Indian Journal of Gastroenterology (September–October 2022) 41(5):446–455
https://doi.org/10.1007/s12664-022-01252-5

ORIGINAL ARTICLE

# Efficacy and safety of biosimilar versus originator infliximab in patients with inflammatory bowel disease: A real-world cohort analysis

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Received: 16 May 2021 / Accepted: 1 February 2022 / Published online: 15 November 2022


## Abstract

**Background** Anti-tumor necrosis factor (anti-TNF) monoclonal antibody, infliximab, is the primary therapeutic modality for patients with Crohn's disease (CD) and ulcerative colitis (UC), refractory to conventional therapy. Biosimilars of infliximab have been shown to have equivalent efficacy to originator infliximab. We compared the safety and efficacy of infliximab biosimilar with the originator in Indian patients with inflammatory bowel disease (IBD).

**Methods** Patients with IBD treated with either originator or biosimilar infliximab from January 2005 to October 2020 were included in this retrospective analysis. The safety and efficacy of originator or biosimilar infliximab in inducing and maintaining clinical remission at weeks 14 and 52 for CD and UC were evaluated. Disease activity was estimated at baseline, after induction therapy, after 1 year of treatment, and during 12 months of follow-up.

**Results** In all, 137 patients (82 CD; 55 UC) were included, of whom 102 were on originator, and 35 patients received biosimilar. In biosimilar group, clinical response and remission rates at weeks 14 and 52 were 84.2%, 58% and 68.4%, 52.6% in CD and 81.2%, 56.2% and 68.7%, 62.5% in UC patients, respectively. Among patients who were on originator, clinical response and remission rates at weeks 14 and 52 were 79.4%, 46% and 57.1%, 43% in CD and 72%, 64.1% and 66.7%, 56.4% in UC patients, respectively. Thirty-three (24.1%) patients experienced adverse events; eighteen developed tuberculosis (TB), of whom 17 received originator and one patient received biosimilar.

**Conclusions** Infliximab biosimilar is comparable to originator infliximab in terms of safety profile and its efficacy in inducing and maintaining remission in patients with IBD.

**Keywords** Anti-tumor necrosis factor · Clinical remission · Clinical response · Crohn's disease · Latent TB · Primary non-response · Secondary loss of response · Steroid-dependent disease · Tuberculosis · Ulcerative colitis

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## Bullet points of the study highlights

***What is already known?***

- Among the biosimilars of infliximab, BOW015 (infimab) is only available in India.
- There are no data available on the efficacy and safety of infimab in patients with inflammatory bowel disease.

***What is new in this study?***

- Originator infliximab and its biosimilar (BOW015) have equal efficacy in inducing and maintenance of remission in both Crohn's disease and ulcerative colitis.

***What are the future clinical and research implications?***

- Biosimilar infliximab can be considered in place of originator without compromising clinical efficacy and safety at a lower cost.

## Introduction

Inflammatory bowel disease (IBD) is a complex immune-mediated disease with variable presentation and a complicated clinical course. Biologics are an important component of the therapeutic armamentarium in IBD. There has been an increase in the use of biologics since their introduction, and early biologic use is associated with better outcomes [1]. The high cost of biologics remains the major limiting factor for their use, especially in developing countries, where the disease burden of IBD is on the rise [2]. Biosimilars are structurally similar to parent compounds with minor variations and are supposed to have similar efficacy, quality, and safety, offer the advantage of lower cost compared to originator biologics [3–5]. Many biosimilars to infliximab are available, among which CT-P13 has been most commonly studied and is equally efficacious to the originator compound with no major differences in terms of safety, in either naive or switched patients [6–9]. According to the European Crohn's and Colitis Organization (ECCO) position statement, switch of biologics from originators to biosimilars is acceptable [10]. The four biosimilars of infliximab (Inflectra, Renflexis, Ixifi, and Avsola) approved by the Food and Drug Administration (FDA) in the USA are not available in India. In India, another biosimilar BOW015 (Infimab) has been approved since 2014 based on phase III randomized controlled study in patients with rheumatoid arthritis [11]. There are no data available on its efficacy and safety in patients with IBD. We conducted a retrospective analysis to assess the efficacy and safety of biosimilar as compared to originator Infliximab in patients with IBD in real-life clinical settings.

