Switching intravenous to subcutaneous infliximab was safe and successful during 1-year follow up in Ulcerative Colitis and Crohn patients – a Belgian single center experience

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Abstract

Background: **Subcutaneous (SC) infliximab CT-P13 (IFX) has recently been registered for the treatment of moderate-to-severe inflammatory bowel disease (IBD). The SC route is an attractive option for patients. However, many open questions remain on how to safely switch patients from maintenance IV to SC administration.**

Objective: **to assess switching from IV to SC IFX therapy in IBD patients through clinical and biochemical evaluation.**

Methods: **Patients in durable remission on eight-weekly (or six-weekly) IV infliximab and therapeutic IFX trough levels were switched to SC therapy every two weeks. All patients were monitored prospectively every 3 months with patient reported outcomes (PRO), labs including IFX concentrations and faecal calprotectin every 6 months for minimum one-year follow up.**

Results: **55 patients (21 UC, 34 CD) agreed to switch to SC therapy. The median follow up in CD patients was 15.5 months, respectively 20 months in UC patients. All patients remained in deep remission according to PRO2, CRP and calprotectin. IFX serum concentrations more than tripled 3 months after the switch (18.31 ± 10.53 µg/mL vs. 4.82 ± 3.06 µg/mL at the start) and remained stable during further follow up. Local pain and injection site reactions both transient were reported in 47% and 42% patients respectively but disappeared in > 50% when injecting in the abdomen or when changing pen to syringe.**

Conclusion: **Switching UC and Crohn patients in clinical remission and adequate trough levels from maintenance IV tot SC infliximab therapy was successful for at least one year. A proportion of patients experienced pain and or injection site reactions. (**Acta gastroenterol belg., **2025**, 88, **18-22**).

Keywords: Infliximab, CT-P13, Subcutaneous therapy, Crohn's disease, Ulcerative colitis.

Introduction

Inflammatory bowel disease (IBD) is a group of chronic inflammatory diseases originating from the gastro-intestinal tract. Crohn's disease (CD) and Ulcerative colitis (UC) are the most distinct disorders. In patients with moderate to severe disease, tumor necrosis factor (TNF) inhibitors are still a cornerstone treatment. As patents have expired on some reference products, new biosimilars are being produced and tested. For infliximab (IFX), a biosimilar has been developed named CT-P13, which proved safe and non-inferior (1-3). Furthermore, CT-P13 has a new subcutaneous (SC) formulation which is an attractive option comparing to the intravenous (IV) route. (4) Subcutaneous administration offers a different pharmacokinetic profile as peak concentration is gradually achieved due to slow absorption, in contrast with IV administration. (5) This may lead to more steady trough concentrations. Furthermore, many practical advantages are associated with SC administration including self-administration by the patients leading to a reduction in medical visits, time saving and a reduction in hospital resources and health care expenditures. Only a few studies with the SC formulation have been published and describe safe, efficacious, and non-inferior results compared to CT-P13 IV. (4) (6-8). However, many open questions remain on how to safely switch patients from maintenance IV to SC administration. We conducted an observational cohort study in IBD patients switching from IV to SC CT-P13 therapy to assess safety, efficacy and immunogenicity.

Materials and Methods

We conducted an observational cohort study with retrospective analysis according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines (9). Patients agreeing upon participating in this study had to sign a patient consent. This study was approved by the Ethical Committee the 23rd of May, 2023 (number B1172023000019.)

According to local reimbursement criteria, patients with ulcerative colitis and Crohn's disease starting April 2021 and September 2021 respectively were offered the option to switch to SC therapy. Patients in durable remission (no symptoms and unaltered C-reactive protein and faecal calprotectin) on eight-weekly (or six-weekly) IFX IV administration (5mg/kg) and therapeutic IFX trough level (>3µg/mL) were eligible. Durable remission was at least 3 months. All patients received a dose of SC CT-P13 of 120mg, regardless of their weight, with intervals of 2 weeks starting 8 weeks (or 6 weeks for those in q6w regimen) after the last IV infusion. Patients were monitored prospectively every 3 months with electronically recorded patient reported outcomes (PRO), clinical visits and biochemistry tests

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including IFX concentrations. Furthermore, faecal calprotectin was measured before the switch at months 6 and 12 during SC treatment. For IFX serum levels an 'apDia Infliximab ELISA' (apDia bvba, Turnhout, Belgium) test was used. For IFX antibodies an 'apDia anti-Infliximab ELISA' (apDia bvba, Turnhout, Belgium) test was used.

