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 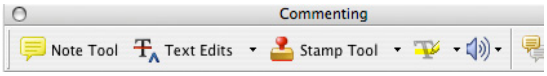

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 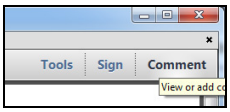

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 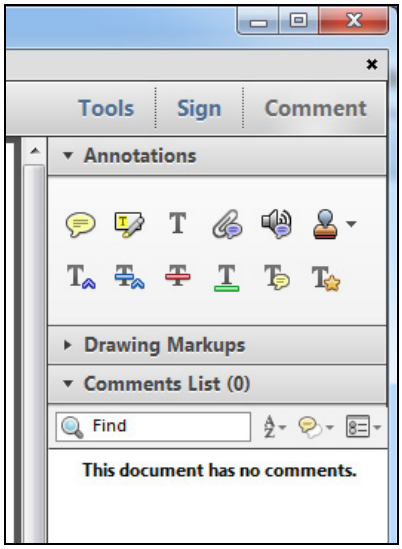
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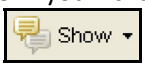
Review	To review your changes, click on the 'Show' button  on the Commenting tool bar. Choose 'Show Comments List'. Navigate by clicking on a correction in the list. Alternatively, double click on any mark-up to open the commenting box.	Your changes will appear automatically in a list below the Comment tool bar. Navigate by clicking on a correction in the list. Alternatively, double click on any mark-up to open the commenting box.
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Outcomes of Patients With Inflammatory Bowel Diseases Switched From Maintenance Therapy With a Biosimilar to Remicade

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BACKGROUND & AIMS: There is evidence that it is safe and effective for patients with inflammatory bowel diseases (IBD) to switch from maintenance therapy with an original infliximab drug to a biosimilar, but little is known about outcomes of reverse switches and/or multiple switches. We aimed to evaluate the effects of a reverse switch (from a biosimilar to Remicade) in a real-life cohort.

METHODS: We performed a prospective observational study of 174 unselected and consecutive patients with IBD (136 with Crohn's disease [CD] and 38 with ulcerative colitis [UC]) who received maintenance therapy with the biosimilar in Hungary. In September 2017, patients were switched from the biosimilar (CT-P13) to Remicade, due to reimbursement policies. In our cohort, 8% (n = 14) patients had been previously exposed to the originator Remicade. We collected clinical and biochemical information from patients at baseline (time of the switch) and 16 and 24 weeks thereafter. Clinical remission was defined as a Crohn's disease activity index <150 points or no fistula drainage, or a partial Mayo score <3 points for patients with UC. Serum drug trough levels and anti-drug antibodies were measured at baseline and week 16.

RESULTS: There was no significant difference in the proportion of patients in clinical remission at week 8 before the switch (82.5% with CD and 82.9% with UC), at baseline (80.6% with CD and 81.6% with UC), at week 16 (77.5% with CD and 83.7% with UC), or at week 24 (CD 76.3% with CD and 84.9% with UC) (P = .60 among groups for patients with CD and P = .98 among groups for patients with UC). For all patients, mean serum trough levels of infliximab were 5.33 ± 4.70 μg/mL at baseline and 5.69 ± 4.94 μg/mL at week 16 (P = .71); we did not find significant differences in prevalence of anti-drug antibody at baseline (16.2%) compared with week 16 (16.9%) (P = .87). Four infusion reactions occurred, until week 24 of follow up. There was no difference in outcomes or trough or antidrug antibody levels between patients with or without previous exposure to Remicade.

CONCLUSIONS: We collected data from a real-life cohort of patients with CD or UC who were switched from maintenance therapy with a biosimilar to Remicade or were treated with only Remicade. No significant changes were observed in remission, trough levels, or antidrug antibodies in patients switched from the biosimilar to Remicade. No new safety signals were detected.

Keywords: Outcome; Originator Drug; TNF Antagonist; Drug Monitoring.

[a]Authors share co-first authorship.

Abbreviations used in this paper: ADA, anti-drug antibody; CD, Crohn's disease; CDAI, Crohn's Disease Activity Index; IBD, inflammatory bowel disease; IFX, infliximab; IQR, interquartile range; NEAK, National Health Insurance Fund of Hungary; pMayo, partial Mayo; TDM, therapeutic drug monitoring; TL, trough level; TNF, tumor necrosis factor; UC, ulcerative colitis.

