline characteristics are summarized in Table 1.

The choice of the biological SC agent was determined by patient's preference in 19 patients, work reasons or distance from the gastrointestinal (GI) centre in 39 patients, and 18 patients came from clinical post-marketing observational studies (data not available for two patients). These latter observational studies were open-labelled studies and the choice of treatment depended only by the prescribing physician according to the prescription status and indication (in Italy: moderate to severe UC in patients non responders or intolerant to immunomodulators). In these observational studies, decisions on treatment optimization, persistence, or interruption depend only on the physician. Treatment duration with ADA as the first SC agent was significantly longer ($p < 0.002$) in patients that switched for LOR compared with PF (Table 2). Originator Remicade or biosimilar CT-P13 were administered to 20 and 56 patients, respectively.

Data for analysis were available from all 76 patients at 3 months, from 59 patients at 6 months, and from 46 patients at 12 months. At 3 months, the overall clinical response was reached in 24/76 (32%) with clinical remission in 29/76 (38%) patients. At 6 months, 10 patients had stopped for treatment failure, 1 patient because of an infusion reaction, and 3 patients did not return to follow-up visits and thus were excluded from further analysis together

Table 2
comparison of variables between the different groups (based on the reason for switch); PF = primary failure, AE = adverse events; LOR = loss of response; t-test for unpaired data for continuous variables (PF vs. LOR); chi-square for categorical variables over all three groups; *chi-square test over groups PF vs. LOR.

	PF (n = 60)	AEs (n = 2)	LOR (n = 14)	p-Value
Age at diagnosis; median (range)	31 (10–76)	46 (35–57)	28 (13–51)	0.212
Age at first SC biologic; median (range)	41 (17–76)	51 (38–64)	35 (19–54)	0.173
Duration of disease from diagnosis to IFX; n(%)				
<18 months	19 (32)	2 (100)	5 (36)	0.133
>18 months	41 (68)	0	9 (64)	
Extension (Montreal Classification)				
E1; n(%)	2 (3)	0	0	
E2; n(%)	24 (40)	2 (100)	7 (50)	0.476
E3; n(%)	34 (57)	0	7 (50)	
First anti-TNF				
Adalimumab; n (%)	26 (43)	1 (50)	11 (78)	0.367
Golimumab; n (%)	34 (57)	1 (50)	3 (22)	
Duration of first anti-TNF; months				
Adalimumab; median (range)	(1–22)	1	10 (4–36)	0.002
Golimumab; median (range)	3 (1–13)	2	4 (3.5–4)	0.621
Optimization of first anti-TNF*				
Interval shortening; n(%)	13(22)	0	6(43)	0.734
Concomitant immunosuppressors; n(%)	9(15)	0	4(28)	
Optimization of second anti-TNF*				
Total; n(%)	23 (38)	0	4 (28)	
Dose increase; n(%)	3 (12)	0	2 (50)	
Interval shortening; n(%)	9 (37)	0	2 (50)	0.250
Interval shortening + dose increase; n(%)	10 (46)	0	0	
Adding immunosuppressors; n(%)	1 (4)	0	0	

