ORIGINAL ARTICLE

Efficacy, tolerability, and safety of infliximab biosimilar in comparison to originator biologic and adalimumab in patients with Crohn disease

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KEY WORDS

biologic treatment, biosimilar, Crohn disease, inflammatory bowel disease

ABSTRACT

INTRODUCTION An infliximab biosimilar has been shown to be equivalent to originator infliximab. However, data concerning the drug's efficacy and safety in patients with Crohn disease (CD) are still limited.
OBJECTIVES The aim of the study was to assess the efficacy, tolerability, and safety of an infliximab biosimilar in the Polish population with CD in comparison to its originator biologic and adalimumab.
PATIENTS AND METHODS This was a retrospective, single-center study of 286 consecutive patients with CD. They received originator infliximab, an infliximab biosimilar, or adalimumab on the basis of the same inclusion criteria. Disease activity was estimated at baseline, after induction therapy, after 1 year of treatment, and during 12 months of follow-up.
RESULTS There were no differences in the Crohn's Disease Activity Index in patients treated with infliximab, infliximab biosimilar, or adalimumab. Clinical response, clinical remission, and glucocorticoid-free remission rates were also comparable between groups. The relapse rate was similar in groups receiving infliximab biosimilar and adalimumab (54% and 61%, respectively), with relapses occurring more often in patients receiving infliximab (83% of patients during 12-month follow-up; $P < 0.001$).
CONCLUSIONS We showed the same efficacy and safety of the infliximab biosimilar in comparison to the originator drug and adalimumab in the Polish population, not only during induction and 1-year therapy, but also during 12-month follow-up.

INTRODUCTION Anti–tumor necrosis factor α (anti-TNF-α) agents constitute an effective treatment for numeorus patients with gastroenterologic and rheumatoid diseases such as Crohn disease (CD), ulcerative colitis (UC), rheumatoid arthritis, ankylosing spondylitis, and psoriatic arthritis.[1-3] Anti-TNF-α agents have been also proved to be the most effective treatment of moderate to severe luminal and fistulizing CD.[4,5] However, due to their cost, their use in Poland is limited. When originator biologic drugs lost patent protection, lower-priced biosimilar versions of the same compounds have appeared on the market. A biosimilar of the anti-TNF-α monoclonal antibody infliximab may be a valid alternative to its originator, with the potential to reduce medical care costs and thus become available to a large number of patients.[6] In Poland, according to the National Health Fund Therapeutic Program for the treatment of patients with CD, 2 anti-TNFα agents can be used: infliximab and adalimumab. Treatment with infliximab is possible with a biosimilar drug (Inflectra, Remsima) or an originator biologic (Remicade). Recently, we have shown that an infliximab biosimilar used in the treatment of patients with UC is equivalent to the originator drug in terms of efficacy and safety.[7]

PATIENTS AND METHODS This was a retrospective, single-center study that included a cohort of 286 consecutive adult patients with CD, hospitalized (day case patients) in the Department of Internal Medicine and Gastroenterology of the Central

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Clinical Hospital of the Ministry of the Interior and Administration in Warsaw, Poland, between March 2013 and September 2015. The aim of this study was to assess the efficacy, tolerability, and safety of an infliximab biosimilar in comparison to its originator biologic (infliximab) and adalimumab in patients with CD. The following 3 endpoints were evaluated: 1) achievement of clinical response and remission, including glucocorticoid (GC)-free remission and normalization of C-reactive protein (CRP) and fecal calprotectin (FC) levels; 2) assessment of the relapse rate; and 3) side effects of biologic treatment.

