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ORIGINAL ARTICLE

Switching to Subcutaneous Infliximab Maintenance Therapy Is Effective in Patients with Inflammatory Bowel Disease

Jaakko Rautakorpi[1,4] · Sara Kolehmainen[2] · Eliisa Löyttyniemi[3] · Clas-Göran af Björkesten[2] · Perttu Arkkila[2] · Taina Sipponen[2] · Kimmo Salminen[1]

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Abstract

Background Recent studies suggest that subcutaneous infliximab is effective and safe for treating patients with inflammatory bowel disease. Real-world studies with larger cohorts are needed to confirm the efficacy of subcutaneous treatment.

Aims The aim was to assess real-world treatment persistence, clinical outcomes, infliximab concentrations, and treatment safety after switching from intravenous to subcutaneous infliximab treatment with patients with inflammatory bowel disease.

Methods This retrospective register-based study included patients with inflammatory bowel disease who were in clinical remission and switched from intravenous infliximab maintenance therapy to subcutaneous infliximab in two tertiary centers.

Results A total of 274 patients (104 Crohn's disease and 170 ulcerative colitis) were included. After the switch, the treatment persistence at 12 months was 94.8% in patients with Crohn's disease and 88.8% in patients with ulcerative colitis. Only 11.3% ($n=31$) of the patients discontinued the treatment during 79-week median follow-up. Compared to the baseline, no change occurred in clinical disease activity at the time points of 3, 6, and 12 months, based on the Harvey–Bradshaw Index or partial Mayo Score ($p=0.792$ and $p=0.426$, respectively). Infliximab median concentrations were higher ($p<0.0001$) during subcutaneous treatment (16.75 µg/ml) compared to the intravenous treatment median trough levels before the switch (6.71 µg/ml). In total, 15.0% ($n=41$) of the patients reported adverse events.

Conclusion Switching to subcutaneous infliximab maintenance therapy was associated with high treatment persistence, a stable disease course, increased infliximab concentrations, and an acceptable safety profile.

Keywords Biologic therapy · Tumor necrosis factor inhibitor · IBD · Crohn's disease · Ulcerative colitis

Introduction

Crohn's disease (CD) and ulcerative colitis (UC) are subtypes of inflammatory bowel diseases (IBD), a heterogeneous group of conditions characterized by chronic, intermitting inflammation in the gastrointestinal tract and an impaired quality of life [1, 2]. The introduction of biologic therapies in moderately to severely active disease has radically improved the therapeutic options for IBD [3].

TNF (tumor necrosis factor) inhibitors, including the monoclonal antibody infliximab (IFX), are widely used as first-line biologic treatment for IBD [4, 5]. IFX biosimilars, the first of them being CT-P13, have demonstrated a similar safety profile and therapeutic effectiveness but reduced expenses compared to the original drug [6]. Although the introduction of biosimilars has led to lower prices, which has allowed more patients to be treated with effective medications [7], the intravenous (IV) administration of IFX binds

Jaakko Rautakorpi and Sara Kolehmainen have contributed equally to the writing of this article.

✉ Jaakko Rautakorpi
jaraut@utu.fi

1 Abdominal Center – Department of Gastroenterology, University of Turku and Turku University Hospital, Turku, Finland

2 Abdominal Center – Department of Gastroenterology, University of Helsinki and Helsinki University Hospital, Helsinki, Finland

3 Department of Biostatistics, University of Turku and Turku University Hospital, Turku, Finland

4 Faculty of Medicine, University of Turku, Kiinamyllynkatu 10, 20520 Turku, Finland

up resources in hospital infusion units. In addition, infusion visits are time-consuming for patients [8].

IFX has been traditionally administered intravenously for patients with IBD, but in 2020, the subcutaneous (SC) IFX biosimilar CT-P13 with a dose of 120 mg every other week (EOW) was approved by the European Medical Agency to be used for maintenance therapy for IBD [9]. The first randomized controlled trial on the maintenance therapy of 131 patients with IBD with SC IFX CT-P13 showed comparable efficacy and safety, with non-inferior pharmacokinetics, compared to IV IFX CT-P13 [10]. There are also more recent observational and real-world data from relatively small patient cohorts on a successful switch from established IV IFX maintenance therapy to SC maintenance therapy, resulting in a stable disease activity and low relapse rate, with the exception of patients with highly escalated IV doses prior to the switch [11, 12]. Current data also suggest that SC IFX results in higher remission rates compared to IV IFX [13]. However, due to the patient-oriented nature of SC dosing, more real-world data are required to evaluate the clinical outcomes and treatment persistence after switching the administration route of IFX.

