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Long-term Efficacy, Safety, and Immunogenicity of Biosimilar Infliximab After One Year in a Prospective Nationwide Cohort

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Background: It has been previously shown that biosimilar infliximab CT-P13 is effective and safe in inducing remission in inflammatory bowel diseases.

Aim: We report here the 1-year outcomes from a prospective nationwide inflammatory bowel disease cohort.

Methods: A prospective, nationwide, multicenter, observational cohort was designed to examine the efficacy and safety of CT-P13 in the induction and maintenance treatment of Crohn's disease (CD) and ulcerative colitis (UC). Demographic data were collected and a harmonized monitoring strategy was applied. Clinical remission, response, and biochemical response were evaluated at weeks 14, 30, and 54, respectively. Safety data were registered.

Results: Three hundred fifty-three consecutive inflammatory bowel disease (209 CD and 144 UC) patients were included, of which 229 patients reached the week 54 endpoint at final evaluation. Age at disease onset: 24/28 years (median, interquartile range: 19–34/22–39) in patients with CD/UC. Forty-nine, 53, 48% and 86, 81 and 65% of patients with CD reached clinical remission and response by weeks 14, 30, and 54, respectively. Clinical remission and response rates were 56, 41, 43% and 74, 66, 50% in patients with UC. Clinical efficacy was influenced by previous anti–tumor necrosis factor (TNF) exposure in patients with a drug holiday beyond 1 year. The mean C-reactive protein level decreased significantly in both CD and UC by week 14 and was maintained throughout the 1-year follow-up (both UC/CD: $P < 0.001$). Thirty-one (8.8%) patients had infusion reactions and 32 (9%) patients had infections. Antidrug antibody positivity rates were significantly higher throughout patients with previous anti-TNF exposure; concomitant azathioprine prevented antidrug antibody formation in anti–TNF-naive patients with CD .

Conclusions: Results from this prospective nationwide cohort confirm that CT-P13 is effective and safe in inducing and maintaining long-term remission in both CD and UC. Efficacy was influenced by previous anti-TNF exposure; no new safety signals were detected.

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Key Words: Crohn's disease, ulcerative colitis, infliximab, biosimilar, antidrug antibody, trough level, therapeutic drug monitoring, efficacy, side effects

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Ethical statement: Ethical approval was acquired from the National Ethical Committee (929772-2/2014/EKU [292/2014]). The study was registered at the EMA European Network of Centres for Pharmacoepidemiology and Pharmacovigilance [ENCEPP/SDPP/9053]. Written informed consent was obtained from all participants.

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Biosimilar infliximab (IFX) CT-P13 was approved by the European Medicines Agency (EMA) in September 2013 and by the U.S. Food and Drug Administration (U.S. FDA) in April 2016 for all indications of the originator product.[1,2] The extrapolation of the use of biosimilar IFX in inflammatory bowel diseases (IBDs) was based on the results from 2 randomized controlled trials conducted in ankylosing spondylitis and rheumatoid arthritis, which demonstrated similarity in pharmacokinetics and clinical efficacy between the biosimilar IFX and the originator product.[3,4] Since May 2014, the use of biosimilar IFX is mandatory in Hungary in all anti–tumor necrosis factor (TNF)-naive patients and in patients who were previously treated with the originator product with a proven clinical benefit but have been on drug holiday for longer than 12 months.

The efficacy and safety of biosimilar IFX in IBD have been studied in the past 2 years, and real-life cohorts show comparable outcomes as in patients treated with the originator IFX.[5–14] As previously reported in the prospective, nationwide, multicenter study by our study group published in 2016 including 210 patients with IBD, high response and remission rates throughout 30 weeks were found in both Crohn's disease (CD) and ulcerative colitis (UC).[7] At week 30, 67.2% and 53.4% of patients with CD showed clinical response or clinical remission, whereas clinical response or remission was demonstrated in 80% and 68% of patients with UC. Early efficacy was affected by previous anti-TNF exposure with no new signal in adverse events.