All patients were enrolled in the National Health Fund Therapeutic Program according to the same criteria for biologic therapy. The program included patients above 18 years of age presenting with moderate and severe CD defined as the Crohn's Disease Activity Index (CDAI) score above 300 points: with insufficient response to standard treatment including GCs or 6-mercaptopurine (6-MP) or azathioprine (AZA), or not tolerating treatment with GCs or 6-MP or AZA, or having contraindications to treatment with GCs or 6-MP or AZA. The second indication for anti-TNF-α therapy was an active perianal fistula after a noneffective treatment with antibiotics, thiopurines, and surgery. Patients were given 1 of the following 3 medications: infliximab (82 patients), infliximab biosimilar (109 patients), or adalimumab (95 patients). Patients treated before May 2014 received infliximab, while those starting treatment later received either adalimumab or infliximab biosimilar (because of the national funding of the treatment program). The decision to choose between the 2 agents was made together with the patient based on his or her preferences and a previous treatment. More than 30% of patients from each group underwent anti-TNF-α treatment before (as some of them had received up to 5 courses of therapy, the choice of the drug in those patients was based on the careful analysis of medical history—we chose the treatment that was most efficacious and well tolerated before).

Patients were treated according to the funding guidelines of the program: treatment was routinely stopped after 12 months and could be only reintroduced after 16 weeks for infliximab or infliximab biosimilar and after 8 weeks for adalimumab if the patient met the inclusion criteria again. The activity of the disease, CDAI, and transrectal ultrasound were assessed at baseline, after induction therapy, at the end of therapy after 1 year, and after additional 12 months of follow-up. Additionally, CRP and FC levels were assessed: CRP for infliximab or infliximab biosimilar at weeks 0, 2, and 6 and then every 8 weeks, and for adalimumab, every 12 weeks (as required by the funding program), while FC at baseline and after 1 year of treatment.

Clinical response was defined as a decrease of more than 100 points in the baseline CDAI score, while remission was defined as a CDAI score of less than 150 points or a nonactive fistula on transrectal ultrasound after 12-month treatment. Relapse was defined as a CDAI score higher than 150 points with an increase of more than 70 points or as a recurrent fistula occurring during the 12-month follow-up.

Statistical analysis All statistical tests were performed with Statistica 12 (StatSoft, Tulsa, Oklahoma, United States). Quantitative variables were tested for normality with the Shapiro–Wilk test. All variables were skewed and were presented as medians with the first and third quartiles. Binary and categorical variables were shown as numbers and percentages. The level of statistical significance for comparisons between applied therapies was assessed by the Kruskal–Wallis test for quantitative variables and by the χ^2 test and Fisher–Freedman–Halton test (when the sample size was smaller than 5) for binary variables. A P value of less than 0.05 was considered significant.

Ethics The study was approved by the bioethical committee of the Central Hospital of the Ministry of the Interior and Administration (decision number, 72/2017).

RESULTS No significant differences between the 3 groups (infliximab, infliximab biosimilar, or adalimumab) were noted with respect to age, sex, disease duration, extension of lesions, use of additional drugs, and smoking. Of the 286 patients, almost 50% had a previous surgery, with no significant differences between groups. More than 30% of patients from each group received previous anti-TNF-α treatment. Most patients were GC-dependent and they were using GCs during anti-TNF-α treatment. Use of thiopurines was noted in 247 patients during 1 year of treatment and during the 12-month follow-up. In some patients, we observed extraintestinal symptoms such as psoriasis, erythema nodosum, dermatitis, spondyloarthritis, pyoderma, and primary sclerosing cholangitis, with no significant differences between groups (TABLE 1).

We did not find any differences between patients receiving infliximab, infliximab biosimilar, and adalimumab in the median CDAI score at baseline (324, 323, and 322 points, respectively, P = 0.95), after induction (79, 74.5, and 86 points, respectively, P = 0.99), and after 1 year of treatment (69, 70, and 66 points, respectively, P = 0.78). Similarly, there were no differences in median CRP levels between infliximab, biosimilar, and adalimumab groups at baseline (7 mg/l, 8.9 mg/l, and 11 mg/l, respectively, P = 0.2), after induction (1.8 mg/l, 2.2 mg/l, and 2.7 mg/l, respectively, P = 0.57), and after 1 year of treatment (1.25 mg/l, 1.50 mg/l, and 1.6 mg/l, respectively, P = 0.58). At the end of treatment, median FC concentrations were similar in patients receiving infliximab, infliximab biosimilar, and adalimumab (235 μg/g, 557 μg/g, and 396 μg/g of stool, respectively, P = 0.24) (TABLE 2).