The aims of this study were to assess real-world treatment persistence, clinical outcomes, safety, and drug concentrations after switching from established IV IFX treatment to SC IFX CT-P13 in a comprehensive group of patients with IBD.

Patients and Methods

Patients

This retrospective register-based study was conducted at two Finnish tertiary care centers responsible for advanced therapies of patients with IBD in their regions. The study included all adult patients with IBD who switched from IV IFX treatment to SC IFX CT-P13 at the abdominal centers of Helsinki University Hospital (HUS) and Turku University Hospital (TUH) from January 1, 2021 to May 31, 2023. In both centers, the switch was offered to all patients in clinical remission on the standard maintenance dose of IV IFX. Additionally, patients in clinical remission who were on IV dosing intervals shorter than 8 weeks or receiving a maintenance dose greater than 5 mg/kg were offered the switch based on the physician's assessment.

The patient identification was carried out from the IBD registers of the hospital databases. IV maintenance therapy was defined as an established treatment with IV IFX for at least 3 months. SC IFX maintenance therapy, a 120-mg injection with a pen or syringe every 7, 10, or 14 days at the discretion of the treating clinician, was initiated when the next intravenous infusion would have been due. Patients were excluded if the follow-up time after switching to SC treatment was less than 6 months.

Data Collection and Management

Study data were manually collected from the hospitals' IBD registers and electronic patient records between November 2023 and January 2024. The Finnish IBD register, provided by the health IT company BCB Medical, is a part of the medical record system and is used by healthcare professionals in most university hospitals and some central hospitals in Finland. Data were managed using REDCap electronic data capture tools, which were maintained at the Universities of Turku and Helsinki. REDCap data were collected separately in both centers and were combined by the Finnish social and health data permit authority Findata to ensure that individual patient data protection policies were followed. The data used in this analysis have been obtained as part of routine clinical assessments, and no patient interventions were performed.

Permission for data collection was obtained from the study centers of the two hospital districts (HUS/23/2022 and T03/006/22), and Findata granted permission for data utilization (THL/4146/14.02.00/2022). Finnish legislation does not mandate separate ethical approval for register-based studies.

Data were collected at baseline and at the time points of 3, 6, 12, and 18 months after the switch to SC therapy. Baseline data included the diagnosis (CD or UC), sex, age, disease duration, body mass index (BMI), smoking status, Montreal classification (including, in CD, age at diagnosis, disease extent, and disease behavior), and extraintestinal manifestations. Treatment history data included the use of previous advanced therapies and previous surgical treatments. Data on concomitant IBD medications were collected, as were available data on adverse effects. The causes of possible SC treatment discontinuation and switching back to IV administration were documented.

Data on IV IFX concentrations (trough concentration before the next IV dose) within 3 months before transitioning to SC treatment, as well as SC IFX concentrations (concentration at any time between SC injections) 3–6 months after the initiation of SC treatment and at later time points, were collected if available. Infliximab concentrations were analyzed with an enzyme immunologic assay and serum anti-infliximab antibodies (ATIs) with a radioimmunoassay (Sanquin, Amsterdam, the Netherlands) in both study centers.

Definitions of Disease Activity

The Harvey–Bradshaw Index (HBI) for CD [14] and the Partial Mayo Score (PMS) for UC [15] served the purpose of scoring the clinical disease activity: an HBI of 0–4 indicated

remission, 5–7 mild, 8–16 moderate, and > 16 severe clinical activity; while a PMS of 0–1 indicated remission, 2–4 mild, 5–6 moderate, and 7–9 severe clinical activity. The disease activity data also included the patient-reported outcome (IBD-VAS) [16], a numerical score from 0 to 7, to estimate how much IBD affects the patient's everyday life, as well as laboratory values (blood hemoglobin, leukocytes, platelets, plasma albumin, serum c-reactive protein, and fecal calprotectin). A fecal calprotectin (FC) level of less than 100 µg/g was considered normal and indicated inactive disease. The baseline FC level and endoscopic activity entailed the most recent reading, measured within 3 months prior to the switch. FCs were analyzed with an enzyme immunologic assay (Calpro AS, Lysaker, Norway) at Helsinki University Hospital or with a fluorescence enzyme immunoassay assay (Thermo Fisher Scientific, Carlsbad, California, USA) at Turku University Hospital. Endoscopic disease severity was assessed using the SES-CD for CD and the endoscopic Mayo score for UC: SES-CD 0–2 indicated inactive, 3–6 mild, 7–15 moderate, and ≥ 16 severe disease; while an endoscopic Mayo score of 0 indicated inactive, 1 mild, 2 moderate, and 3 severe disease activity. [17–19]

Statistical Analysis

Categorical variables are summarized as numbers and percentages, while continuous variables are expressed as medians with range or the interquartile range (IQR).