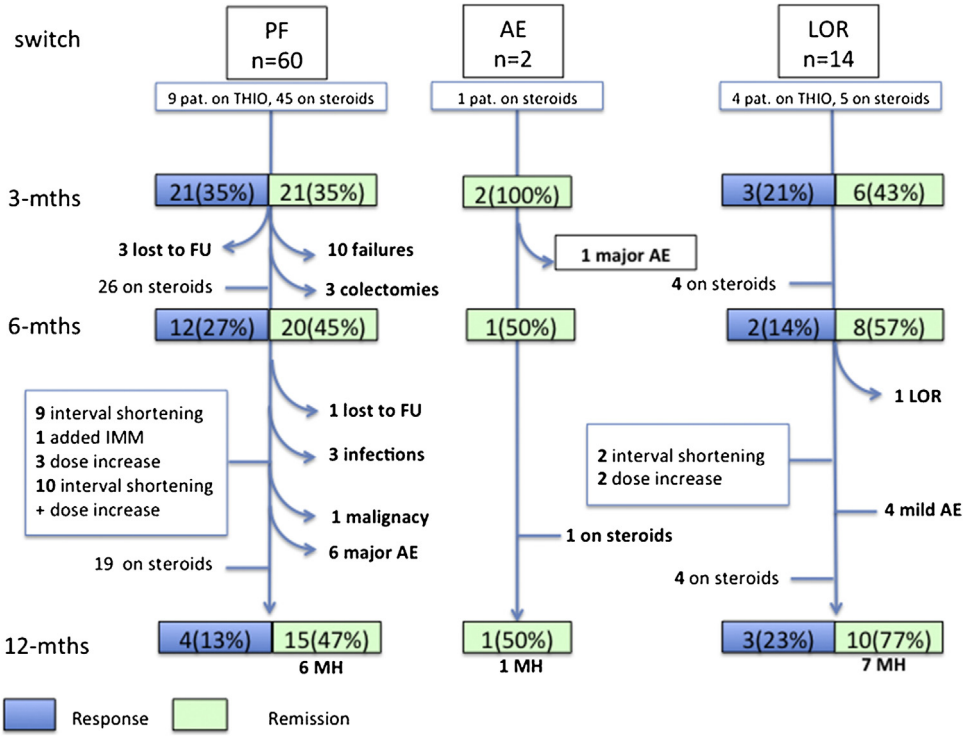

Fig. 1. Flow-chart giving the crude numbers (percentages) in the three groups according to reason for switch; PF = primary failure, AE = adverse events, LOR = loss of response, Pat. = patients, THIO = thiopurines; FU = follow-up; major AE = infusion reactions leading to drug withdrawal; mild AE = patients remained on IV anti-TNF; failures = primary or secondary failures; MH = mucosal healing.

with 3 (4%) patients who underwent proctocolectomy. Data from 59 patients were available for analysis. Clinical response only was achieved in 14/59 (24%) patients, whereas remission was obtained in 29/59 (49%) patients. The 12-month time-point from the initial 76 patients was not reached by an additional 13 patients. Eleven patients stopped because of adverse events (7 infusion reactions, 1 tumour, 3 infections). One patient developed azathioprine-related pancreatitis and was subsequently colectomized; patient not included in Fig. 1) and 1 patient was lost to follow-up. From the 46 assessable patients, 7/46 (15%) patients showed only response and 26/46 (56%) were in clinical remission. In 27 (35%) patients, IV dosing was optimized by increasing dose or reducing dosing interval. At the end of follow-up, 15 patients were on combination therapy with IMM. Endoscopy was available in 34/46 (74%) patients that reached the 12-month time-point and mucosal healing was achieved by 14/46 patients (30%).