## Methods

### Study setting and population

This study included patients with IBD who received infliximab (either originator or biosimilar) and were under follow-up at the IBD Clinic, Department of Gastroenterology, All India Institute of Medical Sciences (AIIMS), New Delhi, from January 2005 till October 2020. Patients were included if they had received either Infliximab originator: Remicade (Johnson & Johnson, New Jersey, USA) or infliximab biosimilar: Infimab (BOW015) (Sun Pharma, Mumbai, India). Biosimilar molecule is available at MRP of Indian rupee (₹) 30,000 and Originator is available at MRP of ₹ 41,000.

### Study design

It is a retrospective analysis of a departmental database of patients with IBD who had received either infliximab or its biosimilar. The following parameters were extracted from the database: demographic features, body mass index (BMI), disease characteristics (including location, extent, severity, behavior, presence of extraintestinal manifestations [EIMs]), age at disease onset, age at biological initiation, baseline blood parameters, details of latent tuberculosis (TB) screening before initiation of therapy and concomitant immunomodulator use, indication for the use of anti-tumor necrosis factor (anti-TNF) agents, number of doses, duration, response, and complications of anti-TNF therapy. The frequency of development of active TB after biosimilar treatment and its site was also recorded. Any missing data was confirmed by interviewing the patient in person. The study was cleared by the institutional ethics committee (IECPG-599/24.10.19).

## Definitions

Diagnosis of UC and CD was made based on ECCO guidelines [12, 13].

1) Clinical remission:

   UC: simple clinical colitis activity score (SCCAI) ≤2 for 7 days [14]
   CD: Crohn's disease activity index (CDAI) < 150 for 7 days [15]

2) Clinical response:

   UC: decrease in SCCAI score by 3 points
   CD: decrease in CDAI by 70 points

3) Primary non-response: Lack of response to an induction dose of anti-TNF therapy, assessed at week 14 [16]
4) Secondary loss of response: loss of response with a maintenance dose of anti-TNF (after an initial response to induction dose)
5) Steroid-refractory disease: active disease despite prednisolone medication up to 0.75 mg/kg/day over a period of 4 weeks was defined as a steroid-refractory disease [12, 13]
6) Steroid-dependent disease: patients who were unable to reduce steroids below the equivalent of prednisolone 10 mg/day within 3 months of starting steroids without recurrent active disease or who had a relapse within 3 months of stopping steroids [12, 13]
7) Clinical relapse:

   UC: increase of 3 or more points of SCCAI for seven consecutive days
   CD: increased CDAI above 150 points or between 150 points and 250 points with a 70-point increase from baseline over two consecutive weeks in CD patients [17].

8) Latent tuberculosis: diagnosed based on positive tuberculin skin test (≥10 mm) or interferon-gamma release assay (IGRA) [18, 19]. Evidence of healed tuberculosis on chest X-ray or computed tomography (pleural thickening, fibrotic scarring, calcified nodules, and calcified hilar or mediastinal lymphadenopathy) was also considered latent TB [20].
9) Active tuberculosis: pulmonary TB was diagnosed in the presence of clinical symptoms (e.g. fever, cough, anorexia, weight loss) and evidence of fresh lesions suggestive of TB on the chest X-ray/contrast-enhanced computerized tomography scan of the chest with or without demonstration of an acid-fast bacillus (AFB) on the sputum smear examination [21]. Extrapulmonary TB was diagnosed based on clinical features, suggestive radiologic findings, and demonstration of AFB on culture or caseating or non-caseating granulomas on biopsy specimens. Diagnosis of pleural TB/peritoneal TB was based on biochemical evaluation of pleural/peritoneal fluid showing high levels of protein along with an adenosine deaminase (> 40 IU/mL) and lymphocytic predominance [21]. Patients with evidence of TB at more than one site were diagnosed with disseminated disease.

## Statistical analysis

Descriptive statistics were used to present patient demographics, clinical response and remission rates, and adverse events. Categorical variables were expressed as percentages, and continuous variables were expressed as mean ± SD or median (interquartile range) as appropriate. $P < 0.05$ was considered statistically significant. The probability of maintaining response between originator and biosimilar group was analyzed with Kaplan-Meier survival analysis. Data were analyzed using IBM Statistical Package for the Social Sciences (SPSS) Statistics software (version 21.0, IBM, Chicago, IL, USA).