Continuous measurements which were taken over time (baseline–12 months) were analyzed with Friedman's test, if the distributions were very skewed. The same time period was analyzed regarding FC using a linear mixed model for repeated measurements. Logarithmic transformation was employed to fulfill assumptions for the model. A compound symmetry covariance structure and Kenward–Roger corrections for degrees of freedom were applied.

The data analysis for this paper was generated using SAS studio, Version 3.81, Basic Edition (SAS Institute Inc., Cary, NC, USA).

Results

Patient Characteristics

A total of 274 patients (104 with CD and 170 with UC) were included in this study. The patient cohort is described in more detail in Table 1. The disease activity at baseline, previous therapy with biologics, and concomitant medications are presented in Table 2. Endoscopic baseline data were limited and only available for 28.8% ($n = 79$, 78 UC and 1 CD) of the patients.

Treatment Persistence

The follow-up time was a minimum of 6 months from the baseline for all patients, and the median follow-up time was 79 weeks (IQR 64–85). At 12 months, treatment persistence was 94.8% in patients with CD and 88.8% in patients with UC (Fig. 1). During the follow-up, 31 (11.3%, $n = 9$ CD and $n = 22$ UC) patients discontinued the SC treatment. The median time from the first SC dose to discontinuation was 28 weeks. Thirteen patients discontinued the treatment due to either an inadequate response or a loss of response. All reasons for SC treatment discontinuation are shown in Fig. 2. Due to a clinical disease relapse, one patient switched back to IV administration after 4.4 months of SC administration and regained clinical and biochemical remission.

Disease Activity at Baseline and After the Switch

At the time of the switch (baseline), 94.2% ($n = 98$) of the patients with CD and 90.0% ($n = 153$) of the patients with UC were in clinical remission based on clinical activity scores (HBI or PMS). At baseline, the FC level was < 100 µg/g in 81.1% ($n = 151$) of the patients with FC data available and the median FC was 36 µg/g for patients with CD and 34 µg/g for patients with UC. Among patients with CD, 26.9% ($n = 28$) had a history of perianal disease. Extraintestinal manifestations had been reported in the history of 9.5% ($n = 26$) of patients in the entire cohort at the baseline.

During the follow-up, clinical disease activity and FC levels remained stable. There was no statistical change in clinical disease activity at 3, 6, and 12 months based on the HBI or PMS ($p = 0.792$ and $p = 0.426$, respectively). No significant changes in FC levels were observed at 3, 6, and 12 months ($p = 0.20$). The clinical disease activity and FC levels during follow-up are presented in Fig. 3a and b. The median IBD-VAS score remained unchanged at 1 at 3, 6, and 12 months.

Concomitant Medications and Previous Biologic Therapy

At baseline, approximately two-thirds of the patients (67.2%, $n = 184$) were using a concomitant immunomodulator, either thiopurine or methotrexate (Table 2). Only a few patients ($n = 6$, 2.2%) were using corticosteroids at the time of the switch. Some patients ($n = 29$) had previously discontinued IV IFX therapy in sustained remission but had been reintroduced to IV IFX after relapsing and achieved remission. Other previous biologic therapies included adalimumab ($n = 15$, 5.5%) and ustekinumab ($n = 1$, 0.3%). A third of the patients with CD ($n = 34$, 32.7%) had a history of surgery for IBD. More detailed information about treatment history is shown in Table 2.

Table 1 Patient characteristics and disease phenotype at baseline

	Crohn's disease, $n = 104$ (38.0%)	Ulcerative colitis, $n = 170$ (62.0%)
Sex, n (%)		
- Female	37 (35.6)	59 (34.7)
- Male	67 (64.4)	111 (65.3)
Age, years, median (range)	37.5 (18–70)	37 (20–69)
Disease duration, years, median (range)	12 (1–53)	8 (1–42)
BMI, median (range)	26.4 (17.2–42.9)	26.3 (16.9–53.2)
Smoking, n (%)		
- Current	17 (16.3)	15 (8.8)
- Previous	22 (21.1)	27 (15.9)
- Never	61 (58.7)	115 (67.6)
- Unknown	4 (3.8)	13 (7.6)
Montreal classification, n (%)		
- A1 (age at diagnosis, < 17 y)	27 (26.0)	
- A2 (17–40 y)	67 (64.4)	
- A3 (> 40 y)	10 (9.6)	
- L1 (disease extent, ileal)	13 (12.6)	
- L1 + L4 (ileal + upper GI)	7 (6.8)	
- L2 (colonic)	21 (20.4)	
- L2 + L4 (colonic + upper GI)	4 (3.9)	
- L3 (ileocolonic)	43 (41.8)	
- L3 + L4 (ileocolonic + upper GI)	15 (14.6)	
- L4 (isolated upper GI)	0	
- Data missing for L (CD location)	1 (1.0)	
- B1 (disease behavior, non-stricturing, and non-penetrating)	61 (58.6)	
- B2 (stricturing)	22 (21.2)	
- B3 (penetrating)	21 (20.2)	
- p (perianal disease)	28 (26.9)	
- E1 (proctitis)		4 (2.4)
- E2 (left-sided)		55 (32.4)
- E3 (extensive)		111 (65.3)
Extraintestinal manifestations*, n (%)	12 (11.5)	14 (8.2)