In this study, our aim was to evaluate the medium- and long-term efficacy, safety, and immunogenicity of biosimilar IFX CT-P13 (Inflectra) in a Hungarian consecutive, nationwide cohort of patients with IBD treated up to 54 weeks.

MATERIALS AND METHODS

This study is a multicenter, nationwide prospective observational study. Eligible patients older than 18 years started on biosimilar IFX therapy were consecutively enrolled. The inclusion started in May 2014 in 12 IBD centers in Hungary.

A harmonized monitoring strategy was applied in all participating centers, as requested by the National Health Fund. Patient demographics, previous, and concomitant medications were collected, and biochemical and clinical assessment was performed at start and every 3 months thereafter. Disease location and behavior in CD and disease extent in UC were assessed according to the Montreal classification.[15] Patients were either naive to anti-TNF or had response to previous anti-TNF therapy but were stopped because of nonmedical reasons with a drug holiday beyond 1 year. A more detailed description of the methodology and case ascertainment of the cohort was published previously.[7]

Patients received intravenous infusions of the biosimilar IFX CT-P13 at a dose of 5 mg/kg of body weight at weeks 0, 2, and 6, and then every 8 weeks. Only patients with a clinical response at week 14 were eligible for maintenance therapy. Clinical response, remission, biochemical response, immunogenicity, and safety were evaluated at weeks 14, 30, and 54. Patients lost to follow-up or with missing data were regarded as nonresponders.

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 less than 3 points in UC.[16–18] Clinical response was defined as a decrease in CDAI with more than 70 points and/or at least 50% reduction in the number of draining fistulas in CD, and a decrease in the pMayo score with more than 3 points in UC. Biochemical activity was evaluated by measuring total blood count, serum C-reactive protein (CRP, normal cut-off: 10 mg/L), and albumin.

For the measurement of biosimilar IFX trough level (TL) and antidrug antibody (ADA), a conventional and bridging enzyme-linked immunosorbent assay was used (LISA TRACKER; Theradiag, France, United Kingdom). The kit was formally validated for the use in patients treated with the biosimilar IFX before commencing on the study. All sample measurements were performed at the Department of Laboratory Medicine, Semmelweis University, Budapest. The enzyme-linked immunosorbent assay kit was validated for accuracy and reproducibility of therapeutic drug level monitoring of the biosimilar IFX (Theradiag). The detection cut-off value of biosimilar IFX TL was 0.1 μg/mL, whereas 3 to 7 μg/mL was defined as therapeutic.[19,20] For ADA level, the standard cut-off value was 10 ng/mL.

Ethical Considerations

Ethical approval was acquired from the National Ethical Committee 929772-2/2014/EKU (292/2014). The study was registered at the EMA European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCEPP/SDPP/9053). Written informed consent was obtained from all participants.

Statistical Analysis

For the characterization of patients' demographic data, remission and response rates at weeks 14, 30, and 54, and adverse events, descriptive statistics were applied. Medians and interquartile ranges were calculated for continuous variables. For the comparison of clinical response, remission rates, and ADA positivity rates between anti–TNF-exposed and naive patients, chi^2 test or Fisher's exact test was used. For the comparison of mean CRP levels at weeks 14, 30, and 54, the paired-sample T test was used. Statistical analysis was performed using SPSS software v. 20.0 (Chicago, IL); $P < 0.05$ was considered statistically significant.

RESULTS

A total of 353 consecutive IBD (209 CD and 144 UC) patients were included, of which 229 patients reached the week 54 endpoint at final assessment. Patient characteristics are shown in Table 1. Until week 54, CT-P13 treatment was stopped in 37 patients because of adverse events, in 11 patients because of primary nonresponse, and in 27 patients because of loss of response. Two CD and 2 UC patients were lost to follow-up

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TABLE 1. Baseline Disease Characteristics of Patients with IBD on Biosimilar IFX Therapy