The following data were collected: disease duration, gender, weight, age, disease activity, concomitant medication, smoking status, total duration of follow up after switching, injections site reaction, IBD-related events (IBD flares, admissions for IBD, IBD complications such as development of stenosis, abcesses and fistulae and serious adverse events and adverse events of special interest e.g. opportunistic infections.), lost to follow up and patient satisfaction (through electronic questionnaire). Disease activity was assessed through clinical and biochemical evaluation. For clinical disease, activity was assessed using the PRO2 score for UC and CD patients either through the app by the patients or at the visits by the physician directly asked to the patients and documented in the chart using standard template questionnaires. PRO2 consisted of stool frequency and abdominal pain; for UC rectal bleeding and stool frequency. Clinical remission was identified as follows: Individual score for stool frequency SF <= 3 and for abdominal pain <= 1 ; for UC rectal bleeding = 0 and stool frequency ≤2). For biochemical evaluation laboratory tests (eg. CRP) and calprotectin was used.

Switching back to IV therapy based on patient's request or medical decision was noted. These data were added to our medical file system (HIX) and specific IBD database (URCARE) until follow-up of 1 year was reached for all patients. To analyse data, we used descriptive statistics and for the patient questionnaire a student t-test was used.

Results

Baseline characteristics

Out of 127 eligible patients, 55 (21 UC, 34 CD) agreed to switch from IV infliximab to SC administration of CT-P13 every 2 weeks. Data registration was ended the first of February 2023 for all patients to reach 1-year follow-up (one patient dropped out of the study because of noncompliance). Of these 54 patients, 2 were switched back to IV infliximab administration. The median follow up in CD patients was 15.5 months, respectively 20 months in UC patients. 25% of UC had extensive disease whereas 57% of CD patients exhibited ileocolonic disease. Detailed baseline demographics and disease characteristics are presented in Table 1. The median disease duration was 8 years for UC and 16 years for CD. At inclusion, 2 patients were on concomitant mesalazine respectively 3 on methotrexate (MTX) and 3 on thiopurine therapy. Interestingly, we could stop azathioprine in all 3 patients and mesalazine in 1 patient due to excellent clinical and biochemical response.

Clinical outcomes

All patients were in clinical remission and stayed symptom free measured by PRO2 scores for UC and CD (Table 2). A few patients did not meet criteria for remission according to PRO2 scores before switching because their stool frequency exceeded the normal range. However, their stool frequency didn't change over time prior to switching and was evaluated to be acceptable for these patients, thus were marked as response to therapy.

Table 1. — **Patient and disease characteristics at baseline**

	CD	UC
Number of patients	34	21
Median months follow up	15.5	20
Median age (years) + min/max	42.5 (23-72)	34 (24-75)
Median body weight (kg) + min/max	74 (54-100)	72.5 (53.6-103)
# patients >=80kg	13	10
# patients <80kg	21	11
Female	17	12
Smoker (current)	2	1
Montreal Classification	L1: 12 (35%)	E1: 6 (29%)
	L2: 3 (9%)	E2: 10 (48%)
	L3: 19 (56%)	E3: 5 (24%)
Median disease duration at the moment of the switch (years)	16	8
Median follow up (months)	15.5	20
Concomittant immunosuppressive therapy	4	4
Disease status (biochemical) at the moment of the switch (median)		
• CRP (mg/L)	1.2	
• Calprotectin (µg/g)	36	
Perianal disease	14	/

CD = Crohn Disease, UC = Ulcerative Colitis.