*Extraintestinal manifestations included arthropathy, erythema nodosum, pyoderma gangrenosum, ophthalmic manifestations, and primary sclerosing cholangitis

IBD Inflammatory bowel disease, *BMI* body mass index, *GI* gastrointestinal, *CD* Crohn's disease

During the follow-up after the switch, the majority of the patients (93.1%, $n = 255$) were corticosteroid free (no concomitant prednisolone or budesonide treatment). Nineteen patients (6.9%) required corticosteroid therapy during follow-up. Of the patients who discontinued SC IFX treatment, none of the 9 patients with CD and 10 out of the 22 patients with UC were on corticosteroid treatment at the time of the observed treatment discontinuation.

Infliximab Treatment

IV IFX treatment variables are shown in detail in Table 3. The median duration of IV IFX therapy before switching was 60 and 44 months for patients with CD and UC, respectively. Of the patients with CD, 16.5% had a shortened (less than 8 weeks) infusion interval before the switch, and the corresponding proportion of patients with UC was 21.2%. An escalated dose of 10 mg/kg was used for 7.3% ($n = 13$ CD, $n = 7$ UC) of the patients. Of the 66 patients with intensified IV IFX therapy (shortened infusion interval or escalated dose), 5 patients discontinued SC IFX treatment due to a loss of response and 5 for other reasons (1 remission, 2 adverse events, and 2 malignancies) during the follow-up.

At the time of the switch, most of the patients ($n = 265$, 96.7%) started SC treatment with a 120-mg dose EOW. Nine patients started SC treatment with a shortened interval of

Table 2 Disease activity and treatment history at baseline

	Crohn's disease $n=104$ (38.0%)	Ulcerative colitis $n=170$ (62.0%)
Previous biologic therapy, n (%)		
- Adalimumab	11 (10.6)	4 (2.4)
- Ustekinumab	1 (1.0)	0
- Previous treatment course of infliximab	13 (12.5)	16 (9.4)
Previous surgical therapy, n (%)	34 (32.7)	
Clinical activity, HBI / PMS, n (%)		
- Remission (0–4/0–1)	98 (94.2)	153 (90.0)
- Mild (5–7/2–4)	3 (2.9)	13 (7.6)
- Moderate (8–16/5–6)	1 (1.0)	2 (1.2)
- Severe (> 16/7–9)	1 (1.0)	2 (1.2)
- Data missing	1 (1.0)	0
Influence of symptoms on daily life (IBD-VAS), median (range)	1 (0–6)	1 (0–7)
Laboratory parameters, median (range)		
- Hemoglobin, g/l	145 (111–167)	146 (107–183)
- Leucocytes, E9/l	6.2 (3.1–10.6)	6.2 (2.6–17.3)
- Platelets, E9/l	267 (114–451)	269 (146–501)
- Albumin, g/l	41.0 (33.9–47.0)	41.0 (33.0–46.0)
- C-reactive protein, mg/l	2 (1–59)	2 (1–52)
- Fecal calprotectin, µg/g	36 (3–1,404)	34 (3–1,944)
Concomitant medication, n (%)		
- Mesalazine/sulfasalazine	10 (9.6)	65 (38.2)
- Thiopurine	59 (56.7)	108 (63.5)
- Methotrexate	8 (7.7)	9 (5.3)
- Prednisolone	2 (1.9)	1 (0.6)
- Budesonide	1 (1.0)	2 (1.2)

HBI Harvey–Bradshaw index, *PMS* partial Mayo score, *IBD* inflammatory bowel disease, *VAS* visual analog scale

every 7 ($n=2$) and every 10 ($n=7$) days. Of these 9 patients, 8 had either their IV infusion interval shortened (range 5–9 weeks, $n=4$) or their IFX dose escalated to 10 mg/kg ($n=4$) before the switch. During follow-up, 28 (10.2%, $n=9$ CD and $n=19$ UC) patients needed to have the SC administration interval shortened during the follow-up (median interval 10 days for patients with CD and 7 days for those with UC). Ten of these patients ($n=1$ CD, $n=9$ UC) experienced another adjustment of SC dosing: for 5 patients, the dosing interval was extended to every 10 days and 5 returned to the 14-day interval. No SC dose escalations occurred.