TABLE 1 Clinical and demographic data of all patients and study groups divided according to biologic treatment

Parameter	All patients (n = 286)	Infliximab (n = 82)	Infliximab biosimilar (n = 109)	Adalimumab (n = 95)	*P* value
Sex, male/female, n (%)	138/148 (48/52)	43/39 (52/48)	52/57 (48/52)	43/52 (45/55)	0.55
Age, y, median (Q1; Q3)	29 (23; 39)	30.5 (22; 39)	28 (23; 38)	30 (24; 42)	0.8
Previous anti-TNF-α therapy	148	30 (36.6)	34 (31.2)	83 (87.4)	<0.001
Previous surgical treatment	138	41 (50)	46 (42.2)	51 (53.7)	0.24
Extraintestinal symptoms	84	25 (30.5)	27 (24.8)	32 (33.7)	0.37
GC-dependent	276	80 (97.6)	105 (96.3)	91 (95.8)	0.53
GC-resistant	10	2 (1.4)	4 (4.6)	4 (4.2)	0.53
Thiopurine use	247	76 (92.7)	94 (86.2)	77 (81.1)	0.08
Tobacco use	18	5 (6.1)	6 (5.5)	7 (7.4)	0.86
Active fistula	52	14 (17.1)	26 (23.8)	12 (12.6)	0.11

Abbreviations: anti-TNF-α, anti–tumor necrosis factor α; GC, glucocorticoid

TABLE 2 Characteristics of the study groups divided according to biologic treatment

Parameter	Infliximab	Infliximab biosimilar	Adalimumab	*P* value
Age of diagnosis, y	24.5 (17; 32)	23 (18; 32)	23 (16; 35)	0.8
Age at baseline, y	30.5 (22; 39)	28 (23; 38)	30 (24; 42)	0.8
FC at baseline, µg/g	1100 (426; 1801)	1801 (525; 1801)	1101 (469; 1801)	0.26
FC after treatment, µg/g	235 (99; 800)	557.5 (99; 1801)	396 (99; 1801)	0.24
CRP at baseline, mg/l	7 (2.4; 22.8)	8.90 (2; 33)	11.1 (4.2; 32.5)	0.2
CRP after induction, mg/l	1.8 (0.5; 10.7)	2.2 (0.7; 6.3)	2.7 (0.8; 7.2)	0.57
CRP after treatment, mg/l	1.25 (0.35; 5.65)	1.75 (0.4; 7.15)	1.6 (0.6; 5.5)	0.59
CDAI at baseline	324 (304; 392)	323 (303; 379)	322 (304; 361)	0.95
CDAI after induction	79 (38; 140)	74.5 (41; 141)	86 (35; 164)	0.99
CDAI after treatment	69 (31; 121)	70 (22; 139)	66 (37.5; 134.5)	0.78
Months to relapse	3.66 (1.31; 5.66)	2.81 (0.63; 4.55)	3.01 (0.35; 6.2)	0.3
Months to the second treatment	7.53 (4.66; 14.93)	5.5 (4.56; 8.53)	6.03 (3.93; 10.4)	0.1

Data are presented as median (Q1; Q3)

Abbreviations: CDAI, Crohn's Disease Activity Index; CRP, C-reactive protein; FC, fecal calprotectin

No significant differences between groups treated with infliximab, infliximab biosimilar, and adalimumab were observed after 1 year of treatment regarding: clinical response (95%, 94%, and 87%, respectively; $\chi^2 = 2.08$, $P = 0.35$); clinical remission (76%, 81%, and 70%, respectively; $\chi^2 = 1.41$, $P = 0.49$); and GC-free remission (78%, 72%, and 74%, respectively; $\chi^2 = 1.41$, $P = 0.49$) (FIGURE 1).