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Biological agents represent a fundamental step in the therapy of inflammatory bowel disease (IBD). Infliximab (brand name Remicade) is a monoclonal antibody directed against tumor necrosis factor (TNF) alpha that has shown distinct efficacy in patients with Crohn's disease (CD) and ulcerative colitis (UC).[1,2] The global expenditure on biological treatments approaching almost unaffordable costs,[3] and the recent expiry of patents for biologics has led to the development of biosimilar products. CT-P13 was the first infliximab (IFX) biosimilar to be approved with the same therapeutic indications as its originator product by the European Medicines Agency and later by the U.S. Food and Drug Administration.[4,5]

The acceptance of biosimilars among physicians encountered some resistance in the past few years, especially when considering switching from the originator product to its biosimilar. To date, data accumulated from real-life cohorts and randomized controlled trials on the clinical efficacy, safety, and immunogenicity of biosimilar CT-P13 show comparable outcomes with the originator IFX in both anti-TNF-naïve and switched patients.[6–15] In January 2017, the ECCO presented a position statement on biosimilars and concluded that there are no clinically meaningful differences between CT-P13 and the originator IFX regarding efficacy and safety and switching from the originator to an approved biosimilar product is acceptable.[16] Nonetheless, physicians may need to also consider reverse switching (switch back to the originator product) or cross-switching, multiple switching among biosimilars in the near future. This tendency will potentially result in a continuous change in prescription preferences of anti-TNF drugs, highlighting the importance of pharmacovigilance. Evidence is currently lacking regarding reverse switching, multiple switching, and cross-switching among biosimilars in IBD patients.

The biosimilar IFX CT-P13 (brand name Inflectra) entered the Hungarian market in 2014 and was adopted for reimbursement by the National Health Insurance Fund of Hungary (NEAK).[17] The use of biosimilar IFX was mandatory in Hungary between May 2014 and September 2017 in all anti-TNF-naïve patients and in patients who were previously treated with the originator product with proven clinical benefit but have been on drug holiday for longer than 12 months. Last year, the national tender for IFX therapy reimbursement by the NEAK has been won by Remicade, and as a consequence the originator became the only fully reimbursed IFX biologic agent in Hungary after September 2017.[18] Due to this policy change, a nationwide nonmedical reverse switch was carried out in all IBD patients from the biosimilar to the originator IFX.

The aim of the present study is to evaluate short-term drug sustainability, efficacy, safety, and immunogenicity profile of reverse switching from a biosimilar to the originator IFX in consecutive IBD patients in a multicenter real-life IBD cohort.

What You Need to Know

Background

There is evidence that it is safe and effective for patients with inflammatory bowel disease to switch from maintenance therapy with an original infliximab drug to a biosimilar drug, but little is known about outcomes of reverse switches or multiple switches. We studied the effects of a reverse switch (from a biosimilar to Remicade) in a real-life cohort.

Findings

We found no significant changes in remission, trough levels, or anti-drug antibodies in patients switched from the biosimilar to Remicade. Good medium-term drug sustainability was observed, with no new safety signals.

Implications for patient care

In a real-life cohort of patients with inflammatory bowel disease, we found no significant changes in patients switched from a biosimilar to Remicade. As the number of biosimilar agents on the market increases, data on reverse or multiple switches are needed to guide decision making and provide information on their interchangeability.

Materials and Methods

This is a multicenter prospective observational study enrolling unselected and consecutive patients who were switched from the biosimilar IFX CT-P13 (Inflectra) to the originator Remicade during maintenance therapy. Patients received intravenous infusions of IFX (5 mg/kg or 10 mg/kg of body weight) every 8 weeks. The inclusion started in September 2017, when Remicade became the only available IFX biologic agent in Hungary, and thus the mandatory reverse switch to the originator was initiated. Four referral IBD centers participated in the study: 3 university centers and 1 county hospital.

Patient demographics, previous and concomitant medications were recorded, disease location and behavior in CD and disease extent in UC were assessed according to the Montreal classification.[19] A harmonized monitoring strategy was applied in all participating centers, as requested by the NEAK. Clinical and biochemical assessment was performed at baseline or switch and 16 and 24 weeks thereafter. Clinical remission was defined as a Crohn's Disease Activity Index (CDAI) <150 points or no fistula drainage as assessed by the fistula drainage assessment in CD and as a partial Mayo (pMayo) score of <3 points in UC.[2,20,21] Patients with induction treatment at baseline were excluded from the clinical activity assessment. Biochemical activity was evaluated using serum C-reactive protein (normal cutoff 10 mg/L). Infusion-related adverse events were registered at baseline and weeks 8, 16, and 24.

Therapeutic Drug Monitoring

Serum drug trough level (TL) and anti-drug antibody (ADA) were measured at baseline and week 16. Patients with induction treatment at baseline or dose intensification or de-escalation during follow-up were excluded from the analysis of therapeutic drug monitoring (TDM). For the measurement of IFX TL and ADAs, conventional and bridging enzyme-linked immunosorbent assay methods were used (Lisa-Tracker infliximab LT-005 Duo; Theradiag, Croissy-Beaubourg, France). The detection cutoff value of IFX TL was 0.1 μg/mL. Therapeutic IFX TL was defined between 3 and 7 μg/mL. The cutoff value of ADA detection was 10 ng/mL as defined by the enzyme-linked immunosorbent assay kit. For better stratification of patients, we defined the ADA titer >200 ng/mL as "high" ADA titer. The enzyme-linked immunosorbent assay measurements were centralized and performed at the Department of Laboratory Medicine, Semmelweis University.