## Results

A total of 6802 patients with IBD were registered at IBD Clinic at AIIMS, New Delhi, between January 2005 and October 2020. Of them, 137 patients (CD: 82 and UC: 55) received at least induction therapy (originator or biosimilar) and were included. Among them 102 (CD: 63 and UC: 39) received originator and 35 (CD: 19 and UC: 16) received biosimilar. Seven patients received both, i.e. originator and biosimilar, and were included in the biosimilar group, as they were induced with biosimilar and have received originator only during hospital admissions at our institute or if biosimilar was unavailable. The age of onset was comparable between patients with UC and CD (27 years, interquartile range [IQR] 19–35 vs. 26 years, 17–41). Among patients with UC, 49% were male with a median disease duration of 201 months (IQR 59–120), and among CD patients, 61% were male with a median disease duration of 105 months (IQR 71–146). In the originator group, therapy was initiated in 37 (58.7%) patients in view of steroid-dependent disease; 6 (9.5%) patients had a steroid-refractory disease. Eleven (17.5%) and 6 (9.5%) patients respectively had perianal and fistulizing disease warranting biological therapy. Three (4.7%) patients had overlapping causes. Among 19 patients on biosimilar, 11 (58%) patients had a steroid-dependent disease; three (15.7%) patients had a steroid-refractory disease. Two (10.5%) patients each had fistulizing and perianal disease, respectively. One (5.2%) patient had overlapping causes. In the originator group who were followed up till 52 weeks, 48/51 (94.1%) and 39/51

**Table 1** Baseline clinical, demographic features and disease characteristics of patients with Crohn's disease

| Parameter | Crohn's disease ($n$=82) | | $p$ value |
|---|---|---|---|
| Type of biological ($n$) | Originator ($n$=63) | Biosimilar ($n$=19) | |
| Age at disease onset (years), median (IQR) | 26.5 (17.5–40.5) | 26.5 (16–49) | 0.804 |
| Gender—males ($n$, %) | 57 (90.5) | 10 (52.6) | <0.001 |
| Disease duration at biological initiation (months) median (IQR) | 60 (36–108) | 46 (26.5–84) | 0.307 |
| Follow-up duration after treatment with biologics (months) median (IQR) | 36 (19.5–72) | 24 (14.5–41) | 0.082 |
| Disease: age, location, behavior (CD), $n$ (%) | | | |
| A1 < 17 years | 16 (25.39) | 5 (26.31) | 0.93 |
| A2: 17–40 years | 30 (47.61) | 7 (36.84) | 0.408 |
| A3: > 40 years | 17 (26.98) | 7 (36.84) | 0.408 |
| B1: inflammatory | 17 (26.98) | 3 (15.78) | 0.34 |
| B2: stricturing | 32 (50.79) | 12 (63.15) | |
| B3: fistulizing | 14 (22.22) | 4 (21.05) | |
| Perianal involvement | 13 (20.63) | 2 (10.52) | 0.318 |
| L1=ileal | 6 (9.52) | 4 (21.05) | |
| L2=colonic | 18 (28.57) | 3 (15.78) | |
| L3=ileocolonic | 22 (34.92) | 1 (5.26) | |
| L4= proximal small bowel | 2 (3.17) | 3 (15.78) | |
| L1+4 | 13 (20.63) | 3 (15.78) | |
| L3+4 | 2 (3.17) | 4 (21.05) | |
| L2+4 | - | 1 (5.26) | |
| Median (IQR) CDAI at baseline | 280 (245–321.5) | 290 (260–320) | 0.533 |
| Smokers, $n$ (%) | 6 (9.52) | 2 (10.52) | 0.897 |
| Extraintestinal manifestation, $n$ (%) | 31/63 (49.20) | 12/19 (63.15) | 0.286 |
| Hemoglobin (g/dL) (mean±SD) | 9.4±2.1 | 9.32±1.8 | 0.952 |
| Serum albumin (g/dL) (mean±SD) | 3.20±1.121 | 3.5±0.88 | 0.584 |
| CRP (mg/L) median (IQR) | 5.96 (2.65±11.5) | 2.3 (1.1±3.4) | 0.018 |
| ESR (mm/h) median (IQR) | 35 (28–45) | 34 (30–43) | 0.569 |
| Steroid dependant (%) | 37 (58.7) | 11 (58) | 0.94 |
| Steroid refractory (%) | 6 (9.5) | 3 (15.7) | |
| Perianal disease (%) | 11 (17.4) | 2 (10.5) | |
| Fistulizing disease (%) | 6 (9.5) | 2 (10.5) | |
| Overlapping causes (%) | 3 (4.7) | 1 (5.2) | |

*CRP* C-reactive protein, *ESR* erythrocyte sedimentation rate, *IQR* interquartile range, *CD* Crohn's disease, *CDAI* Crohn's disease activity index

(76.4%) had clinical response and remission, respectively. In the biosimilar group who were followed up till 52 weeks, clinical response and remission were documented in 19/22 (86.3%) and 17/22 (77.3%), respectively.