The relapse rate was similar in the groups receiving infliximab biosimilar and adalimumab (54% and 61%, respectively), but it was higher in the group receiving infliximab (83% of patients during 12-months follow-up; $P < 0.001$). There was no difference between the 3 groups in the number of months to relapse (TABLE 2, FIGURE 2).

We did not observe significant differences in the safety of the originator drug, infliximab biosimilar, and adalimumab. Complications during treatment occurred in 39 patients with a similar rate in the 3 groups (infliximab, 15%; infliximab biosimilar, 17%; adalimumab, 9%; $P = 0.33$). The most common complications were skin lesions including psoriasis or local dermatitis at the drug injection site in the adalimumab group. However, they were not serious enough to terminate treatment. Some patients developed arthritis. Allergic reactions occurred in 3 patients from the group treated with infliximab biosimilar and in 2 patients from the infliximab group. All 5 patients presenting with allergic reactions were treated with an anti-TNF-α drug at least once in the past. One patient treated with infliximab biosimilar was diagnosed with serum sickness. We did not observe any serious adverse events. One woman from the group receiving infliximab biosimilar was pregnant, and the treatment was stopped after induction.

DISCUSSION TNF-α inhibitors have improved the treatment of CD, UC, spondyloarthritis, rheumatoid arthritis, psoriatic arthritis, and

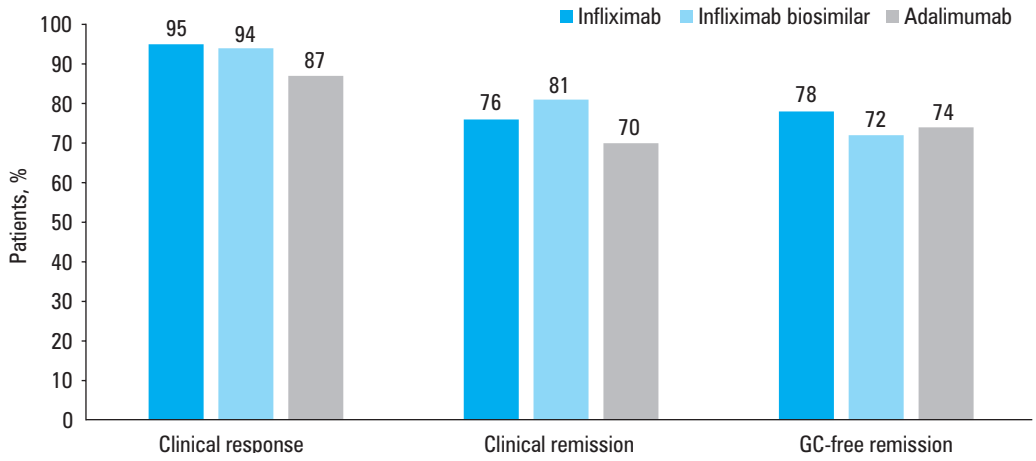

FIGURE 1 Clinical response, clinical remission, and glucocorticoid (GC)-free remission in patients treated with originator infliximab, an infliximab biosimilar, and adalimumab