Statistical Analysis

Data were analyzed with the use of SPSS 20.0 software (IBM Corporation, Armonk, NY). Descriptive statistics were used to characterize patients' demographics, clinical remission and disease activity rates, and adverse events. Clinical remission rates and ADA positivity rates were compared by chi-square test or Fisher exact test. Biochemical response and infliximab TLs were evaluated by 1-way analysis of variance, using Scheffé post hoc analysis, t test with separate variance estimates, and Mann–Whitney U test. The value of $P < .05$ was considered statistically significant.

Ethical Considerations

Ethical approval was acquired from the National Ethical Committee 929772-2/2014/EKU (292/2014). Written informed consent was obtained from all participants.

Results

A total of 174 IBD patients (136 CD and 38 UC) were included in this cohort. Patient characteristics at baseline are shown in Table 1. Complicated disease behavior and perianal manifestation was present in 39.7% and 48.5% of CD patients. 54.1% of UC patients had extensive colitis. Concomitant steroid and immunosuppressive therapy (azathioprine) was present in 8.8% and 50.7% and 27.0% and 35.1% of CD and UC patients at baseline, respectively. Previous anti-TNF use was 19.9% and 16.2% in CD and UC patients, respectively. A total of 11% and 7.9% of CD and UC patients, respectively, have already been exposed to the originator IFX previously. Previous resective surgery rates were 26.1% among CD patients.

Table 1. Baseline Patient Characteristics

	CD (n = 136)	UC (n = 38)
Female/male	67/69 (49.3/50.7)	16/21 (44.7/55.3)
Age at disease onset, y	27.5 (20–32.7)	25 (19.5–34.25)
Disease duration, y	8 (4-14)	7 (4-14)
Location (L1/L2/L3/all L4)	11.0/32.4/56.6/10.7	—
Extent (E1/E2/E3)	—	5.4/40.5/54.1
Behavior (B1/B2/B3)	55.9/18.4/21.3	—
Perianal	48.5	—
Previous resective surgery/ colectomy, %	26.1	—
Concomitant steroid/AZA	8.8/50.7	27.0/35.1
Previous anti-TNF[a]	19.9	16.2
Originator IFX (Remicade)	8.1	7.9
Biosimilar IFX (Inflectra)	1.5	—
Adalimumab	7.4	5.3
Both IFX (Remicade) and adalimumab	2.9	—

Values are n (%),median (interquartile range), or %.
AZA, azathioprine; CD, Crohn's disease; IFX, infliximab; TNF, tumor necrosis factor; UC, ulcerative colitis.
[a]All patients who were previously exposed to the originator IFX had been on a drug holiday for at least 12 months before the initiation of their current IFX treatment regimen.

Clinical Outcomes and Drug Sustainability After Reverse Switch

A total of 129 CD and 38 UC patients had available clinical data at baseline. Median CDAI and pMayo scores were 57 (IQR, 32–112) and 1 (IQR, 0–2) at baseline and switch; 68 (IQR, 35–125.5) and 1 (IQR, 0–1) at week 16; and 60 (IQR, 31–100) and 1 (IQR, 0–2) at week 24. Median clinical activity scores and mean C-reactive protein levels during the complete follow-up period are shown in Table 2. Mean CDAI and pMayo scores at week 8, baseline, week 16, and week 24 were compared, with 1-way analysis variance analysis showing no statistically significant variance between clinical activity scores (CD: $P = .53$; UC: $P = .57$). Mean C-reactive protein levels also showed no statistically significant difference throughout the follow up-period (CD: $P = .23$; UC: $P = .53$).

The change in clinical disease activity based on CDAI and pMayo scores during follow-up are presented in Figures 1 and 2; 90.3% of all patients who were in clinical remission at switch and baseline sustained clinical remission up to week 16 and 88.2% up to week 24. There was no significant difference between the proportion of patients in clinical remission at week 8 before switch, at switch and baseline, and at week 16 and 24 (CD: 82.6%, 80.6%, 77.5%, and 76.3%, respectively, $P = .60$; UC: 82.9%, 81.6%, 83.7%, 84.8%, respectively, $P = .98$). Three patients required dose optimization between baseline and week 16; however none of them were in clinical remission at baseline. Of note, concomitant low-dose (≤10 mg) steroid use in UC and CD patients with remission at baseline (n = 7 of 31,

Table 2. Clinical and Biochemical Activity During Follow-Up

Patients on Maintenance IFX Therapy	Week 8 Before Switch[a]	Switch/Baseline	Week 16	Week 24[a]
CD	n = 115	n = 129	n = 118	n = 98
CDAI	52.5 (30.25–99.25)	57 (32–112)	68 (35–125.5)	60 (31–100)
CRP	9.89 ± 13.21	8.74 ± 12.88	8.41 ± 9.79	6.69 ± 6.56
UC	n = 34	n = 38	n = 35	n = 30
pMayo	1 (0–2)	1 (0–2)	1 (0–1)	1 (0–2)
CRP	5.06 ± 5.74	4.73 ± 5.17	7.47 ± 10.66	5.99 ± 6.26