Infliximab Concentrations

The median IFX concentrations during SC administration (16.75 µg/ml) were significantly ($p<0.0001$) higher compared to the baseline IV IFX trough levels (6.71 µg/ml). One hundred and twenty-six (46.0%) patients had provided samples for IFX concentration analyses during both IV and SC therapies, and the median difference in IFX concentrations was + 9.7 µg/ml (IQR 5.85–14.22).

Of the 31 patients who discontinued SC therapy, 12 (38.7%, $n=6$ CD and $n=6$ UC) had data available on IFX concentrations, and the median concentration at the time of discontinuation was 9.85 µg/ml in patients with CD and 10.2 µg/ml in patients with UC. In total, six patients (2.2%) generated ATIs during follow-up.

Adverse Events

A total of 37 (13.5%) patients reported mild adverse events and 4 (1.5%) serious adverse events during SC IFX treatment (Table 4). Six patients discontinued SC IFX treatment due to variable adverse effects: a rash ($n=3$), local reactions ($n=1$), general symptoms (a sense of balance difficulty, dizziness, $n=1$), and neutropenia ($n=1$). Two mild infections (herpes zoster, $n=2$) and two infections requiring hospitalization (Pneumocystis pneumonia $n=1$, urosepsis

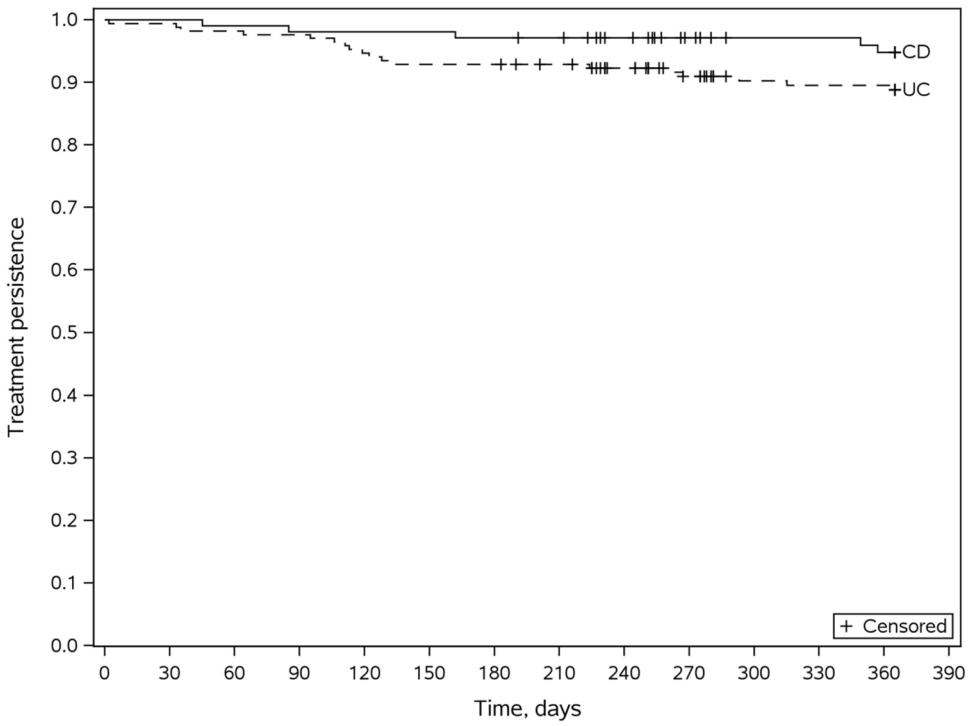

Fig. 1 Kaplan–Meier survival curve for treatment persistence after the switch from intravenous to subcutaneous maintenance therapy with infliximab. CD, Crohn's disease; UC, ulcerative colitis

