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360 Hot Topics

Subcutaneous Infliximab in Refractory Crohn's Disease Patients: A Possible Biobetter?

Karin Cerna, MD,[*,†] Dana Duricova, MD, PhD,[*,‡] Martin Lukas, MD,[*,§,¶] Martin Kolar, MD,[*,§] Nadezda Machkova, MD,[*] Veronika Hruba, MD,[*] Katarina Mitrova, MD, PhD,[*,‖] Kristyna Kubickova, MD, PhD,[*] Marta Kostrejova, MD,[*,] Jakub Jirsa, MD,[*] Kristyna Kastylova, MD,[*] Stepan Peterka, MD,[*,††] Gabriela Vojtechova, MD, PhD,[*,‡‡] and Milan Lukas, MD, PhD[*]**

From the [*]Clinical and Research Center for Inflammatory Bowel Disease ISCARE and First Faculty of Medicine, Charles University, Prague, Czech Republic
[†]GENNET, Prague, Czech Republic
[‡]Institute of Pharmacology, First Faculty of Medicine, Charles University, Prague, Czech Republic
[§]Institute of Animal Physiology and Genetics, Czech Academy of Sciences, Libechov, Czech Republic
[¶]Department of Surgery, Third Faculty of Medicine, Charles University and Kralovske Vinohrady University Hospital, Prague, Czech Republic
[‖]Department of Pediatrics, University Hospital Motol and Second Faculty of Medicine, Charles University, Prague, Czech Republic
[**]Department of Internal Medicine, Hospital of the Sisters of Mercy of St. Charles Borromeo, Prague, Czech Republic
[††]Department of Internal Medicine, Hospital Jindrichuv Hradec, Jindrichuv Hradec, Czech Republic
[‡‡]ResTrial GastroEndo, Prague, Czech Republic

Address correspondence to: Karin Cerna, MD, Clinical and Research Center for Inflammatory Bowel Disease ISCARE, First Faculty of Medicine, Charles University, Ceskomoravska 1510/19, 190 00 Prague 9, Czech Republic;. Tel: +420 234 770 299 (cernak@iscare.cz).

Background: A subcutaneous formulation of infliximab (IFX-SC) approved to treat patients with inflammatory bowel disease may offer improved efficacy versus intravenous infliximab.

Methods: Patients with refractory Crohn's disease (CD, $n = 32$) previously treated unsuccessfully with at least 2 biologics were treated with IFX-SC and followed from baseline at Week 0 (W0) to Week 30 (W30). The study's primary endpoint was the treatment's persistence at W30, while secondary goals included the analysis of serum infliximab trough levels (TL IFX), dynamics of anti-IFX antibodies (ATIs), and clinical, serum and fecal markers of CD activity during IFX-SC treatment.

Results: Midterm treatment persistence with the continuation of treatment after W30 was 53%. TL IFX median values showed rapid, significant upward dynamics and exceeded 15.5 μg/mL at W30, whereas median ATI levels significantly declined. Among ATI-negative patients at W0 ($n = 15$), only one showed IFX immunogenicity with newly developed ATIs at W30. Among ATI-positive patients at W0, ATI seroconversion from ATI-positive to ATI-negative status was observed in 10 of 17 patients (58.8%). Patients who had continued IFX-SC treatment at W30 showed significant decreases in C-reactive protein ($P = .0341$), fecal calprotectin ($P = .0002$), and Harvey–Bradshaw index ($P = .0029$) since W0.

Conclusions: Patients with refractory CD previously treated with at least 2 biologics exhibited clinically relevant improvement with IFX-SC, which showed less immunogenic potential than IFX-IV and highly stable TL IFX.

Lay summary

Infliximab is currently administered intravenously to treat Crohn's disease patients. In this study, subcutaneous administration of infliximab was found to have advantages for refractory CD patients, including stable, consistently higher levels of the drug and significantly lower immunogenicity.

Key Words: Inflammatory bowel disease, Crohn's disease, infliximab, subcutaneous, infliximab trough levels, antibodies to infliximab, immunogenicity, treatment persistence

Introduction

Inflammatory bowel disease (IBD) is a chronic condition that causes gut and systemic inflammation in millions of people worldwide. Despite the availability of several treatment options, including conventional anti-inflammatory and immune-modifying drugs, monoclonal antibodies, and small molecules, many patients continue to experience symptoms and disease progression. A potential solution to that challenge is a newer class of biologics called *biobetters* that generally aim to improve upon existing therapies with biologics.[1] Biobetters are designed to have efficacy and safety profiles similar to or better than their original biologics, albeit with enhanced pharmacokinetic properties or reduced immunogenicity.