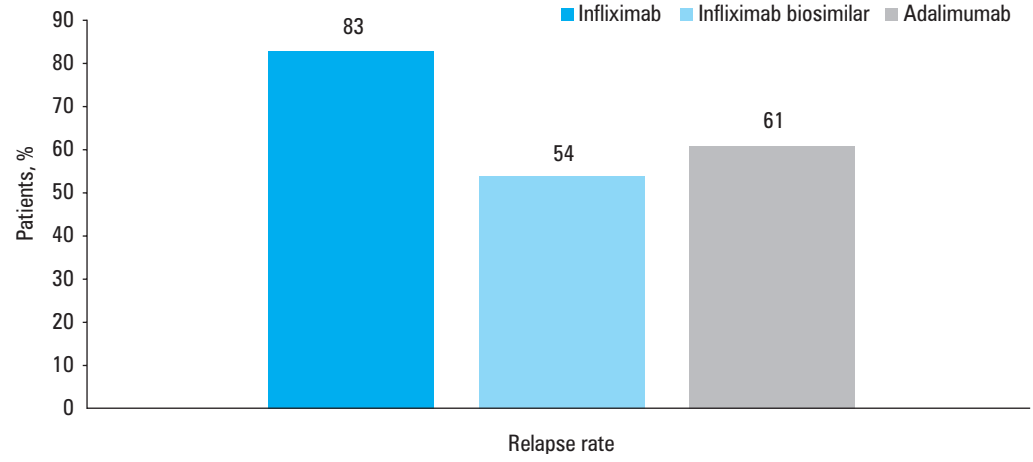

FIGURE 2 Relapse rates during 12-month follow--up in patients treated with originator infliximab, infliximab biosimilar, and adalimumab

chronic plaque psoriasis, but this is an expensive therapy.[8] After obtaining approval from the European Medicines Agency, biosimilar anti-TNF-α agents were introduced to the Polish market in 2015, both for children and adults, but there are still limited data about their efficacy and safety in adult Polish population. First, patients were enrolled in the National Health Fund Therapeutic Program. In order to do that, they had to fulfill the inclusion criteria, as outlined in the Patients and methods section. In our study, it was allowed to administer biologic treatment to patients that had been earlier included in the program, but we had to wait 16 weeks for patients using infliximab or 8 weeks for patients using adalimumab before they could be put on another treatment. In other countries (eg, Czech Republic or Germany), the criteria for patients starting biologic treatment are not as strict. Our results showed that infliximab biosimilar is as effective for the induction and maintenance treatment of CD as both the originator drug and adalimumab.

Our study is the first to reveal the effects of treatment with infliximab, infliximab biosimilar, and adalimumab in the Polish population. Similar studies were performed in other countries. Kolar et al[9] investigated patients treated for CD and CU at a single center in the Czech Republic. One cohort consisted of prospectively followed patients who were switched from infliximab to infliximab biosimilar between January and March 2015, and the other cohort included retrospectively assessed patients who were naive to anti-TNF-α treatment and who started therapy between January 2015 and January 2016. As in our study, there were no significant differences in CRP and FC levels between groups. The type and frequency of adverse events in both cohorts were comparable to those observed in our study.[9]

In 2017, the results of the NOR-SWITCH study were published.[8] The aim of that study was to examine the effect of switching from infliximab to a less expensive infliximab biosimilar and to assess the biosimilar's efficacy, safety, and immunogenicity. Disease worsened in 26% of patients in the infliximab group and 30% of patients in the infliximab-biosimilar group. The frequency of adverse events was similar between groups.[8] In our study, we did not have to switch patients from infliximab to infliximab biosimilar. Patients were assigned either to the group treated with infliximab biosimilar or with infliximab; therefore, the number of our patients with clinical response might have been higher.

Guerra Veloz et al[10] compared the loss of efficacy of the treatment with infliximab biosimilar vs infliximab in patients with inflammatory bowel disease (IBD), who were switched from infliximab. This was an observational ambispective cohort study with a 12-month follow-up. There were 2 groups of patients: a retrospective group included patients with

IBD who were treated with original infliximab, and a prospective group included patients who were switched from infliximab to an infliximab biosimilar. In the prospective cohort, 83.6% of patients with CD were in remission at the time of the switch and 67.7% remained in remission at 12 months. In the retrospective cohort, 76.1% of patients with CD were in remission at baseline and 68.7% remained in remission at 12 months. When the loss of efficacy was compared in both periods, no significant differences were observed.[10] Compared with this study, we observed higher remission rates after 1-year treatment. After 12 months from treatment cessation (in Poland, patients can be treated only for 1 year), the relapse rate was high and was similar between groups receiving infliximab biosimilar and adalimumab, while it was higher in patients receiving originator infliximab. The only possible explanation for this finding is the drug effect, because we did not find any differences between patients' demographic data, duration of disease, or response rates.