	CD (n = 209)	UC (n = 144)
Sex (male/female)	99/110	74/70
Age at disease onset (median [IQR]; yr)	24 (19–34)	28 (22–39)
Disease duration (median [IQR]; yr)	5 (2–11)	5 (2–11)
Baseline disease activity (median [IQR]; points)	CDAI: 319 (301–352; n = 172)	Mayo: 9 (7–11; n = 136)
	PDAI: 9 (5–11; n = 77)	pMayo: 7 (6–9; n = 89)
Disease location (L1/L2/L3/L4/all L4; %)	16.3/31.1/41.1/1.5/8.3	—
Disease extent (E1/E2/E3; %)	—	9.7/34.1/56.2
Disease behavior (B1/B2/B3; %)	56.5/21.0/22.5	—
Perianal disease (%)	39.2	—
Previous surgery (%)	21.5	—
Previous anti-TNF therapy (%)	23.4 (n = 49)	19.4 (n = 28)
IFX	18.2 (n = 38)	12.5 (n = 18)
Adalimumab	4.2 (n = 9)	6.2 (n = 9)
IFX + adalimumab	1 (n = 2)	0.7 (n = 1)
Concomitant steroid therapy (%)	42.6	64.6
Concomitant AZA therapy (%)	60.3	51.4

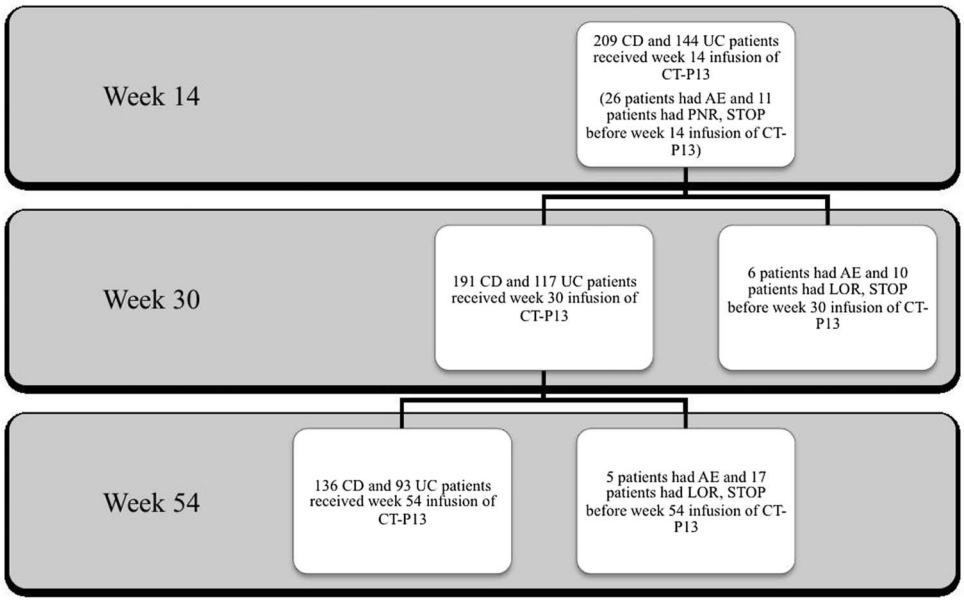
IQR, interquartile range; PDAI, Perianal Disease Activity Index.

F1 (Fig. 1). Dose optimization was performed in 17 and 16 of CD/UC patients during the follow-up period.

Clinical Remission and Response Rates at Weeks 14, 30, and 54

In CD, 49%, 53%, 48% and 86%, 81% and 65% of the patients reached clinical remission and response by weeks 14, 30, F2 and 54, respectively (Figs. 2A, 3A and 4A).

Stratifying patients with CD according to previous anti-TNF exposure, 53.8%, 57%, and 53.5% of the anti–TNF-naive patients reached clinical remission by weeks 14, 30, and 54, whereas 91.1%, 85.9%, and 73.3% of the anti–TNF-naive patients reached clinical response by weeks 14, 30, and 54, respectively. In patients with a previous anti-TNF exposure, clinical remission and response rates were 36.7%, 43.5%, and 32.4% and 67.3%, 67.4%, and 44.1% by weeks 14, 30, and 54, respectively (Figs.



AU10 FIGURE 1. Patients and follow-up. PNR, primary nonresponse; LOR, loss of response; AE, adverse event; 2 patients with CD and 2 patients with UC AU11 were lost to follow-up.