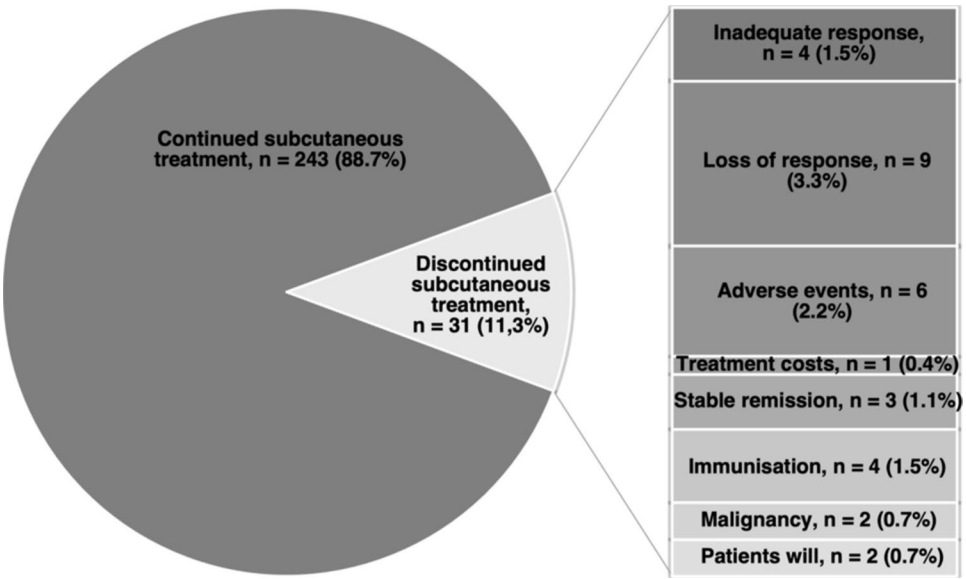

Fig. 2 Reasons for the discontinuation of subcutaneous infliximab therapy after switching from intravenous maintenance therapy

$n = 1$) occurred during the follow-up. Two patients with UC required hospitalization due to a disease flare-up.

Discussion

This study supports the understanding that SC IFX maintenance therapy after switching from IV administration is associated with high treatment persistence, a stable disease course, and an acceptable safety profile. The drug concentrations during SC IFX treatment are significantly higher than the IV IFX trough levels. Data from our comprehensive real-world cohort encourage the switch from established IV IFX maintenance therapy to SC IFX maintenance therapy in patients in clinical remission.

Our findings of high treatment persistence support the previously observed real-world SC IFX treatment persistence rates of 95.2% at six months [20] and 92.3% at 12 months after switch [11]. The number of patients who continued with the SC IFX treatment was even higher than the

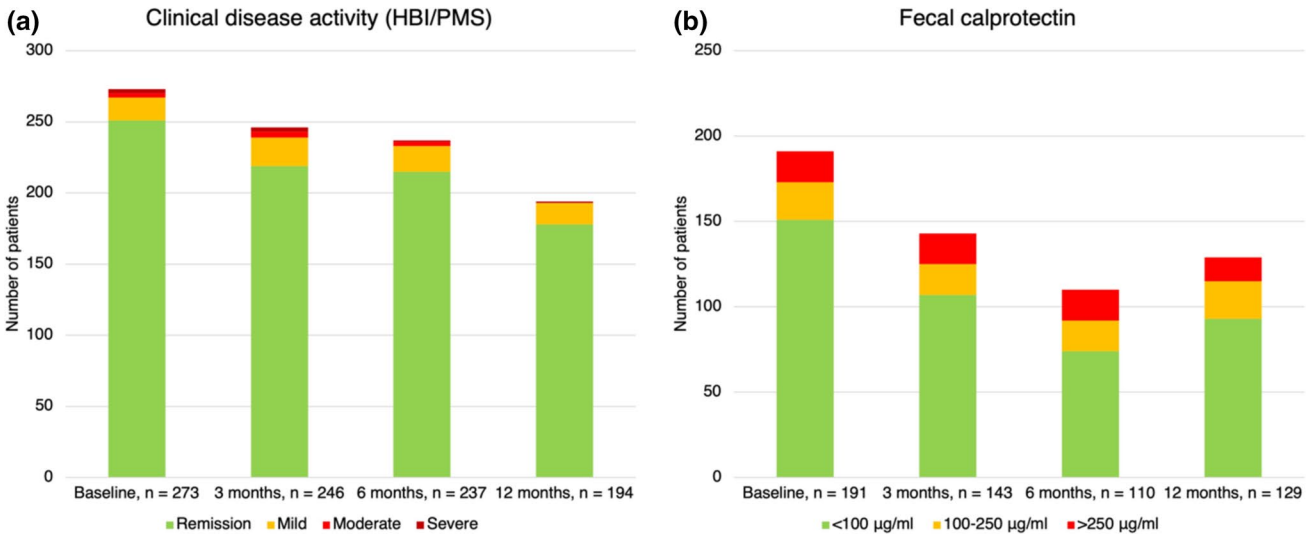

Fig. 3 **a** and **b** Clinical activity and fecal calprotectin levels at baseline and after switching from intravenous to subcutaneous infliximab maintenance therapy. HBI, Harvey–Bradshaw index; PMS, partial Mayo score

Table 3 Infliximab therapy-related variables during intravenous and subcutaneous administration