## Comparison of originator and biosimilar in patients with Crohn's disease

### Baseline clinical and demographic features

Among 82 patients with CD, 63 were managed with an originator and 19 were managed with biosimilar infliximab. The proportion of males were higher in the originator group compared to the biosimilar group (90.5% vs. 52.6%, $p$<0.001). Patients in the originator group had higher ileocolonic involvement than patients in the biosimilar group (35% vs. 5.3%; $p$=0.0173). Other parameters like age at onset, CDAI, disease behavior, disease duration at the initiation of biologics, and laboratory parameters like hemoglobin, serum albumin, and erythrocyte sedimentation rate (ESR) were comparable between both the groups (Table 1). A similar proportion of patients in the originator and biosimilar group (66.6% and vs. 74%, $p$=0.56) received concomitant immunomodulators. The median duration of therapy was 12 months in the

**Table 2** Comparison of treatment outcomes between originator and biosimilar forms of infliximab in patients with Crohn's disease

| Parameter | Crohn's disease (*n*=82) | | *p* value |
|---|---|---|---|
| Type of biological (*n*) | Originator (*n*=63) | Biosimilar (*n*=19) | |
| Concomitant medications, *n* (%) | 42 (66.6) | 14 (74) | 0.563 |
| Oral corticosteroids | 7 | 2 | |
| AZA/6-MP | 27 | 8 | |
| MTX | 4 | 4 | |
| AZA+ Oral corticosteroids | 4 | - | |
| Duration of anti-TNF, months (IQR) | 12 (6–21.5) | 18 (13–29) | 0.70 |
| Response: decrease in CDAI >70, (%) | | | |
| 14 weeks | 50 (79.4) | 16 (84.2) | 0.64 |
| 52 weeks | 36 (57.1) | 13 (68.4) | 0.38 |
| Remission CDAI < 150, *n* (%) | | | |
| 14 weeks | 29 (46) | 11 (58) | 0.36 |
| 52 weeks | 27 (43) | 10 (52.6) | 0.45 |
| Adverse drug reactions | 20 (31.7) | 3 (15.8) | 0.247 |
| Tuberculosis | 13 (20.6) | 0 | 0.032 |
| Infusion reaction | 2 (3.2%) | - | |
| Bronchospasm | 1 (1.6%) | - | |
| Intra-abdominal abscess | 1 (1.6%) | - | |
| Chicken pox | 1 (1.6%) | - | |
| Zoster infection | 1 (1.6%) | 1 (5.3%) | |
| Ingrown toenail | 1 (1.6%) | - | |
| Drug-induced lupus | - | 1 (5.3%) | |
| Septic shock | - | 1 (5.3%) | |

*AZA* azathathioprine, *IQR* interquartile range, *MTX* methotrxate, *6-MP* mercaptopurine, *CDAI* Crohn's disease activity index, *anti-TNF* anti-tumor necrosis factor

originator group and 18 months in the biosimilar group. Both groups were followed for a median duration of 36 and 24 months in the originator and biosimilar groups, respectively.

## Comparison of response

Twenty-one percent (*n*=13) in originator group and 16% (*n*=3) in biosimilar group have primary non-response at 14 weeks, whereas 32% (*n*=16) had secondary loss of response with originator compared to 31% (*n*=5) with biosimilar at 52 weeks. After induction therapy (at 14 weeks), both clinical response (79.4% vs. 84.2%, OR: 1.39 [0.35–5.49], *p*=0.75) and remission (46% vs. 58%, OR: 1.61 [0.57–4.55], *p*=0.37) were comparable between originator anti-TNF vs. biosimilar group. At 52 weeks, 57.1% (*n*=36) and 68.4% (*n*=13) maintained clinical response with originator and biosimilar

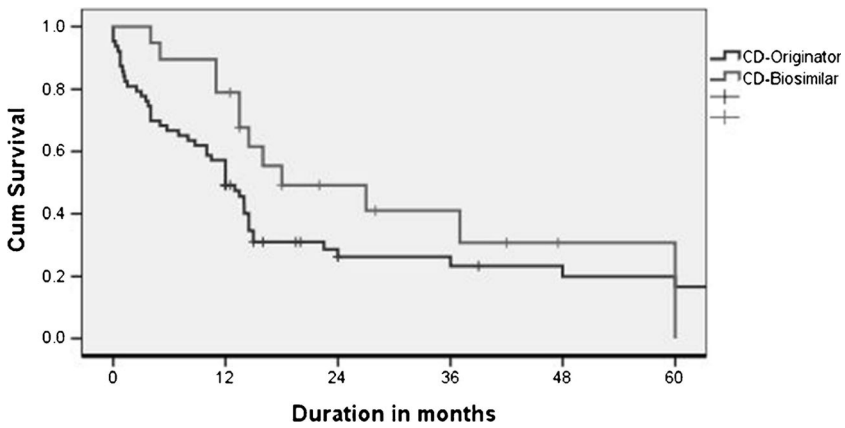


**Fig. 1** Kaplan-Meier survival graph comparing the proportion of patients maintaining response with originator vs. biosimilar in patients with Crohn's disease