Table 2. — **Patient Reported Outcome (PRO)* before and after switching from intravenous to subcutaneous infliximab**

	UC		CD	
	Before switch (n)	After switch (n)	Before switch (n)	After switch (n)
Remission$^{\varphi}$	17	16	22	22
Response$^{\Psi}$	4	5	12	12

*For clinical evaluation the PRO2 score was used for UC and CD patients. PRO2 consisted of stool frequency and abdominal pain; for UC rectal bleeding and stool frequency. Clinical $^{\varphi}$remission was identified as follows: Individual score for stool frequency SF <= 3 and for abdominal pain <= 1; for UC rectal bleeding = 0 and stool frequency ≤2).
$^{\Psi}$Response was identified as continuous improvement of symptoms leading to therapy ongoing.
CD = Crohn Disease UC = Ulcerative Colitis PRO2 = Patient Reported Outcome.

Biochemical outcomes

The median (+ interquartile range (IQR)) CRP remained stable in all patients throughout the study from at last IFX infusion (1.2 (0.6-3.4) mg/L) to 3 months follow up (1.2 (0.7-2.3) mg/L), 6 months follow up (1.4 (0.6-2.7) mg/L), 9 months follow up (1.2 (0.6-2.2) mg/L) and 12 months follow up (1.4 (0.6-3.25 mg/L) (Figure 1A). Likewise, median (+IQR) faecal calprotectin concentrations did not alter after 6 months (19 (7-58)µg/g) and 12 months (15 ± (8-62) µg/g) comparing to initial faecal calprotectin levels (36 (13-66) µg/g) (Figure 1B).

Pharmacokinetic outcomes

Median IFX (+IQR) trough levels rose considerably from 5 (3.3-7.1)µg/mL at the time of the last IFX infusion to 17.9 (12.1-23.0) µg/mL at 3 months, 20.6 (12.7-27.8) µg/mL at 6 months, 20.5 (15.4-31.7) µg/mL at 9 months and 20.38 (14.6-29.2) µg/mL at 12 months. (Figure 1C) There were no antibodies to IFX detected.

Patients' experiences

MA patient questionnaire was sent 6 months after switching from IV to SC IFX. There was a high response rate of 80% (44/55). Patients were asked for satisfaction between 0 and 100% on a visual analogue scale, a mean of the responses was calculated. In the perception of the patient the mean disease control was stable (mean 88% IV vs. mean 90% SC). Whereas for the IV IFX 45 % (20/44) of the patients still experienced end-of-dose (EOD) effect only one patient on SC still reported EOD-effect before a new injection.

Patients reported a major positive impact on their QoL by having less hospital visits, less check-ups with the doctor and less time spent by receiving SC treatment (3 minutes for SC treatment compared a minimum of 2h00 total time for IV treatment). This result led to significantly ($p<0.05$) more satisfaction in those patients

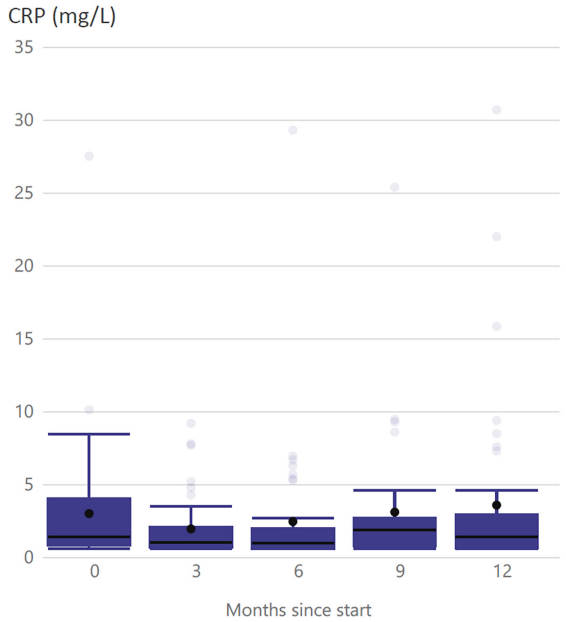

Figure 1A. — CRP levels (mg/L) with median (black stripe), mean (black dot) and IQR (whiskers) for every 3 months until 12 months follow up. Gray dots represent outliers.