Values are mean ± SD or median (interquartile range).
CD, Crohn's disease; CDAI, Crohn's Disease Activity Index; CRP, C-reactive protein; IFX, infliximab; LOR, loss of response; pMayo, partial Mayo; UC, ulcerative colitis.
[b]Lost to follow-up (up to week 16): n = 5 patients discontinue IFX due to LOR (active disease at baseline), n = 1 patient discontinue IFX due to LOR (remission at baseline), n = 3 patients presented infusion reaction, n = 2 patients underwent surgery (active disease at baseline).
[c]Lost to follow-up (after week 16): n = 1 patient discontinue IFX due to LOR (remission at baseline), n = 1 patient discontinue IFX due to LOR (active disease at baseline), n = 1 patient underwent surgery (active disease at baseline), n = 1 patient presented infusion reaction, n = 1 patient had suspected malignancy, n = 1 patient was lost to follow-up.
[d]Lost to follow-up (up to week 16): n = 2 patients discontinue IFX due to LOR (active disease at baseline), n = 1 patient was lost to follow-up.
[e]Lost to follow-up (after week 16): n = 1 patient discontinue IFX due to LOR (active disease at baseline).
[a]Week 8 data before baseline and week 24 data are only available from 3 centers.

22.6%; n = 6 of 104, 5.8%, respectively) was not predictive for clinical relapse at weeks 16 and 24.

Clinical outcomes were not different in the cohort of patients with a previous exposure to the originator IFX (13.9% of all patients, n = 18; clinical remission rates at week 8 before switch, at switch and baseline, and at week 16 and 24 were 86.7%, 100%, 94.4%, and 93.3%, respectively; $P = .46$) or in patients with the biosimilar IFX as first IFX (82.4%, 78.5%, 77.0%, and 76.7%, respectively; $P = .65$).

TDM: TLs and Immunogenicity After Reverse Switch

Serum IFX TLs and ADAs of all IBD patients receiving week 16 infusion are presented in Table 3. No significant difference was observed in mean serum IFX TLs between switch and baseline and week 16 (5.33 ± 4.70 μg/mL vs 5.69 ± 4.94 μg/mL; $P = .71$). Patients were stratified based on subtherapeutic serum IFX TLs (<3 μg/mL), adequate serum IFX TLs (7 μg/mL ≥ TL ≥3 μg/mL), and supratherapeutic serum IFX TLs (> 7 μg/mL) as shown in Supplementary Figure 1. Mean serum IFX TLs were 4.89 ± 4.39 μg/mL and 5.33 ± 4.58 μg/mL for CD

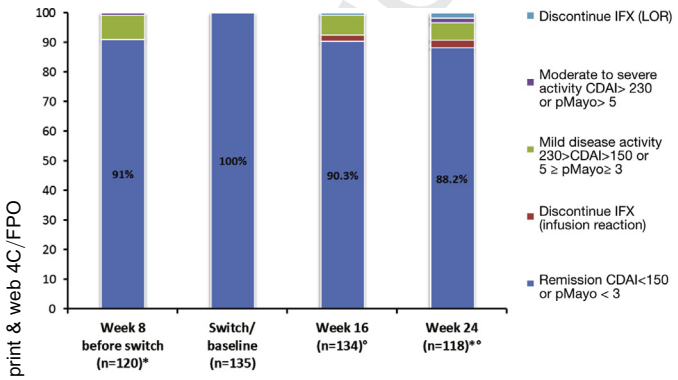

Figure 1. Clinical activity before and after reverse switch in IBD patients in remission at switch *Week 8 data before baseline and week 24 data are only available from 3 centers. °Two patients were lost to follow-up. LOR, loss of response.