At least for a distinct group of patients with IBD, such a biobetter could be subcutaneous infliximab (IFX-SC). IFX-SC, as a newer formulation of the biologic anti-tumor

Key Messages

What is already known?

Subcutaneous infliximab has already been shown to be effective, safe, and non-inferior to intravenous infliximab in patients with Crohn's disease.

What is new here?

Due to its low immunogenicity, subcutaneous infliximab can be used to reinduce therapy in a part of refractory patients with positive neutralizing anti-infliximab antibodies.

How can this study help patient care?

Subcutaneous infliximab can be efficient also in refractory Crohn's disease patients with severe disease course even after the failure of intravenous infliximab treatment.

necrosis factor alpha (iTNFa), has emerged as an alternative to the traditional intravenous infliximab (IFX-IV). The development of IFX-SC was driven by the need for a more convenient, patient-friendly method of administration, for IFX-IV infusions require hospital visits and can be time-consuming.[2] By contrast, the subcutaneous administration of IFX has been shown to have other, perhaps more important advantages, including stable, consistently higher levels of the drug and significantly lower immunogenicity.[3] Beyond that, as Schreiber et al. have shown, IFX-SC is not inferior to IFX-IV infliximab in terms of clinical response and safety.[4]

However, because clinical data on IFX-SC remain limited,[5] particularly in patients with IBD with complicated (ie, severe and aggressive) disease courses, in our study we aimed to assess the midterm (ie, 30-week) efficacy and safety of IFX-SC in patients with Crohn's disease (CD) with severe disease phenotypes following the failure of treatments with multiple biologics.

Patients and Methods

Patients

A total of 32 CD patients from one tertiary IBD center who have failed at least 2 monoclonal antibodies and started on IFX-SC treatment were included. Patients were followed from baseline at Week 0 (W0) to Week 30 (W30), with study visits scheduled at Weeks 0, 2, 14, and 30. Patients' clinical and demographic data prior to inclusion were obtained from their medical records.

Examinations

The Montreal Classification of IBD was used to classify CD,[6] while the Harvey–Bradshaw Index (HBI) was used to assess the degree of disease activity.[7] The Magnetic Resonance Index of IBD Activity (ie, MaRIA) was used to assess ileocolonic CD activity on contrast-enhanced MRI enterography and was calculated according to Rimola et al.'s method.[8] Simple endoscopic CD score (SES-CD), used to measure mucosal inflammation, was calculated according to Daperno et al.[9] Intestinal ultrasound score was determined with the expertise developed in the STARDUST clinical study according to Kucharzik et al.[10]

Blood samples were taken from the peripheral vein during each clinical visit. Serum C-reactive protein (CRP) levels were measured using the BN II nephelometer (Siemens, Germany), with the upper normal limit of 5 mg/L. Trough levels of serum infliximab (TL IFX) were measured using a monoclonal-based enzyme immunoassay from ImmunoGuide (IG-AB101, AybayTech Biotechnology, Turkey), with a cutoff trough level of 3 μg/mL. Anti-IFX antibodies (ATIs) were measured using drug-sensitive enzyme immunoassay from ImmunoGuide (IG-BB101), with cutoff anti-drug antibody level of 4.5 ng/mL. Fecal calprotectin (FC) concentrations were measured using chemiluminescent immunoassay (LIAISON Calprotectin, code 318960, DiaSorin, Italy), with a cutoff value of 50 μg/g.

Statistical Analysis

Data were statistically evaluated using Statistica version 13 (Tibco, USA). Quantitative variables were tested for normality using the Shapiro–Wilk test, and because a normal distribution of the data was not demonstrated, non-parametric statistical approaches were adopted. Continuous variables were recorded as medians and in upper and lower quartiles, whereas categorical variables were recorded as numbers and percentages. The Mann–Whitney *U* test and Fisher's exact test were used to compare the analyzed groups. Two-tailed *P* values were reported, and values of $\leq .05$ were considered as significant in all analyses.