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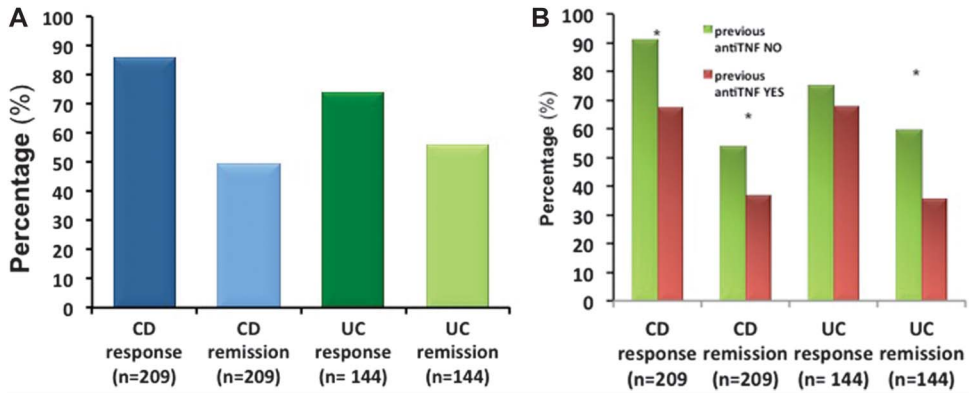

FIGURE 2. A, Clinical response and remission rates at week 14 in patients with IBD treated with the biosimilar IFX. B, Clinical response and remission rates at week 14 in patients with IBD treated with the biosimilar IFX stratified by previous anti-TNF exposure; *$P < 0.05$.

2B, 3B and 4B). Clinical response rates were significantly different at weeks 14, 30, and 54 ($P < 0.01$, $P = 0.005$, and $P = 0.001$, respectively), whereas clinical remission rates were significantly different at weeks 14 and 54 ($P = 0.04$ and $P = 0.02$, respectively) between anti–TNF-naive and anti–TNF-exposed patients with CD.

In patients with UC, clinical remission and response rates were 56%, 41%, and 43% and 74%, 66%, and 50% of the patients by weeks 14, 30, and 54, respectively (Figs. 2A, 3A and 4A).

In anti–TNF-naive patients with UC, 59.5%, 45.7%, and 47.3% of the patients reached clinical remission by weeks 14, 30, and 54 and 75%, 71.3%, and 51.4% of the patients reached clinical response by weeks 14, 30, and 54, respectively. In patients with UC with a previous anti-TNF exposure, 35.7%, 21.7%, and 26.5% of the patients reached clinical remission and 67.9%, 43.5%, and 42.1% of the patients reached clinical response by weeks 14, 30, and 54, respectively (Figs. 2B, 3B and 4B). Clinical response rates were significantly different at week 30 ($P = 0.01$), whereas clinical remission rates were significantly different at weeks 14 and 30 ($P = 0.02$ and $P = 0.04$) between anti–TNF-naive and previously anti–TNF-exposed patients with UC, respectively.

Biochemical Response

In patients with CD, the mean CRP level significantly decreased between weeks 0 and 14 from 23.7 to 9.8 mg/L, respectively ($P < 0.001$). The mean CRP levels were 9.4 and 9.6 mg/L at weeks 30 and 54, respectively ($P < 0.001$ and $P = 0.001$ compared with baseline).

Trends were similar in UC. The mean CRP levels were 27.6, 8.7, 12.2, and 11.7 mg/L at weeks 0, 14, 30, and 54 with a significant decrease by weeks 14 ($P < 0.001$), 30 ($P = 0.002$), and 54 ($P = 0.009$).

Therapeutic Drug Level Monitoring

In patients with CD, the mean biosimilar IFX TLs at weeks 2, 6, 14, 30, and 54 are presented in Table 2. Biosimilar IFX TLs were significantly lower in previously anti–TNF-exposed patients at weeks 2 ($P = 0.03$), 14 ($P = 0.02$), and 30 ($P = 0.03$) but not at weeks 6 ($P = 0.148$) and 54 ($P = 0.91$) (Table 2). T2

In patients with UC, the mean biosimilar IFX TLs at weeks 2, 6, 14, 30, and 54 are presented also in Table 2. No significant difference was found in biosimilar IFX TLs between anti–TNF-naive and previously exposed patients at any time points, with a trend toward higher TLs in the anti–TNF-naive patient group (Table 2).