The PROSIT-BIO Cohort study (A Prospective Observational Study of Patients with Inflammatory Bowel Disease Treated with Infliximab Biosimilar) included 313 patients with CD and 234 patients with UC.[11] After 2061 infusions, the rate of serious adverse events was reported at 12.1%, 6.9% of which were infusion-related reactions. The biosimilar treatment had to be stopped in 5.3% of cases due to severe infusion reactions, and in another 2.9% of patients due to other serious adverse events. Infusion reactions were significantly more frequent in patients pre-exposed to infliximab than to other anti-TNF-α agents.[11] In contrast, in our study, we did not observe any serious adverse events. In their review, Radin et al[6] discussed available data from 11 studies that included a total of 1007 patients with IBD. Overall, no significant difference in efficacy and safety between infliximab and infliximab biosimilar was observed. When assessing the safety of infliximab biosimilar, they found that 9.2% of patients experienced adverse events (infusion-related reactions in 4.1% and infections in 4.3%). Their results were in line with our findings.

In the literature, there are few papers comparing adalimumab and infliximab biosimilar. In 2018, Singh et al[12] reported data of 2908 Danish adults with CD who had been treated with adalimumab or infliximab as their first biologic agent between 2005 and 2014. Over a median follow-up of 2.3 years after starting biologic treatment, there were no significant differences in the rates of CD-related hospitalization or major abdominal surgery between adalimumab- and infliximab-treated patients, although the rate of all-cause hospitalization was lower in the adalimumab group. There were no significant differences in the incidence of serious infections requiring hospitalization.[12] Unfortunately, the authors compared only infliximab and adalimumab, and the period of treatment was much longer than in our study. Another study compared infliximab and adalimumab use in a local population in Austria.[13] At 12 months, a similar number of patients treated with infliximab and adalimumab maintained clinical remission and GC-free remission.[13]

A promising but unintentional finding of our study is that we did not find any significant differences in the number of men and women treated at our center (148 women vs 138 men). Therefore, it seems that treatment availability is similar for both sexes, as strongly advocated by Selinger and Hall.[14] This finding is contrary to a Polish report from 2017.[15]

The undisputed strength of our study is that it was conducted in a large single center, which allowed inclusion of a large number of patients, a similar level of care for all patients, the use of 3 different drugs, and a fairly long observation (12 months of treatment and 12 months of follow-up). The study has also some limitations. First, it was conducted in a single center (which can be also an advantage, as described above), it had a retrospective design and heterogeneous patient population (although it reflects a real-world patient population), and the choice of available drugs might have been biased (although the decision was made together with the patient after a thorough discussion).

In conclusion, biologic treatment is the best way to achieve clinical remission in patients with CD who do not respond to other drugs (thiopurines and GCs). In our study, we included both anti-TNF-α-naive and nonnaive patients, most of whom were treated with thiopurines and GCs in the past. We showed the same efficacy and safety of infliximab biosimilar in comparison to infliximab and adalimumab not only during induction and 1 year of therapy but also during 12 months of follow-up. Relapse rates in patients receiving infliximab biosimilar were even lower than in those receiving the originator drug. In summary, this is the first study to compare different biologic drugs (both originators and biosimilars) in terms of their safety and efficacy in the adult Polish population.

ARTICLE INFORMATION

CONTRIBUTION STATEMENT GR conceived the concept of the study. MR and MK contributed to the design of the research. MR and MK were involved in data collection. MR and MK analyzed the data. GR coordinated funding for the project. All authors edited and approved the final version of the manuscript.

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