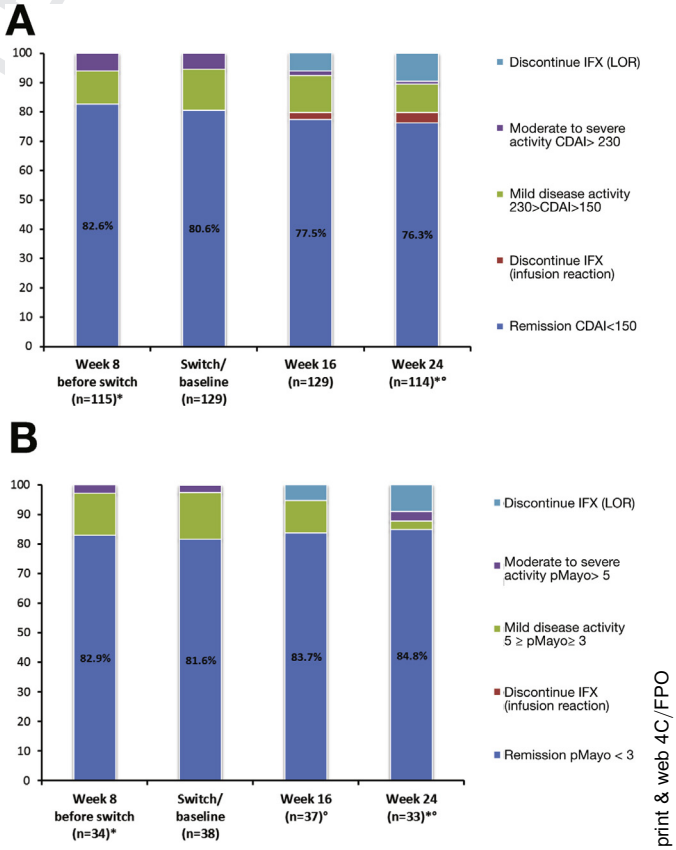

Figure 2. (*A*) Clinical activity before and after reverse switch in CD patients. *Week 8 data before baseline and week 24 data are only available from 3 centers. °One patient was lost to follow-up. (*B*) Clinical activity before and after reverse switch in UC patients. *Week 8 data before baseline and week 24 data are only available from 3 centers. °One patient was lost to follow-up. LOR, loss of response.

Table 3. Trough Levels and Anti-Drug Antibodies in IBD Patients

All IBD Patients on Maintenance IFX Therapy (n = 130)	Switch		Week 16	
	Single-Dose IFX[a] (n = 111)	Increased-Dose IFX[b] (n = 19)	Single-Dose IFX[a] (n = 111)	Increased-Dose IFX[b] (n = 19)
Serum IFX trough level, μg/mL	5.33 ± 4.70		5.69 ± 4.94	
	5.34 ± 4.62	5.26 ± 5.31	5.49 ± 4.62	6.87 ± 6.52
Anti-drug antibody positivity (>10 ng/mL)	16.2		16.9	
High anti-drug antibody positivity (>200 ng/mL)[c]	8.5		8.5	

Values are mean ± SD or %.
IBD, inflammatory bowel disease; IFX, infliximab.
[a]IFX dose: 5 mg/kg of body weight.
[b]IFX dose: 10 mg/kg of body weight.
[c]●●●.

patients at baseline vs week 16 ($P = .59$); and 6.66 ± 5.41 μg/mL vs 6.81 ± 5.84 μg/mL for UC patients ($P = .92$) (Supplementary Tables 1 and 2)

Stratification of CD and UC patients based on subtherapeutic, adequate and supratherapeutic TLs are shown in Supplementary Figures 2 and 3. No significant differences were observed in ADA formation (overall ADA positivity: 16.2% vs 16.9% at baseline and week 16, $P = .87$; rates of high ADA positivity: 8.5% and 8.5%, $P = 1$). One CD patient developed high ADA positivity (>200 ng/mL) from ADA-negative status at baseline.

Fourteen patients with TDM at baseline and week 16 of this cohort have previously been exposed to the originator IFX. All patients had been on a drug holiday for at least 12 months before the initiation of their current IFX treatment regimen. By separately analyzing these patients, also no statistically significant difference was observed between baseline and week 16 TLs (6.51 ± 4.65 μg/mL vs 8.11 ± 4.44 μg/mL, $P = .25$). ADA positivity rates were also identical at baseline and week 16 (14.3%; n = 2 for both).

The rate of concomitant azathioprine therapy remained unchanged during the follow-up period. By separately analyzing patients with combined immunosuppressive therapy and IFX monotherapy, there were no statistically significant differences between baseline and week 16 TLs in either group. Mean TLs were somewhat higher among azathioprine-treated patients at baseline (5.80 μg/mL vs 4.86 μg/mL; $P = .13$), and significantly higher at week 16 (6.63 μg/mL vs 4.76 μg/mL; $P = .006$) as well. There were also no statistically significant differences in ADA positivity rates at baseline compared with week 16 by analyzing combined and monotherapy separately. However, ADA positivity was significantly lower in patients with combined immunosuppression at both baseline (4.6% vs 27.7%; $P = .001$) and week 16 (7.7% vs 26.2%; $P = .005$).

Adverse Events After Reverse Switch

A total of 174 patients were evaluated for infusion related adverse events. Three infusion reactions occurred up to week 16 follow-up and altogether 4 infusion reactions up to week 24 (Table 4). No anaphylactic reaction was observed. All patients with infusion reaction had detectable ADAs at baseline and none of these patients have previously been exposed to the originator IFX. Drug sustainability in patients with clinical remission at baseline and switch is presented in Table 4.

Discussion

As the registration clinical trials for CT-P13 were performed in non-IBD patients, significant amount of

Table 4. Adverse Events in Patients With Reverse Switch and Drug Sustainability in Patients in Clinical Remission at Switch and Baseline

	Switch/ Baseline	Week 8	Week 16	Week 24
Infusion-related adverse events (n = 174)				
Infusion reaction	1	2	0	1
Anaphylaxis	0	0	0	0
Drug sustainability in patients with remission at switch (n = 142)				
Patients discontinued IFX treatment up to week 16				
LOR, clinical relapse				1 (0.7)
Infusion reaction				3 (2.1)
Patients discontinued IFX treatment up to week 24				
LOR, clinical relapse				2 (1.4)
Infusion reaction				3 (2.1)

Values are n or n (%).
IFX, infliximab; LOR, loss of response.