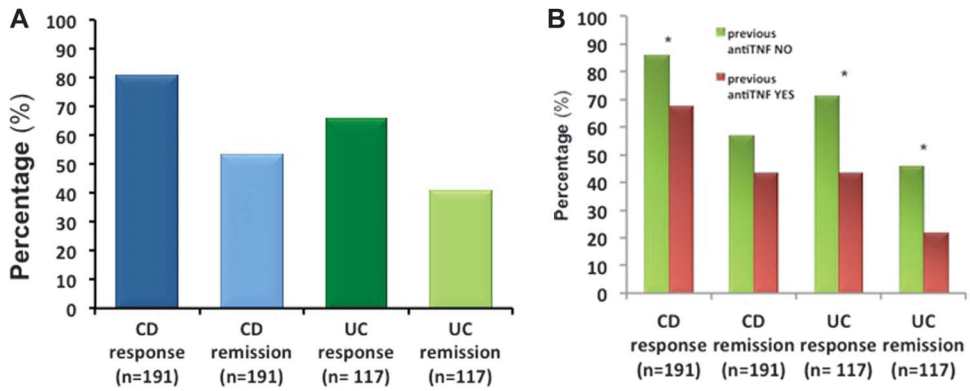

FIGURE 3. A, Clinical response and remission rates at week 30 in patients with IBD treated with the biosimilar IFX. B, Clinical response and remission rates at week 30 in patients with IBD treated with the biosimilar IFX stratified by previous anti-TNF exposure; *$P < 0.05$.

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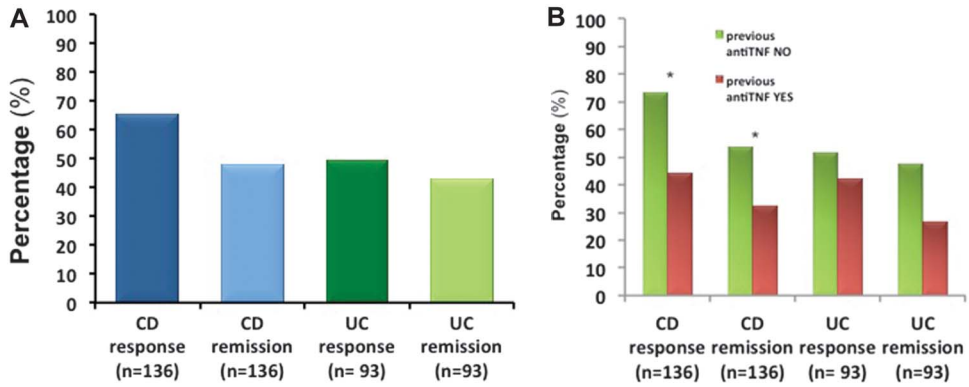

FIGURE 4. A, Clinical response and remission rates at week 54 in patients with IBD treated with the biosimilar IFX. B, Clinical response and remission rates at week 54 in patients with IBD treated with the biosimilar IFX stratified by previous anti-TNF exposure; *$P < 0.05$.

Cumulative ADA positivity rates were 9.8% (26/266), 18.6% (58/312), 24.1% (70/290), and 33.8% (71/210) at weeks 0, 14, 30, and 54, respectively, in all patients with IBD. In anti–TNF-naive patients with IBD, cumulative ADA positivity rates were 4.3% (9/213), 12% (30/249), 20.9% (48/230), and 28.6% (50/175) at weeks 0, 14, 30, and 54, respectively. The cumulative ADA positivity rates were significantly higher at all time points in anti–TNF-exposed patients 32% (17/53), 34.9% (22/63), 36.6% (22/60), and 46.6% (21/45) at weeks 0, 14, 30, and 54, respectively ($P < 0.001$ for all).