Ethical Considerations

Data were analyzed in accordance with the principles of the Declaration of Helsinki, and the project was approved by an institutional ethics committee (No 2022/IVa). All participants provided their written informed consent to participate in the study.

Results

Thirty-two patients with CD initiated IFX-SC treatment, and their data were collected and analyzed over the course of 30 weeks of treatment. Baseline characteristics of the analyzed CD cohort are shown in Table 1.

Prior to our study, all 32 patients in our cohort had been treated with 2 or more therapeutic monoclonal antibodies. For 14 of them (47.3%), IFX-SC was the third-line biologic, whereas the rest had a history of 3 or 4 failed treatments with different biologics, see Table S1. Of the 20 patients (62.5%) who had previously been treated with IFX-IV, 17 showed neutralizing serum antibodies to infliximab (ie, ATIs) before starting IFX-SC. The cohort consisted of young patients with a median age of 34.5 years, albeit with a median CD duration of up to 11 years. More than a third of patients were diagnosed before the age of 16 years and exactly half were between the ages of 16 and 40 years. Stricturing and/or penetrating behavior and ileocolic involvement were the most frequent clinical categories, and nearly half of the patients had perianal CD.

In patients naive to IFX or previously exposed to IFX-IV but with baseline ATI negativity ($n = 15$), 2 intravenous infusions of IFX-IV of 5 mg/kg at Weeks 0 and 2 were administered, followed with IFX-SC maintenance doses of 120 mg every other week beginning at Week 6. By contrast, for patients previously exposed to IFX-IV with baseline ATI positivity, induction treatment was implemented by administering four 120

Table 1. Patients' baseline demographic and clinical characteristics.

Gender, *n* (%)	
M	18 (56%)
F	14 (44%)
Age in years, median (IQR)	34.5 (27; 42.75)
Duration of IBD, median (IQR)	11 (7.75; 17)
Montreal CD classification	
A1, age at diagnosis ≤16 years	12 (37.5%)
A2, age at diagnosis 17-39 years	16 (50%)
A3, age at diagnosis ≥40 years	4 (12.5%)
B1, non-stricturing and non-penetrating behavior	3 (9.4%)
B2, stricturing behavior	16 (50%)
B3, penetrating behavior	13 (40.6%)
L1, ileal localization	0
L2, colonic localization	3 (9.4%)
L3, ileocolonic localization	27 (84.4%)
L4, isolated upper disease	2 (6.2%)
PACD, perianal disease	13 (40.6%)
MaRIA score, median (IQR)	6 (1; 13)
SES-CD score, median (IQR)	11 (1; 25)
IUS score, median (IQR)	11.45 (3; 19.1)
HBI score, median (IQR)	6 (1; 28)
Concomitant immune-modifying drugs	
None	13 (40.6%)
Systemic corticosteroids	8 (25%)
Azathioprine	6 (18.7%)
Methotrexate	3 (9.4%)
Ustekinumab	2 (6.3%)
Number of previously failed treatments with biologics	
2	14 (43.7%)
3	9 (28.15%)
4	9 (28.15%)
Previous IV-IFX treatment, *n*	20 (62.5%)
Positive serum anti-IFX antibodies, *n*	17/20 (85%)
History of infusion allergic reaction on IV-IFX, *n*	3/20 (15%)

Abbreviations: A, age at Crohn's disease onset; B, behavior of Crohn's disease; CD, Crohn's disease; F, female; HBI, Harvey–Bradshaw Index; IBD, inflammatory bowel disease; IFX, infliximab IQR, interquartile range; IUS, intestinal ultrasound score; IV, intravenous; L, localization of Crohn's disease; M, male; MaRIA, Magnetic Resonance Index of IBD Activity; PACD, perianal Crohn's disease; SES-CD, simple endoscopic score for Crohn's disease; W, treatment week.

mg IFX-SC injections at weekly intervals, followed by IFX-SC maintenance doses of 120 mg every other week beginning at Week 5. If IFX-SC treatment needed to be intensified, then the dose was increased to 240 mg every other week (EOW).

Treatment Persistence at W30

Overall, midterm treatment persistence with the continuation of treatment after W30 was 53%.