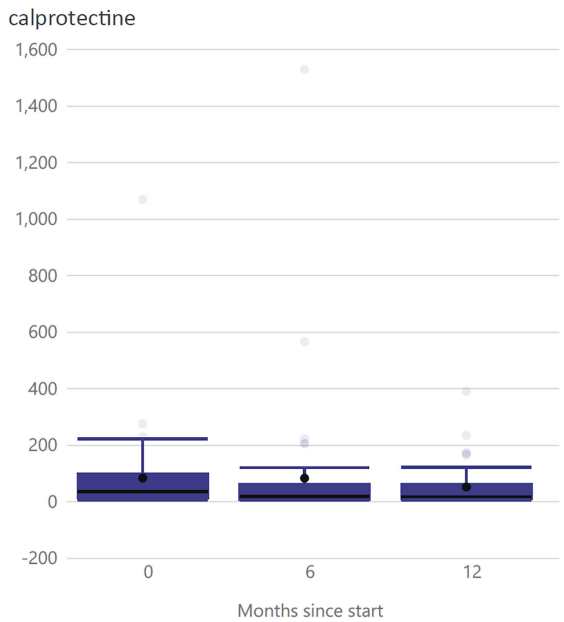

Figure 1B. — Calprotectin levels (µg/g) with median (black stripe), mean (black dot) and IQR (whiskers) for every 6 months until 12 months follow up. Gray dots represent outliers.

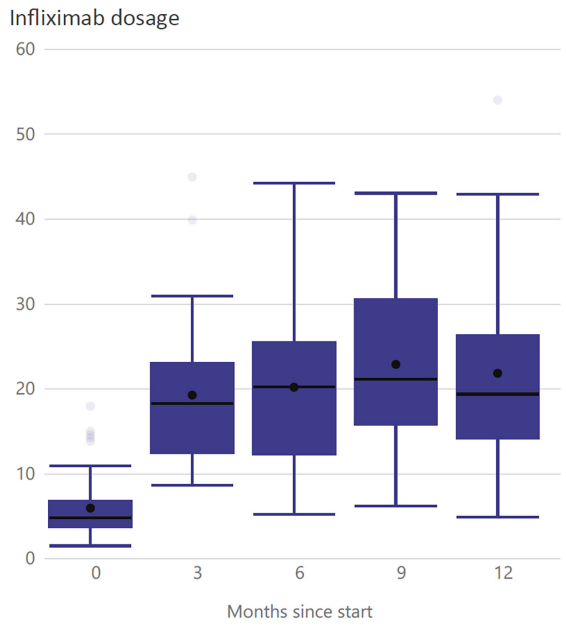

Figure 1C. — IFX trough levels (µg/mL) with median (black stripe), mean (black dot) and IQR (whiskers) for every 3 months until 12 months follow up. Gray dots represent outliers. Levels of IFX did not go beneath target level of 3µg/mL.

who opted for switching. Other motivators were to be less dependent of the hospital, a better balance between work-treatment and obviating (difficult) venous punctures. Seventy one percent reported less absence at work since the switch IFX SC.

Disadvantages of the SC IFX were reported by 10% of the patients including a higher cost, local injection site reactions (transient pain and itching) during and after the injection, risk of forgetting the injections. In terms of compliance only one patient reported having skipped an injection more than once. However, several patients confessed having delayed the injection for more than one day in a period of 6 months (1 patient always, 1 patient frequently, 6 sometimes, 7 rarely). Only (28/44) 63% reported sticking strictly to the exact injection biweekly regimen.

Finally, patients were asked if they wanted to switch back to IV IFX. Two patients requested to switch back, one patient because of non-compliance on the SC IFX and the other person had the impression that the SC treatment was not powerful enough.