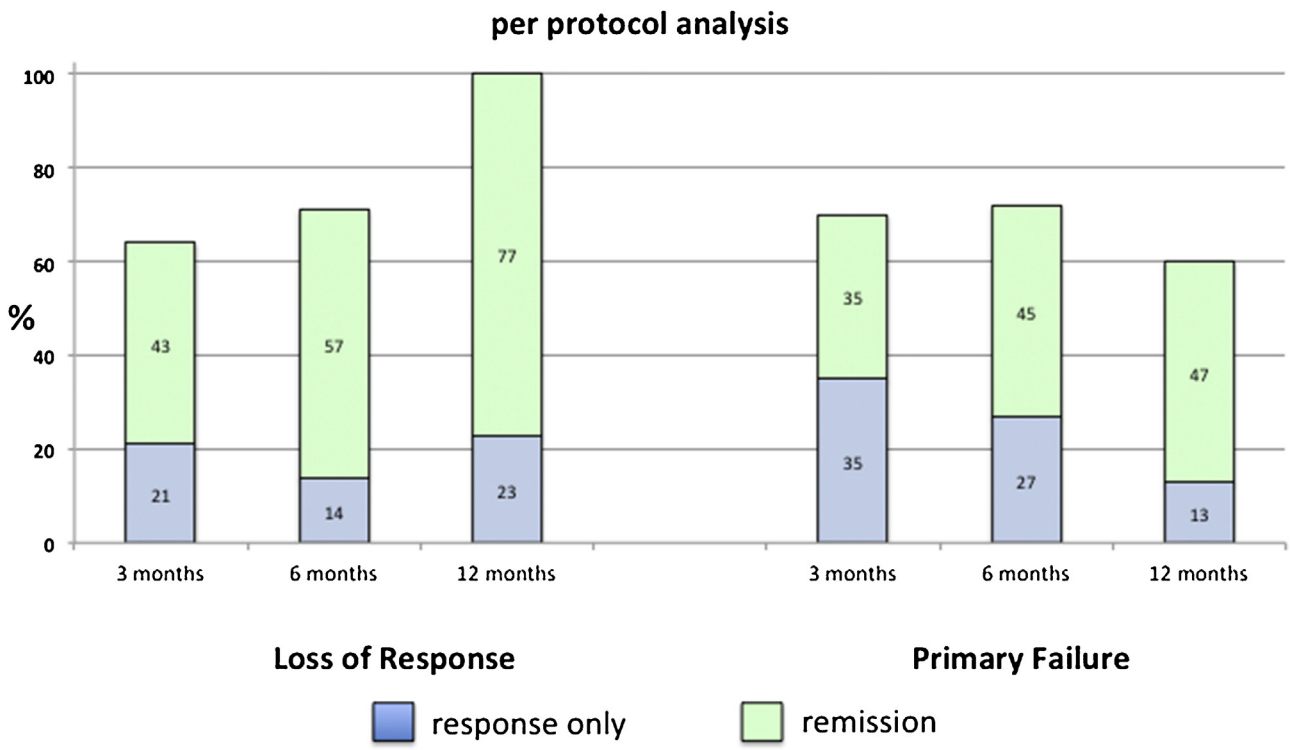

Fig. 2. clinical response and remission to second-line IFX in UC patients in relation to the reason for switch; numbers are given as percentages; per protocol analysis.

3.1. Switch due to primary failure

Stratifying the patients based on reason for switch (Fig. 1), 60/76 (79%) patients discontinued SC anti-TNF treatment for primary failure, 26 were treated with ADA and 34 with GOL. The disease extent was proctitis (E1) in 2 patients, proctosigmoiditis (E2) in 24 patients and subtotal or pancolitis (E3) in 34 patients. Nine were on combination therapy with IMM. Originator Remicade or biosimilar CT-P13 were administered to 12 and 48 patients, respectively. Forty-five patients (75%) were on co- treatment with steroids at the moment of switch. Clinical response at 3, 6, and 12 months was reached in 21/60 (35%), 12/44 (27%) and 4/32 (13%) patients, respectively (Fig. 1) but clinical remission at 3, 6, and 12 months was reached in 21/60 (35%), 20/44 (45%), and 15/32 (47%) (Fig. 2).

At 12 months, 17 patients had stopped IFX due to primary failure or LOR (including 3 colectomies). Six patients stopped treatment because of adverse events and 4 patients did not return to follow-up visits.

3.2. Switch due to loss of response

Fourteen patients discontinued SC anti-TNF treatment for loss of response (Fig. 1), 11 with ADA and 3 with GOL. Disease extension was proctosigmoiditis (E2) in 7 patients and subtotal or pancolitis (E3) in 7 patients. Four were on combo therapy with IMM. Originator or biosimilar CT-P13 was administered equally to 7 patients. Five patients (36%) were in co-treatment with steroids at time of switch. Thirteen patients completed follow-up at 12 months, 1 patient stopped due to secondary failure.

Clinical response at 3, 6, and 12 months was reached in 3/14 (21%), 2/14 (14%) and 3/13 (23%) patients, respectively. Clinical remission at 3, 6, and 12 months was reached in 6/14 (43%), 8/14 (57%), and 10/13 (77%) (Fig. 2). Four patients had mild adverse events without treatment interruption (psoriasis, herpes, arthralgia and pharyngitis).

3.3. Switch due to adverse events

One patient discontinued ADA after one month of treatment for CMV infection and one patient discontinued GOL after two months for skin reaction. Both patients were females with proctosigmoiditis. One patient was in co-treatment with steroid at time of switch. The first patient started with IFX originator with clinical remission at 3, 6, and 12 months reaching mucosal healing at colonoscopy after one year of treatment. The second patient started CT-P13 with clinical remission at 3 months but with discontinuation of treatment after three months due to an infusion reaction. Due to the small number of patients, these patients were excluded from statistical analysis, except for chi square testing in Table 2, as indicated.

3.4. Predictive factors for remission at 12 months

At univariate analysis remission at 3 months (OR 15.0, 95% CI 4.411–141.679; $p < 0.0001$) and at 6 months (OR 53.3, 95% CI 5.81–489.4; $p < 0.0001$) were the only significant predictors of remission at 12 months. Other variables including gender, disease duration, extension of disease, reason for switch, or combined therapy at the moment of switch did not achieve significance. At multivariate analysis the only predictor for remission at 12 months remained clinical remission at 6 months (OR 20.8; 95%: 1.94–223.4; $p = 0.012$).