In the subgroup of patients who were ATI-negative at W0, 10 (66.7%) continued on IFX-SC treatment up to W30. Five (33.3%) patients stopped prematurely due to the inconvenience of SC administration ($n = 1$), progression of ischemic heart disease ($n = 1$), acute infusion reaction during the second dose of IFX-IV ($n = 1$), and non-response ($n = 2$), as shown in Figure 1. One patient with non-response exhibited newly developed neutralizing ATIs during treatment with IFX-SC.

In the subgroup of patients who were ATI-positive at W0, treatment persistence at W30 was observed in 7 patients (41.2%), whereas 10 patients (58.8%) dropped out of the treatment prematurely. The reasons for discontinuing treatment were severe delayed hypersensitivity reactions manifested after doses at Weeks 0, 2, and 3 ($n = 4$), disease progression despite high TL IFX ($n = 3$), and non-response with persistent ATI positivity ($n = 4$), as also shown in Figure 1.

A total of 13 out of 32 CD patients had active perianal disease at baseline. Of these, 9 (69%) reached W30 with reduced perianal symptoms or closure of draining fistulas. However, endoscopic evaluation, pelvic MRI, and/or surgical examination under anesthesia will be performed at W52, and the 12-month healing rate will be determined.

Immunogenicity of IFX-SC at W30

In the subgroup of patients who were ATI-negative at W0 ($n = 15$), only one showed IFX immunogenicity with newly developed ATIs. By comparison, in the subgroup of 17 patients who were ATI-positive at W0, ATI seroconversion from ATI-positive to ATI-negative status was observed in 10 patients (58.8%).

TL IFX median values showed rapid, significant upward dynamics and exceeded 15.5 μg/mL at W30, whereas median ATI levels significantly declined, as shown in Figure 2.

Dynamics of Clinical, Serum, and Fecal Biomarkers

Patients who continued IFX-SC treatment at W30 regardless of baseline ATI status showed a significant decrease in CRP, FC, and HBI during the 30 weeks of follow-up, as shown in Figure 3.

Dose Intensification

In 10 patients, dose intensification to 240 mg EOW was realized because of inadequate treatment response characterized by symptomatic and clinical criteria. In 7 patients, dose intensification to 240 mg IFX-SC every other week led to higher TL, clinical improvement, and was followed by treatment persistence. In 3 patients, such intensification did not lead to clinical improvement, and their ATI status remain positive.

Possible Predictors for W30 Treatment Persistence

None of the baseline clinical or laboratory parameters emerged as a possible predictor of treatment response or failure, with one exception: baseline concentration of ATIs. Higher ATI serum levels at W0 were significantly associated with the failure of treatment at W30, as shown in Table 2.

Discussion

Our study has demonstrated that patients with refractory CD characterized by a severe disease course can be treated safely with IFX-SC even after the failure of multiple other treatments, including IFX-IV, and midterm clinical improvement is possible in more than half of them.

Managing IFX non-response is an important challenge in clinical practice. Although IFX is effective in inducing and maintaining remission in CD and has significantly advanced