	Crohn's disease, $n = 104$ (38.0%)	Ulcerative colitis, $n = 170$ (62.0%)
Duration of IV infliximab medication, months, median (range)	60 (3–219)	44 (3–173)
IV infliximab infusion interval, n (%)		
- 8 weeks	84 (81.6)	132 (77.6)
- 7 weeks	9 (8.7)	7 (4.1)
- 5 or 6 weeks	8 (7.8)	29 (17.1)
- 9 or 10 weeks	0	2 (1.2)
IV infliximab dosing		
- 5 mg/kg	90 (86.5)	160 (94.1)
- 10 mg/kg	13 (12.5)	7 (4.1)
Serum infliximab trough concentration during IV administration, µg/ml, median (IQR)	7.0 (4.5–8.8)	6.4 (4.7–8.4)
- Data missing, n (%)	34 (12.4)	88 (32.1)
Serum infliximab concentration with SC administration, µg/ml, median (IQR)	17.1 (13.3–21.0)	16.2 (12.2–23.0)
- Data missing, n (%)	24 (8.8)	43 (15.7)

IV Intravenous, *IQR* interquartile range, *SC* subcutaneous

corresponding persistence rates observed with IFX IV biosimilars, with rates ranging from 70.1 to 87.0% [21]. One recent single-center real-world study comparing IV and SC IFX maintenance therapy directly found SC IFX dosing to achieve higher durable remission rates than that did IV dosing [13]. In our study, less than five percent of patients discontinued the SC treatment after the switch due to an inadequate response or a loss of response. This is in line with the rate (3.9%) reported in a recent French study on 128 patients with IBD with a median follow-up of 18 months after a switch from IV maintenance therapy to SC IFX administration [22]. The treatment persistence was moderately higher in the subgroup of patients with CD, which may be associated with a higher proportion of patients being in clinical remission at baseline.

The loss of a clinical response is an important endpoint when comparing the efficacy of SC and IV administration. Similarly to previous real-world studies, significant changes in clinical remission after the switch were not detected in our study [11, 20, 23]. FC is widely used as a surrogate marker for endoscopic disease activity [24, 25]. We found no significant difference between baseline FC levels and the repeated

Table 4 Incidence of adverse events during subcutaneous infliximab therapy

	Crohn's disease, $n = 104$ (38.0%)	Ulcerative colitis, $n = 170$ (62.0%)
Mild adverse event, n (%)		
- Abdominal pain	2 (0.7)	0
- Arthralgia	2 (0.7)	1 (0.4)
- Faintness	0	1 (0.4)
- Headache	1 (0.4)	1 (0.4)
- Local reactions	5 (1.8)	1 (0.4)
- Mild infection	2 (0.7)	0
- Rash	3 (1.1)	14 (5.1)
- Other (*)	2 (0.7)	1 (0.4)
Serious adverse event, n (%)		
- Infection requiring hospitalization	2 (0.7)	0
- Disease flare requiring hospitalization	0	2 (0.7)

*Self-reported memory loss, 1 neutropenia, 1 self-reported feeling of balance difficulty/dizziness

measurements at 3, 6, and 12 months after the switch. Similar rates of biochemical remission stability have been observed in some other previous studies [11, 12]. Therefore, the unchanged and low FC levels during follow-up objectively support the maintenance of remission, reducing the need for follow-up endoscopies. This may be a reason for the limited number of endoscopic data in this study.

The physician's assessment of treatment persistence is certain. However, the patient's subjective evaluation should also be considered, as the change in the method of administration is so significant [26]. In our analysis, patients reported the impact of IBD on their daily lives before and after the switch using a numeric scale (IBD-VAS) in the IBD register. Our findings showed that the IBD-VAS score remained stable after the switch during maintenance therapy.

We observed that the intensification of IFX SC therapy occurred only by increasing the SC injection interval from the standard 120-mg EOW to 120 mg every 7 or 10 days and not by increasing the initial single dose. In addition, a few patients with intensified IV IFX at baseline started directly with a shortened SC interval. These adjustments were made based on the treating physicians' clinical judgment. There are limited data on whether it is better to increase the single SC dose or to shorten the dose interval. In the randomized phase 3 Liberty studies, approximately half of patients who experienced a loss of response with regular SC dosing regained clinical remission or the response with 240-mg EOW dosing [27]. Interestingly, research on the pharmacokinetics of SC IFX have found that, contrary to what might be expected, a 240 mg dose administered SC EOW led to higher drug concentrations than did 120 mg every 7 days [28]. A French study witch SC IFX also showed a high rate of regaining remission after a relapse with a dose escalation to 240-mg EOW [12]. However, in an extension study, the authors observed that the dose escalation to 120 mg once weekly in the case of a relapse would be as effective as 240-mg EOW [22]. The proportion of patients needing an escalated SC IFX dose was smaller in our study, but the cohort lacked patients who were on highly intensified IV IFX therapy at the baseline.