Cumulative ADA positivity rates in CD and UC patients with and without previous anti-TNF exposure are presented in Table 3. In CD, a significant difference was found in ADA positivity rates between anti–TNF-naive and previously anti–TNF-exposed patients at baseline ($P < 0.001$), weeks 14 ($P < 0.001$), 30 ($P = 0.03$), and 54 ($P = 0.03$).

In UC, the difference was significant in baseline ADA positivity rates between anti–TNF-naive and previously anti–TNF-exposed patients ($P < 0.001$), but this difference became nonsignificant by week 14 and thereafter (week 14: $P = 0.14$; week 30: $P = 0.16$; and week 54: $P = 0.27$).

Concomitant azathioprine (AZA) prevented ADA formation at weeks 14 (6.5% versus 21.2%, $P = 0.01$) 30 (12.7% versus 29.2%, $P = 0.02$), and 54 (15% versus 45.2%, $P = 0.004$) in anti–TNF-naive but not in previously exposed patients with CD (week 14: 40% versus 33.3%, $P = 0.75$; week 30: 37.5% versus 38.5%, $P = 0.95$; and week 54: 50% versus 50%, $P = 1.0$).

By contrast, concomitant AZA did not prevent ADA formation either in anti–TNF-naive (week 14: 19.2% versus 18.4%, $P = 0.91$; week 30: 24% versus 22.4%, $P = 0.85$; and week 54: 29.3% versus 35%, $P = 0.58$) or in previously exposed patients with UC (week 14: 30% versus 36.4%, $P = 0.76$; week 30: 40% versus 36.4%, $P = 0.86$; and week 54: 40% versus 50%, $P = 0.71$).

Clinical efficacy at week 14 or 30 was not affected by concomitant AZA use in either patients with CD or UC (CD: week 14 response: 87.2% versus 81.6%, $P = 0.28$; week 14 remission: 52% versus 47.4%, $P = 0.52$; week 30 response: 84.1% versus 76.8%, $P = 0.22$; and week 54 response: 69.1% versus 56.9%, $P = 0.15$; week 54 remission: 50.6% versus 39.2%, $P = 0.2$; UC: week 14 response: 73% versus 74.3%, $P = 0.85$; week 14 remission: 52.7% versus 57.1%, $P = 0.59$; week 30

TABLE 2. Mean TLs in Patients with IBD on Biosimilar IFX Therapy

	Week 2, μg/mL	Week 6, μg/mL	Week 14, μg/mL	Week 30, μg/mL	Week 54, μg/mL
CD					
Mean biosimilar IFX TLs	18.9 (n = 85)	17.3 (n = 74)	6.1 (n = 136)	4.3 (n = 119)	5.3 (n = 53)
Without previous anti-TNF	20.4[a]	16.5	6.5[a]	4.6[a]	5.4
With previous anti-TNF	11.7[a]	10.7	3.7[a]	2.1[a]	5.0
UC					
Mean biosimilar IFX TLs	19.0 (n = 67)	11.8 (n = 50)	4.9 (n = 97)	3.9 (n = 63)	4.5 (n = 39)
Without previous anti-TNF	20.6	12.9	4.9	4.0	4.9
With previous anti-TNF	9.9	5.7	4.8	3.3	1.9

[a]Mean biosimilar IFX TLs differed significantly between anti–TNF-naive and previously anti–TNF-exposed patients at week 2 ($P = 0.03$), at week 14 ($P = 0.02$), and at week 30 ($P = 0.03$) in CD.