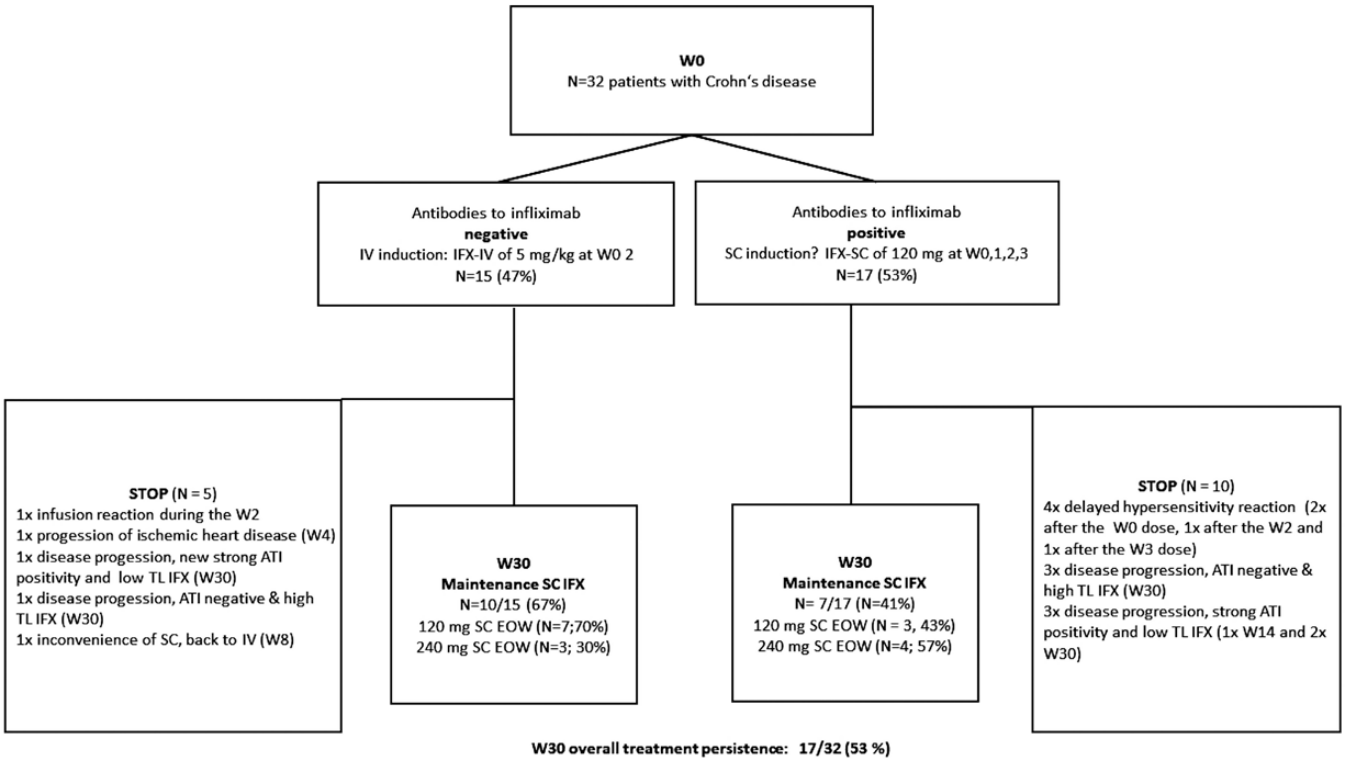

Figure 1. IFX-SC treatment process flowchart, Weeks 0–30. ATI, antibodies to infliximab; EOW, every other week; IFX, infliximab; IV, intravenous; SC, subcutaneous; TL, trough level; W, treatment week.

the treatment of chronic inflammatory disease,[11] its long-term effect is detected in only a third of patients with CD.[12] Primary non-response therapy occurs in approximately 40% of patients in clinical trials and up to 20% in clinical practice,[13,14] both groups of whom have generally shown a relatively complicated prognosis,[15] including an increased risk of needing gut surgery. Among individuals with the initial treatment response, 30%-50% have lost response over the course of a year.[16] Patients with any loss of treatment response generally do not respond as well to other biologics as biologic-naive patients do.[17] Against that background, the concept of biobetters, or biosuperiors, a new category of biopharmaceuticals with better efficacy, longer half-lives, lower dosing frequency, or reduced risk of immunogenicity and side effects, has been guided by efforts to enhance treatment persistence.

Our midterm results show that IFX-SC could serve as a biobetter for at least some patients with CD and complicated disease courses, including ones for whom previous treatments have failed. IFX-SC showed less immunogenic potential than IFX-IV, and only one patient in our sample exhibited newly developed ATI during the study period. Only 7% ATI positivity in the sample during the first 30 weeks of IFX-SC treatment is a promising sign, especially because data for IFX-IV have differed. According to Ungar et al. and the ABIRISK consortium,[18] the prevalence of the formation of ATIs during IFX-IV treatment can reach nearly 50%, whereas the median time of their emergence was 1.5 months, which implies that 75% of patients had developed ATIs by Week 22.

On top of that, the subcutaneous administration of IFX may induce seroconversion and the disappearance of ATIs from circulation. In the group of patients after stopping IFX-IV for failure due to immunogenicity/ATI positivity, we were inspired by Caron et al.'s experience with exclusive SC induction treatment. This French working group hypothesized that the mode of IFX administration influences this risk of adverse treatment reaction more than the drug itself, and has proposed IFX-SC induction with 120 mg at weeks 0, 1, 2, 3, and 4.[19] In our cohort, the disappearance of ATIs by the W30 was observed in nearly 60% of patients who were ATI-positive at W0, and who underwent SC-only induction. Therefore, IFX-SC may allow the reinduction of IFX in a significant portion of patients even after previous sensitization to IFX. Our results might be promising in showing that reversing anti-infliximab positivity could be possible by changing the route of infliximab administration.