As with the dose escalation regimen, clinicians are also faced with the question of whether and how therapeutic drug monitoring should be performed with SC IFX. For instance, a recently published retrospective study with patients with IBD who received maintenance SC ustekinumab showed that proactive therapeutic drug monitoring was associated with increased treatment persistence and a decrease in IBD-related hospitalizations [29]. Our findings on IFX concentrations after a switch from IV to SC administration are consistent with those of previous research, observing 3–sevenfold increases in IFX concentrations [28]. The higher concentrations should not be misinterpreted to mean that the overall drug exposure would be higher with SC than with IV administration at standard doses, but they should rather be understood as a result of more frequent dosing and different pharmacokinetics [10–12, 20]. However, it has been discussed that continuously higher and more stable IFX concentrations during SC therapy could support the maintenance of remission better than the more variable concentrations during IV administration with higher peak and lower trough levels. The optimal monitoring and target levels of therapeutic drug concentrations remain partially unclear with SC IFX therapy [28, 30]. Nevertheless, it appears that an increase in the IFX concentration after the switch from IV to SC administration predicts favorable clinical outcomes. It has been observed that stable or decreased changes in serum IFX concentrations following the switch from IV to SC

administration were associated with an increased risk of relapse [12]. Recently, a French multicenter study was the first to suggest an optimal SC IFX concentration cut-off of 20 µg/ml for maintaining deep remission, whereas a concentration of less than 10 µg/ml associated with lower deep remission rates [31]. In our study, among patients who discontinued SC treatment for any reason, we observed median SC IFX concentrations at a level of 10 µg/ml. Published anti-drug-antibody formation rates during SC IFX therapy have ranged from 0 to 7.7% [11, 12, 20], and our observations also support the low risk of anti-drug-antibody formation after the switch.

The adverse effects reported in previous studies during SC treatment have primarily entailed local injection site reactions or erythema, and no severe safety issues have emerged [10–12]. In our cohort, the most common adverse effects also included rashes and injection site reactions. Due to our retrospective study design, some minor adverse effects, such as minor local injection site reactions, may have been unreported and missed. Although most adverse effects were classified as mild, we observed two cases of UC flare-up and infections requiring hospitalization. However, these results do not raise concerns about safety issues with SC IFX.

The strengths of this study include the large size of the patient cohort, as well as the long follow-up and data availability from the IBD register. In addition, this large real-life cohort represents clinical practice and experiences from a period when their research on the use of SC IFX was still limited. Both centers had clear guidelines for the switch and uniform treatment practices. However, we acknowledge this study to have certain limitations, including the absence of a control group continuing IV therapy and the retrospective study design, which limited the availability of clinical FC data and particularly endoscopic data at specific time points. Only completed switches were included in the study, so patients who remained on IV treatment were excluded. Therefore, the reasons why the switch may not have been made cannot be reported. However, the switch in the route of administration should be based on an individual patient assessment, as was the case in this study. Based on the results, the switch should be considered for patients with IBD who are in remission.

In conclusion, switching to SC IFX from maintenance IV therapy was effective and safe in patients with IBD, with a high treatment persistence. These results encourage switching from IV IFX maintenance therapy to self-administered SC therapy in the treatment of patients with IBD.

Author Contributions All authors have contributed in planning the study design. J.R. and S.K. have collected the data. E.L. has done the statistical analysis. J.R. and S.K. contributed equally to the writing of this manuscript. All authors reviewed the manuscript.

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Data Availability Raw data for dataset of the manuscript are not publicly available to preserve individuals' privacy under the European General Data Protection Regulation.

Declarations

Conflict of interest J.R. has received support from Abbvie, Pfizer, and Takeda for meeting attendance and travel expenses and has participated in planning educational meetings for Abbvie. C.G.B. has received speaker and consultant fees from Abbvie, BMS, Galapagos, Johnson & Johnson, Lilly, Pfizer, Takeda, and Tillotts. P.A. has participated in planning educational meetings for Takeda, is a shareholder in Orion Pharma, and has received lecture fees from Celltrion. K.S. has received speaker and consultant fees from Abbvie, BMS, Janssen, Pfizer, Takeda, and Tillotts Pharma. T.S. has received speaker fees from Abbvie, Celltrion, Johnson & Johnson, Lilly, and Takeda, as well as consultation fees from Abbvie, BMS, Johnson & Johnson, Pfizer, and Takeda and a research grant from Johnson & Johnson. S.K. and E.L. have no conflicts of interest to declare. J.R. has received grant from the Mary and Georg C. Ehrnrooth Foundation.

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