postmarketing data have accumulated in the past few years on the biosimilar IFX. Results from real-word observational cohorts and randomized controlled trials evaluating IFX naïve patients and switching showed that the biosimilar IFX CT-P13 is effective and safe in inducing and maintaining clinical remission in CD and UC. Immunogenicity and pharmacokinetic profile of CT-P13 is comparable to that of the originator product and there have been no reports that switching from the originator to the biosimilar IFX would have any meaningful effect on clinical efficacy or safety.[6–14]

The most compelling data are reported by Kim et al[12] in a phase III randomized controlled trial comparing CT-P13 with the originator IFX in patients with active CD. A total of 220 patients were randomized to 4 groups; maintenance groups (CT-P13 vs originator IFX) and switching groups (CT-P13 to originator IFX vs originator IFX to CT-P13; switch was performed at week 30). Rates of CDAI-70 response, CDAI-100 response and clinical remission were similar for CT-P13 and the originator IFX at week 30. At week 54, clinical remission as well as CDAI-70 response rates were maintained, results were comparable in all 4 treatment groups. There were no meaningful differences in ADA positivity rates between the treatment groups. One-year safety including adverse drug reactions, serious adverse events, and infections was similar among all treatment groups.[12] The NOR-SWITCH study evaluated the clinical efficacy and safety of the biosimilar IFX through 52 weeks after switching from the originator in a merged cohort of multiple immune-mediated diseases including IBD; however, the study was not powered to allow for conclusions on individual diseases.[11] In the 26-week open label NOR-SWITCH EXTENSION part of the study,[13] treatment efficacy, safety, and immunogenicity were assessed regarding CT-P13 treatment throughout the 78-week study period (maintenance group) compared with switching from the originator IFX to CT-P13 at week 52 (switch group). The primary endpoint was overall disease worsening during follow-up. Exploratory subgroup analyses of IBD (124 CD and 74 UC patients) showed that disease worsening occurred in 20.6% and 13.1% in CD patients and in 15.4% and 2.9% in UC patients in the maintenance and switch groups, respectively. These results were within the predefined noninferiority margin of 15%. The incidence of adverse events and ADA rates were comparable between arms.[13] Another recent prospective trial is the SECURE trial[22] with the objective to demonstrate the noninferiority of IFX serum concentrations of biosimilar IFX CT-P13 (Remsima) to IFX concentrations of Remicade. No significant changes were observed in IFX TLs (ratio of biosimilar and originator IFX serum concentrations: 107.6% [90% confidence interval, 97.44–118.81] and 110.1% [90% confidence interval, 95.99–126.29] for CD and UC, respectively).[23]

The SB2 IFX biosimilar has recently been approved by the European Medicines Agency and the Food and Drug Administration for all indications of the originator product, as well.[24,25] Fischer et al[23] performed a study on clinical outcomes and immunogenicity analysis following a switch from originator IFX (Remicade) to the biosimilar SB2 (Flixabi). Median change in disease activity was 0 (interquartile range [IQR], −0.8 to 1.8) at week 16 and 1 (IQR, 0.0 to 2.0) at week 24 in CD; 0 (IQR, −1.0 to 0.0) at week 16 and 0 (IQR, −1.0 to 0.0) at week 24 in UC using Harvey Bradshaw Index and clinical Mayo score. No statistically significant difference in median TLs and ADA rates were observed after switch.[26]

Based on the accumulating data, the ECCO statement on biosimilars concluded that switching from the originator IFX to an approved biosimilar product in patients with IBD can be regarded as safe and acceptable after discussing with the patients individually.[16] It is also outlined that robust pharmacovigilance program is needed for each biosimilars to support traceability and safety. Nonetheless, because of the growing number of biosimilars or different tender arrangements with multiple available products, physicians may need to prepare for different scenarios including not only 1-way switching from the originator to its biosimilar, but also reverse, multiple, or cross-switching among biosimilars. This tendency will potentially result in a continuous change in prescription preferences of anti-TNF drugs, leading to the question of interchangeability. Currently, the evidence supporting interchangeability between the originator and biosimilar IFX and among biosimilars is lacking. The main concern is that substitution/interchangeability may lead to an increase in therapeutic failures and decreased drug sustainability. Of note, multiple confounders may affect drug sustainability, including the larger number of potentially available biological therapies and the reluctance of physicians to strive for rigorous optimization of a given molecule, thus the interpretation of the data will be more complex. Thus far, no clinical trials have addressed the efficacy, safety, and immunogenicity of reverse switching (switching from a biosimilar to its originator), multiple or repeated switches, or cross-switching among biosimilars.