The rate of midterm (ie, by W30) treatment persistence (53%) with IFX in our study was less than previously published. In Smith's cohort of 181 patients with IBD (n = 115 with CD), only 14 patients (7.7%) stopped IFX-SC treatment during the 12-month follow-up period after switching from IFX-IV; however, more than 90% of the examined cohort was in clinical remission at the time of that non-medical switching.[3] The explanation of significantly lower treatment persistence in our cohort could be that IFX-SC was administered as a third- or fourth-line treatment after several previous failed treatments. In that case, treatment persistence is not comparable with non-medical switching.

The only factor predicting the persistence of IFX-SC treatment in our study was ATI negativity at W0. High concentrations of ATIs at baseline were connected with a high rate of early and midterm non-response.

Among patients who responded to IFX-SC treatment at W30, significant declines in HBI, CRP, and FC values were

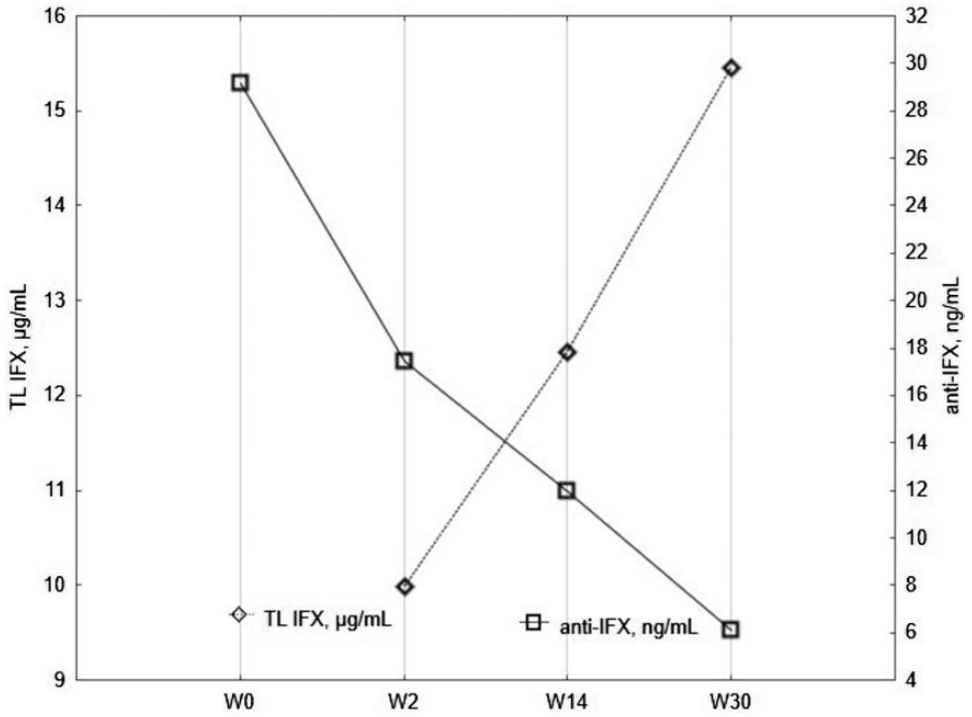

Figure 2. Medians of upward TL IFX and downward ATI dynamics during the first 30 weeks of IFX-SC treatment. ATI, antibodies to infliximab; IFX, infliximab; TL, trough level; W, treatment week.