4. Discussion

To the best of our knowledge, this is the first full report evaluating the efficacy and outcome of UC patients that switched from first-line treatment with SC anti-TNF alpha to IV treatment. There is only one other report published in abstract form from France reporting on 80 patients from 7 centres with UC in a similar setting [13]. First of all, the absence of studies on this topic and the fact that more than 8 referral centres (France: 7 centres) were needed to put together 76 patients (France: 80 patients) point to a

clear policy, at least in Italy and in France, i.e. to start UC patients with IV anti-TNF. The reasons for starting SC agents in the present study were represented primarily by patient's decisions because of business reasons (job incompatibility), patients' concerns with regard to IV administrations, or the patient had participated in post-marketing observational studies on SC anti-TNFs. Therapeutic regimens seem to promote, primarily, IV treatments and several reasons may account for this. First, IV treatment was licensed prior to SC treatments, so most patients were started with the only available regimen in UC and, second, new patients were primarily set on biosimilar infliximab (the only one available at data collection was represented by CT-P13) to reduce health care costs. Similarly, in CD, in a recent systematic review [4], only one study [14] was evaluated which describes a switch from SC to IV anti-TNF treatment and one additional small case series was published thereafter [15].

The main finding of our study suggests that switching from SC to IV anti-TNF, leads to 12 months' clinical remission in up to 77% of patients that stopped the SC agent for LOR, and in up to 47% of patients that discontinued ADA or GOL due to PF. The overall remission rate was 50%. Similar data on long-term clinical response were reported also in the French study [13].

Data on the more frequent switch from IV to SC agents after secondary failure of the first (IV) anti-TNF are available from one prospective study with adequate numbers of patients that reported a 10% remission rate at 52 weeks [9]. Retrospective studies including more than 20 patients reached 30% [11] and 22% [12] remission at 12 months, whereas in a Spanish cohort of 30 patients, only the remission rate at 12 weeks, 27%, was reported [8] which is inferior to our 38% cumulative remission rate. Finally, in an Italian multicentre study, Armuzzi et al. showed a cumulative remission rate of 43% at 12 months [10]. Concerning the question if former anti-TNF responders do better on a second anti-TNF, we were not able to show statistical differences although, numerically, patients with LOR did better than those with PF similar to another study [10], but such differences have been reported in other settings [8,12].

In their systematic review, Gisbert et al. [4] showed that the efficacy of a switch to a second anti-TNF is related to the cause for switching. In CD, studies on IFX to ADA switching showed a higher remission rate in the long term in patients who switched for intolerance (83%) or secondary failure (60%) compared to primary non-response towards the first anti-TNF (28%).

Our study, despite its retrospective nature, showed an important difference between literature data on CD and our data on UC. Whereas in the former disease there are, if any, only slight differences between the IV and SC agents, in UC, a switch from IV to SC agents is accompanied by a poorer outcome compared to a vice versa switch.

Switches due to adverse reactions were not evaluable since only 2 patients presented with this indication. Contrarily to IFX where infusion reactions are known to occur in 5–23% [16] of patients, SC anti-TNF treatment rarely leads to drug withdrawal because of immune reactions during administration of the therapeutic agent. In a former study in UC, such indication was followed by similar figure as a switch due to LOR [10].

Limitations of our study are its retrospective nature and the small sample size, although a study in a similar setting appears to confirm our results [13]. Larger studies are needed to confirm our results of a superior outcome with IFX in UC patients after SC anti-TNF failure and, thus an out-of-class strategy may not be indicated after SC anti-TNF failure.

5. Conclusions

Treatment of UC has evolved over the past 15 years with the introduction of anti-TNF alpha from IFX to the approval of ADA and, more recently, of GOL. Biological therapies are effective in inducing and maintaining steroid-free remission and in achieving mucosal healing [17–21]. However, some patients have to stop treatment due to inadequate response, loss of response, or development of adverse events. Switching between different anti-TNFs in CD has been extensively studied and reported with good results, but in UC only the switch from SC to IV anti-TNF agents seems to have adequate success.

Conflict of interest

A.V.: none to declare.

D.P.: lecture fees (Abbvie).

S.R.: none to declare.

F.F.: none to declare.

F.C.: advisory boards (Abbvie, Takeda, MSD), speaker fees (Takeda).

R.d'I.: none to declare.

F.B.: consulting and/or advisory board fees for MSD, Janssen; lectures and/or speaker for MSD, Janssen and Mundipharma.

S.M.: none to declare.

G.C.: none to declare.

M.F.: consultant fees from: Takeda, Abbvie, Janssen Cilag, MSD.

G.F.: consultant and advisory boards (MSD, Takeda).

An.Al.: none to declare.

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W.F.: advisory boards (Abbvie, Zambon, MSD), speaker fees (Zambon, Mundipharma), research grant (Pfizer).

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