Although confidence in biosimilars is growing, immunogenicity is still one of the main concerns considering multiple switches. Biosimilar antibodies are not structurally identical to the originator molecule, raising the concern that substitution in patients whose immune system has developed tolerance to the originator may become sensitized and produce drug-neutralizing antibodies. The current data on immunogenicity do not support this phenomenon, at least for CT-P13.[6,27,28] More recently, the NOR-SWITCH study has reported no differences in terms of ADA formation in patients switched to CT-P13.[11] A study of Ben-Horin et al[26] showed almost complete similarity in immunogenicity with the presence of shared immune-dominant epitopes in CT-P13 and IFX originator sequences. Recent studies reported that antibodies to IFX in patients treated with either the originator biologic or the biosimilar present similar epitope recognition and reactivity

toward biosimilars CT-P13 and also SB2 as well as that tested TDM assays can equivalently measure either the reference IFX drug or any of the approved biosimilars CT-P13 or SB2.[29–32] Continuous robust capture of pharmacovigilance data with long-term follow-ups and multiple switching sequences are needed to support decision making around interchangeability of biosimilars.

Results from the present study show no evidence of change in clinical efficacy, safety and immunogenicity after reverse switching from a biosimilar to the originator IFX. Clinical remission rates remained unchanged up to the 24-week follow-up period in parallel with a good short- and medium-term drug sustainability in both CD and UC. No statistically significant difference was observed in mean serum drug TLs at 16 weeks after switch, nor was there any change in ADA rates. Eighteen patients of this cohort have previously been exposed to the originator IFX and experienced back-and-forth switch. There was also no statistically significant change in TLs or ADA status, nor in clinical outcomes. Adverse event rates were also low, with 4 infusion reactions occurring up to week 24; all of these patients presented detectable ADAs at baseline.

To our knowledge, this is the first cohort to evaluate reverse switching from a biosimilar to the originator IFX. Strengths of our study include a robust unselected, consecutive patient cohort with harmonized follow-up and monitoring practices across all the centers. A further advantage of the cohort is that a substantial number of patients have had previous exposure to the originator IFX before being treated with the biosimilar (multiple switches). A possible shortcoming of or study is that it provides only short- and medium-term follow-up (24 weeks).

Conclusions

According to our knowledge, this is the first real-life cohort on mandatory reverse switch from biosimilar to originator IFX in IBD patients. No significant changes were observed in clinical remission rates, drug TLs, or ADA status after the reverse switch during a 24-week follow-up, in parallel with good short-term drug sustainability. No new safety signals were detected.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Clinical Gastroenterology and Hepatology* at www.cghjournal.org, and at https://doi.org/10.1016/j.cgh.2018.12.036.

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Conflicts of interest
These authors disclose the following: Petra Anna Golovics has been a speaker and/or advisory board member: AbbVie. Klaudia Farkas has been a speaker: Abbvie, Ferring; ES: has been a speaker Abbvie, Takeda, Ferring; AV has been a speaker and/or advisory board member: AbbVie, Ferring, MSD, Falk Pharma GmbH, Roche and Takeda. Tamas Szamosi has served as advisory board member for AbbVie, EGIS and Takeda, received speaker's honoraria from Abbvie, Takeda and Ferring and served as part time medical advisor for Hungarian National Health Insurance Fund (OEP-NEAK). Tamas Molnar has been a speaker and/or advisory board member: AbbVie, Ferring, MSD Kéry Pharma, Mundipharma, Falk Pharma GmbH, Olympus and Takeda. Peter Laszlo Lakatos has been a speaker and/or advisory board member: AbbVie, Falk Pharma GmbH, Ferring, Genetech, Jansen, Kyowa Hakko Kirin Pharma, Mitsubishi Tanabe Pharma Corporation, MSD, Pfizer, Roche, Shire and Takeda and has received unrestricted research grant: AbbVie, MSD, and Pfizer. The remaining authors disclose no conflicts.

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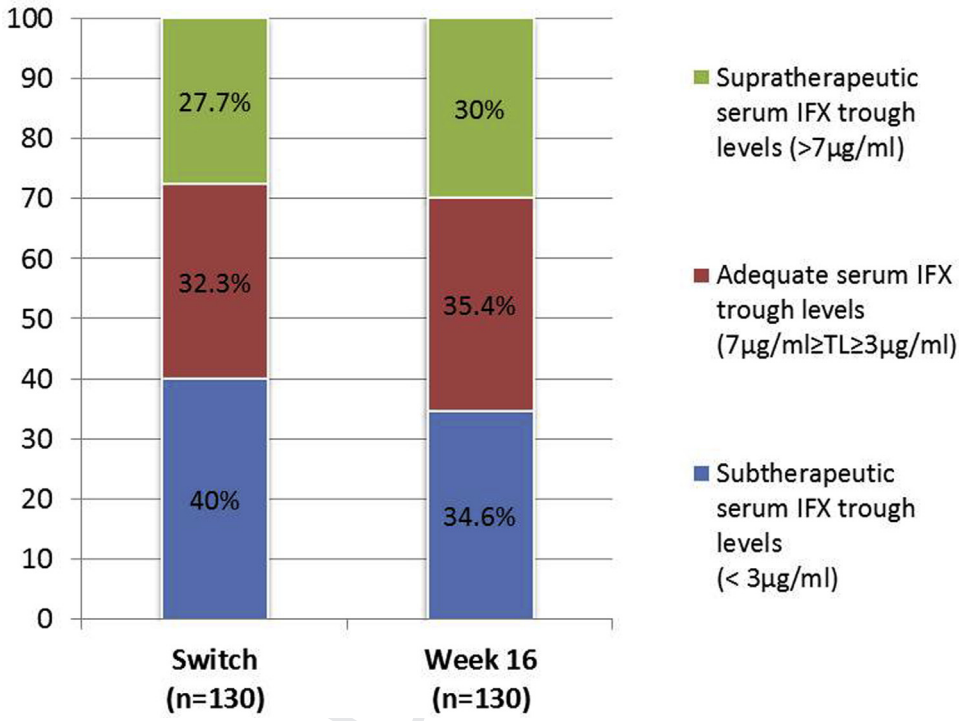