Adverse events

All reactions relating to injection site were thoroughly questioned for every visit. 23 of 55 patients (42%) mentioned at some point injection site reactions. Most reactions concerned eczema or a dry red mark. Two patients experienced psoriasiform eruption. For 11 of these 23 patients, these lesions were of temporary nature and resolved with continued registration. Twenty-six (26) of 55 patients (47%) experienced pain at the injection site, mostly with the first series of injections. This eventually resolved spontaneously in 4 patients. This was partially solved offering solutions including injection in the abdominal region instead of the thigh this helped for 14 patients or switching IFX formulation from the pen to the prefilled syringe helping for 2 patients. Pain of injections site reactions were transient (usually 2-3 days and maximum 1 week). None of the injection site reactions or pain resulted in therapy withdrawal.

One patient developed neurosarcoidosis. This could not be linked to immunosuppressive treatment but for safety measures SC CT-P13 was discontinued, and glucocorticoids were started. Three patients developed herpes virus related infections: 2 patients with herpes labialis and 1 patient with zona ophtalmica for which antiretroviral therapy was started. These patients were not receiving concomitant immunosuppressives.

Discussion

In our study, we investigated clinical and biomarker response for one year in 55 patients after switching from IV infliximab to SC CT-P13. Results demonstrated persistent durable clinical and biochemical remission. Two patients were switched back to IV administration which was not the result of inadequate response but rather a therapy compliance related problem for one patient and an adverse event not directly linked to the therapy for another patient. In addition, IFX trough levels rose considerably and remained nicely elevated after switching to SC administration which contributed to the adequate response. This is in accordance to previous studies (4)(8). We used 120mg SC CT-P13 biweekly in every patient irrespective of body weight and interestingly observed no differences for patients with higher BMI compared to those with normal or low BMI. This is in contrast with registration studies where patients received a dose 120 mg for body weight <80kg, 240mg for >80kg, respectively. (6) In our opinion, dosing above 120mg is not necessary - unless IFX concentrations would drop over time.

Furthermore, because IFX trough levels remained consistent above target levels, we could de-escalate our 3 patients previously on concomitant azathioprine because of rather low IFX concentration (< 4 µg/mL) after switching. We therefore hypothesize that combination therapy with immunosuppressants may be less needed in patients on SC therapy. Moreover, if these data are confirmed in larger cohorts and during longer term, follow-up proactive therapeutic drug monitoring (TDM), a common practise in patients during IFX maintenance treatment, may no longer offer an added value. Finally, future studies may focus on exploring prolonging injection intervals longer than 2 weeks once steady IFX concentrations have been reached.

Overall, the mean patient satisfaction with the switch was very high (90%) due to an improved QoL and

importantly less end-of-dose effect on SC compared to IV therapy.

Injection pain was observed in 42% of patients and injection reactions in 47%, respectively. The number of injection site reactions was larger than those observed in the registration study of Westhovens et al. (10) (17.9%) and of Schreiber et al. (6) (22.7%) as they are subject to clinical interpretation and patient perception. However, most reactions or pain were mild transient or resolved spontaneously and/or decreased with repeated use. Changing formulation or the site of injection helped for almost half of patients experiencing problems. None of these side effects resulted in withdrawal of therapy.

Serious adverse events were seen in 4 patients including neurosarcoidosis in 1, herpes zoster in 3 patients. According to a recent large, nested case-control analysis anti-TNF treatment results in higher risk of herpes zoster infection with an incidence rate of 9.3 per 1000 person-years (11).

Limitations of our study include a smaller sample size. Furthermore, the retrospective analysis although data were collected prospectively. Finally, given the small sample size and since all patients entered this study in remission, we can not claim superiority or even non inferiority on a statistical basis.

We conclude that switching from IV infliximab to SC infliximab biosimilar results in steady faecal calprotectin and CRP markers as well as IFX levels. Furthermore, clinical remission was maintained as PRO2 score did not change. Patient satisfaction was high as they experienced less end-of-dose effects and improved QoL. Injection site reactions and pain occurred in a significant number of patients with the first series of injections but is mostly transient. Through adaptations of medication administration, we could further reduce this number. Although IV infliximab has its well-known efficacy, most patients in addition experience less disease-related symptoms when switching to the SC route which makes it an attractive alternative option.

Declarations

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Competing interests: The other authors declare that they have no conflict of interest.

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