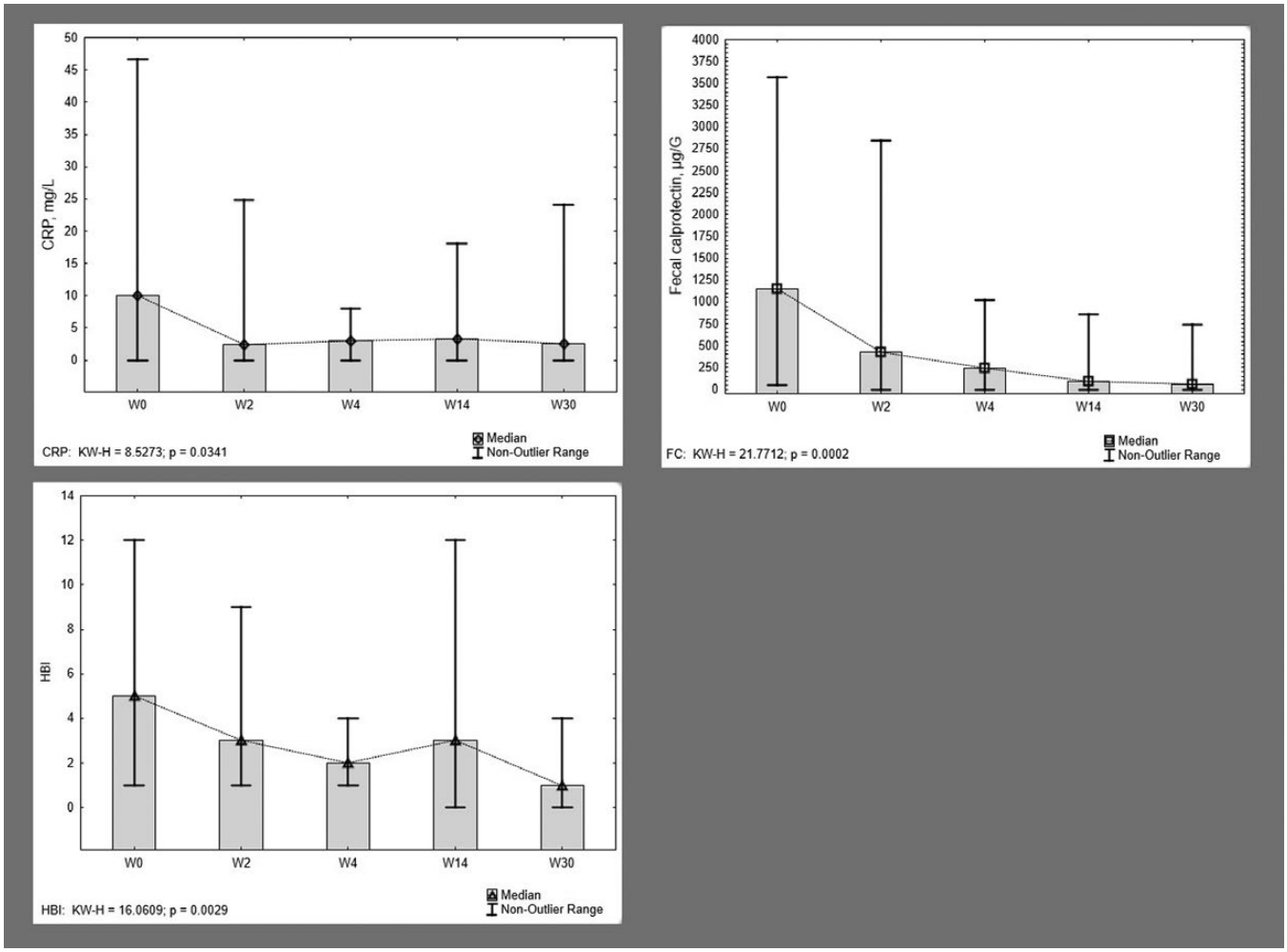

Figure 3. Dynamics of CRP, FC, and HBI during the first 30 weeks of IFX-SC treatment. CRP, C-reactive protein; FC, fecal calprotectin; HBI, Harvey–Bradshaw Index; W, treatment week.

Table 2. Predictors of persistence of IFX-SC treatment through Week 30.