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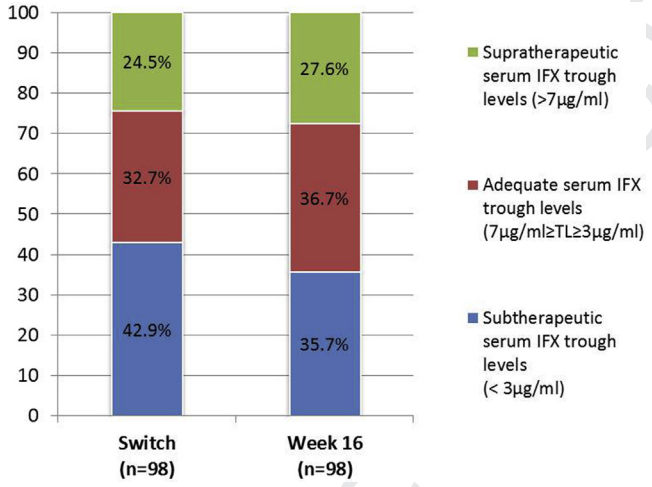
Supplementary Figure 1. Trough levels in IBD patients before and after reverse switch.



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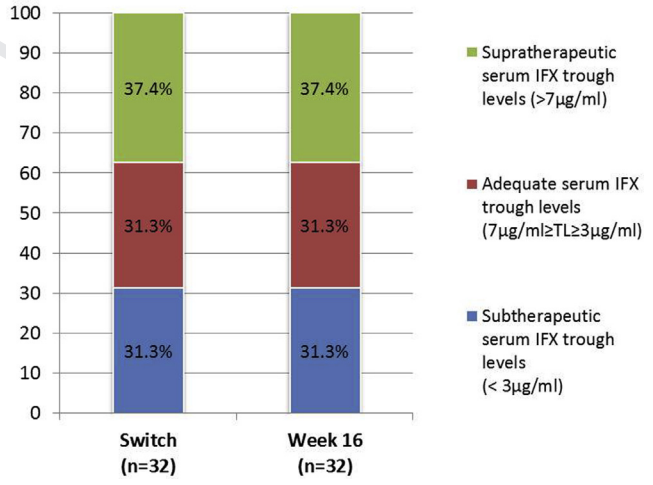
Supplementary Figure 2. Trough levels in CD patients before and after reverse switch.



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Supplementary Figure 3. Trough levels in UC patients before and after reverse switch.

Supplementary Table 1. Trough Levels and Anti-Drug Antibodies in CD Patients

CD Patients on Maintenance IFX Therapy (n = 98)	Switch		Week 16	
	Single-Dose IFX[a] (n = 83)	Increased-Dose IFX[b] (n = 15)	Single-Dose IFX[a] (n = 83)	Increased-Dose IFX[b] (n = 15)
Serum IFX trough level, μg/mL	4.89 ± 4.39		5.33 ± 4.58	
	4.98 ± 4.31	4.41± 4.94	5.31 ± 4.32	5.47 ± 6.01
Anti-drug antibody positivity (>10 ng/mL)	17.3		15.3	
High anti-drug antibody positivity (>200 ng/mL)[c]	8.2		8.2	

Values are mean ± SD or %.
CD, Crohn's disease; IFX, infliximab.
[a]IFX dose: 5 mg/kg of body weight.
[b]IFX dose: 10 mg/kg of body weight
[c]•••.

Supplementary Table 2. Trough Levels and Anti-Drug Antibodies in UC Patients

UC Patients on Maintenance IFX Therapy (n = 32)	Switch		Week 16	
	Single-Dose IFX[a] (n = 28)	Increased-Dose IFX[b] (n = 4)	Single-Dose IFX[a] (n = 28)	Increased-Dose IFX[b] (n = 149)
Serum IFX trough level, μg/mL	6.66 ± 5.41		6.81 ± 5.84	
	6.41 ± 5.37	8.44 ± 6.17	6.05 ± 5.48	12.13 ± 6.31
Anti-drug antibody positivity (>10 ng/mL)	12.5		21.9	
High anti-drug antibody positivity (>200 ng/mL)[c]	9.4		9.4	

Values are mean ± SD or %.
IFX, infliximab; UC, ulcerative colitis
[a]IFX dose: 5 mg/kg of body weight.
[b]IFX dose: 10 mg/kg of body weight.
[c]•••.