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TABLE 3. Cumulative ADA Positivity in Patients with IBD on Biosimilar IFX Therapy

	ADA Positivity at Baseline	ADA Positivity at Week 14	ADA Positivity at Week 30	ADA Positivity at Week 54
CD	15/169 (8.9%)	32/190 (16.8%)	39/170 (22.9%)	38/124 (30.6%)
Without previous anti-TNF	5/134 (3.7%)[a]	17/148 (11.5%)[a]	25/131 (19.1%)[a]	24/94 (25.5%)[a]
With previous anti-TNF	10/35 (28.6%)[a]	15/42 (35.7%)[a]	14/39 (35.9%)[a]	14/30 (46.7%)[a]
UC	11/97 (11.3%)	26/122 (21.3%)	31/120 (25.8%)	33/96 (34.4%)
Without previous anti-TNF[a]	4/79 (5.1%)[a]	13/101 (18.8%)	23/99 (23.2%)	26/81 (32.1%)
With previous anti-TNF	7/18 (38.9%)[a]	7/21 (33.3%)	8/21 (38.1%)	7/15 (46.7%)

[a]ADA positivity rates differed significantly between anti–TNF-naive and previously anti–TNF-exposed patients at baseline ($P < 0.001$), at week 14 ($P < 0.001$), at week 30 ($P = 0.03$), and at week 54 ($P = 0.03$) in CD and at baseline ($P < 0.001$) in UC.

response: 65.6% versus 66.1%, $P = 0.95$; week 30 remission: 41% versus 41.1%, $P = 0.99$; and week 54 response: 48% versus 51.2%, $P = 0.76$; week 54 remission: 40% versus 46.5%, $P = 0.53$). Of note, the clinical remission rates were significantly different in CD at week 30 (63.7% versus 40.6%, $P = 0.002$) and clinical response at week 30 in previously exposed patients with CD (80.8% versus 44.4%, $P = 0.01$).

Adverse Events

At week 54, the cumulative rate of adverse events was 24%. Infusion reactions occurred in 31 (8.8%) patients. Sixteen of 31 patients previously received anti-TNF therapy. Infections occurred in 32 (9%) patients with no cases of tuberculosis. One patient developed invasive fungal sepsis, resulting in death. No cases of malignancy occurred during follow-up of the cohort. T4 Detailed adverse event data are presented in Table 4.

DISCUSSION

In the present prospective, multicenter, nationwide study of patients with IBD treated with the biosimilar IFX, clinical remission and response rates were maintained throughout 54 weeks and were in line with the previously published data on the originator product or CT-P13 biosimilar. In addition, previous anti-TNF exposure affected clinical efficacy, whereas parallel AZA was effective in preventing ADA formation in anti–TNF-naive patients.

The efficacy of maintenance IFX therapy in active CD was demonstrated in the ACCENT I trial, where clinical remission rates at week 30 were significantly higher in week 2 responder patients receiving IFX 5 mg/kg and 10 mg/kg compared with the placebo group (39% and 45% versus 21%), and the difference between the treatment groups remained significant also at week 54.[21] In a retrospective Hungarian study, the overall response rate was 86.2% (313 of 363 patients), and the overall remission rate was 46% (167 of 363 patients) at the end of induction therapy with the originator IFX in patients with CD.[22] In addition, in the ACT 1 trial, clinical response and remission rates at week 54 were 45.5% and 34.7%, respectively, in patients with UC receiving 5 mg of IFX compared with 19.8% and 16.5% in the placebo group.[18]

Clinical response, remission rates, and safety data[23] in the present cohort were in line with the above findings and with data presented in real-life cohorts treated with IFX. In the retrospective study by Jung et al, clinical response and remission were achieved by 87.5% and 75% of the anti–TNF-naive patients with CD and 100% and 50% of the anti–TNF-naive patients with UC at week 54, respectively.[5] In a Norwegian single-center study, 34 (79%) patients with CD achieved a Harvey–Bradshaw score of ≤4, and 18 (56%) patients with UC achieved a pMayo score of ≤2 at week 14. In addition, the mean serum CRP levels significantly decreased from baseline to week 14 both in CD (22.5 versus 4.9 mg/L, $P = 0.006$) and UC (36.8 versus 9.6 mg/L, $P = 0.012$).[6]

TABLE 4. Adverse Events in Patients with IBD on Biosimilar IFX Therapy

Adverse Event	Patients (%)
Mortality	1 (0.3)
Infections	
Upper respiratory tract infection	9 (2.5)
Gastroenteritis	10 (2.8)
Viral infections (influenza, herpes, varicella)	7 (2)
Clostridium difficile colitis	3 (0.8)
Invasive fungal infection	1 (0.3)
Pneumonia	1 (0.3)
Urinary tract infection	1 (0.3)
Tuberculosis	0 (0)
Allergy	
Infusion reaction	31 (8.8)
Anaphylaxis	1 (0.3)
Others	
Arthralgia	11 (3.1)
Delayed hypersensitivity	10 (2.8)
Malignancy	0 (0)