	IFX-SC W30 treatment persistence (*n* = 17)	IFX-SC W30 treatment failure (*n* = 15)	*P*
Previous IV-IFX, *n* (%)	6 (54.5%)	5 (50%)	.602
HLA-DQA1*05 (rs2097432) positive, *n* (%)	5 (29.4%)	7 (46.6%)	.467
PACD, *n* (%)	9 (52.9%)	4 (26.7%)	.166
Induction treatment mode SC, *n* (%)	10 (58.8%)	9 (60%)	.615
Age in years, median (IQR)	35 (25;41)	31 (29;40.5)	.550
Duration of CD in years, median (IQR)	10 (7;15)	14 (9;19.5)	.189
Previous treatments with biologics, *n*, median (IQR)	2 (2;3)	3 (2;4)	.411
Concomitant corticosteroids at W0, *n* (%)	5 (29.4%)	3 (20%)	.691
Concomitant immunosuppressants at W0, *n* (%)	7 (41.2%)	5 (33.3%)	.726
HBI at W0, median (IQR)	4 (2;7)	5 (4;7)	.390
SES-CD at W0, median (IQR)	11 (5;18)	10.5 (6.25;16.3)	.984
IUS at W0, median (IQR)	6.5 (4.98;8.34)	7.95 (5.1;9.15)	.358
MaRIA at W0, median (IQR)	6 (5;7.75)	6 (5;11)	.781
CRP at W0, mg/L, median (IQR)	10.1 (2.8;26.8)	6.9 (2.1;19.99)	.654
FC at W0, µg/g, median (IQR)	1,153 (456;1,920)	1,021 (260;1,453)	.467
Anti-IFX, ng/m at W0, median (IQR)	0 (0;21)	60 (5.8; 60)	**.013**

Analysis of baseline (W0) clinical and laboratory parameters in relation to patients IFX-SC treatment persistence at week 30. Bold value indicates statistical significance.
CD, Crohn's disease; CRP, C-reactive protein; FC, fecal calprotectin; HBI, Harvey–Bradshaw Index; IFX, infliximab; IQR, interquartile range; IQR, interquartile range; IUS, intestinal ultrasound score; MaRIA, Magnetic Resonance Index of IBD Activity; PACD, perianal Crohn's disease; SES-CD, simple endoscopic score for Crohn's disease; W, treatment week.

observed. We are aware that error bars as revealing the uncertainty of our data points for HBI, CRP, and FC are relatively large, and this may indicate that the values are spread out and less reliable. The explanation for this is primarily in the heterogeneity of examined cohort and our patient population.

The treatment response could be a result of the higher IFX drug levels achieved. Lack of fluctuations in IFX levels during the administration of IFX-SC may protect against the development of immunogenicity previously documented with IFX-IV. Among such patients, IFX-SC appears to be safe, and no seriously adverse events have been reported, only positive patient feedback and overall satisfaction.

The strength of our findings rests in the fact that patients with refractory CD with a severe disease course in our real-world study demonstrated that IFX-SC was an efficacious treatment. The same group of patients with IBD was not included in a previous randomized controlled trial.[20] As for our study's limitations, the weakest point is that our cohort is small—much smaller than the Smith's randomized controlled trial,[20] so it is difficult to extrapolate our results. Moreover, no placebo or controlled arm was included.

Altogether, IFX-SC seems to be a promising alternative to IFX-IV for treating IBD. Our results suggest that it is a safe, effective treatment option even for patients with a complicated disease course. However, midterm treatment persistence may be lower, especially among patients with preexisting IFX immunogenicity and strong ATI positivity before the start of treatment. Stable, persistent IFX-SC blood levels may indeed be a factor of effective biobetters for some patients, and further controlled studies are needed for their more precise identification.

Supplementary Data

Supplementary data are available at *Crohn's & Colitis 360* online.

Author Contributions

The authors confirm their contribution to the paper as follows: study conception and design: M.L., K.C.; data collection: K.C., D.D., M.L., M.K., N.M., V.H., K.M., K.K., M.K., J.J., K.K., G.V., S.P., M.L.; analysis and interpretation of results: K.C., M.L., D.D.; draft manuscript preparation: K.C., M.L., D.D. All authors reviewed the results and approved the final version of the manuscript.

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Conflicts of Interest

K.C.: has consulted for Celltrion and Biogen. D.D.: has consulted for Takeda, AbbVie, Pfizer, and Janssen. M.L.: has consulted for Takeda and Pfizer. M.K.: has consulted for Pfizer. N.M.: has consulted for Takeda and Janssen. V.H.: has consulted for Biogen and Janssen. K.M.: has consulted for Takeda and Janssen. K.K.: has consulted for Abbott. M.K.: has consulted for Takeda and Janssen. J.J.: none. K.K.: none. G.V.: none. S.P.: none. M.L.: provided consultations and received fees for lectures by Celltrion, Abbvie, Janssen, Takeda, and Ferring.

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