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High early clinical remission and response rates were found in the previous publication from the present cohort in 210 patients with IBD throughout 30 weeks. Clinical response and remission rates at week 14 were 81 and 54% in CD and 78 and 59% in UC, respectively. At week 30, steroid-free clinical remission was achieved in 50% of the patients with CD and 56% of the patients with UC.[7] In a Czech study including 52 patients, clinical response (≥70 point decrease in CDAI score from baseline in CD and ≥2 point decrease in pMayo score from baseline) and remission rates (CDAI <150 in CD and total score on partial Mayo Score index ≤2 points) at week 14 were 50% and 50% in CD and 54.4% and 40.9% in UC, respectively.[9]

We observed a cumulative adverse event rate of 24% in the present cohort. The rate of infusion reactions was 8.8%, of which approximately half of the patients were previously exposed to the originator anti-TNF therapy. The rate of infections (9%) is in line with published data on biosimilar or originator IFX. Of note, no cases of tuberculosis were identified during follow-up.[7] In the study by Keil et al including 52 patients, 4 adverse events occurred during the 14-weeks follow-up period, including allergic reaction, phlebothrombosis of the lower extremity, pneumonia, and herpes labialis.[9] Balint et al investigated the incidence and characteristics of infusion reactions in 384 patients from 13 Hungarian and 1 Czech IBD centers. The rate of infusion reactions was 7.2% (21 patients) among Hungarian patients and 13 patients of those received previous anti-TNF therapy.[24]

In this study, ADA positivity rates were significantly higher in patients with previous exposure of anti-TNF therapy throughout week 54 in CD, but this difference was nonsignificant after week 14 in UC. In addition, significantly lower early IFX TLs were observed in patients previously exposed to IFX, compared with naive patients. Farkas et al reported significantly higher IFX TLs in patients with UC with mucosal healing or steroid-free mucosal healing compared with patients without mucosal healing at week 14.[8] In a Norwegian single-center study, 4 CD and 4 patients with UC had an IFX TL of 0 mg/L, and 3 of them received anti-TNF therapy previously. Two of these patients had high (≥80 AU/L), 5 had medium/high (<80 AU/L), and 1 had low ADA levels (<10 AU/L).[6] ADA and TL data are awaited from the international crossover study from patients with CD treated with originator or biosimilar IFX.[25,26]

Parallel AZA was effective in preventing ADA formation in anti–TNF-naive CD but not patients with UC. Similarly, lower rates of antibodies against IFX were reported by Baert et al in patients with CD taking immunosuppressives compared with patients without immunosuppressive use during IFX therapy (43% versus 75%, $P <$ 0.01).[27] Vermeire et al studied the rate of ATI formation in a multicenter cohort of patients with CD receiving methotrexate and IFX, AZA, and IFX or IFX alone. Lower ATI formation was observed in patients with CD receiving methotrexate or AZA compared with those receiving IFX alone (46% versus 73%, $P < 0.001$).[28]

Strengths of this study are the prospective study design and the harmonized, standardized follow-up and monitoring strategy in all participating centers. A limitation of our study is that mucosal healing was not systematically evaluated. Furthermore, our cohort includes patients with previous drug exposure and drug holiday, but not switch.

In conclusion, in the present multicenter, nationwide cohort including a large cohort of patients with IBD treated with biosimilar IFX, the efficacy, safety, and immunogenicity of the biosimilar IFX were comparable with those of the originator compound reported in previous studies. Data on immunogenicity and drug TLs obtained in this study support the routine use of therapeutic drug level monitoring in patients treated with biosimilar IFX. In addition, parallel AZA was effective in preventing ADA formation in anti–TNF-naive patients, while previous anti-TNF exposure affected clinical efficacy.

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