**Table 3** Baseline clinical, demographic features and disease characteristics of patients with ulcerative colitis

| Parameter | Ulcerative colitis (*n*=55) | | *p* value |
|---|---|---|---|
| Type of biological (*n*) | Originator (*n*=39) | Biosimilar (*n*=16) | |
| Age at disease onset, median (IQR) | 27 (19–35) | 30 (23–35) | 0.86 |
| Gender, males (*n*, %) | 22 (56.4) | 5 (31.2) | 0.09 |
| Disease duration at biological initiation (months) median (IQR) | 50 (24–76.5) | 45 (23.5–61.2) | 0.18 |
| Follow-up duration after treatment with biologics (months) median (IQR) | 27 (21–50) | 30.5 (22.25–48) | 0.91 |
| Early initiation of biological in disease course (<2 years) *n* (%) | 12 (30.76) | 7 (43.75) | 0.35 |
| Disease: extent (UC) E1: E2:E3, *n* (%) | E2-6 (15.30) E3-33 (84.61) | E2-6 (37.5) E3-10 (62.5) | 0.07 |
| Median (IQR) SCCAI for UC | 8 (6–8.5) | 8 (7–9) | 0.15 |
| Smokers, *n* (%) | 4 (10.25) | 3 (18.75) | 0.40 |
| Extraintestinal manifestation, *n* (%) | 10 (25.64) | 5 (31.25) | 0.67 |
| Hb (g/dL) (mean±SD) | 10.40 ±1.56 | 10.12±1.47 | 0.72 |
| Serum albumin (g/dL) (mean±SD) | 3.62±0.50 | 3.58±0.75 | 0.59 |
| CRP (mg/L) (median, IQR) | 3.5 (2–5.75) | 4 (2–6) | 0.12 |
| ESR (mm/h (median, IQR) | 33 (25.5–40.75) | 34 (26–42.25) | 0.17 |
| Indications for treatment with biologics, *n* (%) | | | |
| Steroid dependent | 27 (69.23) | 11 (68.75) | 0.76 |
| Steroid refractory | 1 (2.5) | - | |
| Acute severe ulcerative colitis | 11 (28.20) | 5 (31.25) | |

**Table 4** Comparison of treatment outcomes between originator and biosimilar forms of infliximab in patients with ulcerative colitis

| Parameter | Ulcerative colitis (*n*=55) | | *p* value |
|---|---|---|---|
| Type of biological (*n*) | Originator (*n*=39) | Biosimilar (*n*=16) | |
| Concomitant medications, *n* (%) | 33 (84.6) | 13 (81.2) | 0.71 |
| Oral corticosteroids | 9 | 1 | |
| AZA/6-MP | 20 | 10 | |
| MTX | 1 | 2 | |
| AZA+ Oral corticosteroids. | 3 | - | |
| Duration of biological, months (IQR) | 13 (5–23.5) | 14.5 (6.12–23.8) | 0.70 |
| Response: decrease in SCCAI >3, *n* (%) | | | |
| 14 weeks | 28 (72) | 13 (81.2) | 0.52 |
| 52 weeks | 26 (66.7) | 11 (68.7) | 0.88 |
| Remission SCCAI ≤ 2, *n* (%) | | | |
| 14 weeks | 25 (64.1) | 9 (56.2) | 0.58 |
| 52 weeks | 22 (56.4) | 10 (62.5) | 0.68 |
| Adverse drug reaction | 7 (18) | 3 (18.7) | >0.99 |
| Tuberculosis | 4 (10.2) | 1 (6.3) | >0.99 |
| Infusion reaction | 2 (5.2) | - | |
| NYHA Grade II heart failure | 1 (2.6) | - | |
| Inflammatory arthritis | - | 1 (6.3) | |
| Infective vocal cord growth | - | 1 (6.3) | |

*AZA* azathathioprine, *6-MP* 6-mercaptopurine, *IQR* interquartile range, *MTX* methotrxate, *SCCAI* simple clinical colitis activity index, *NYHA* New York Heart Association

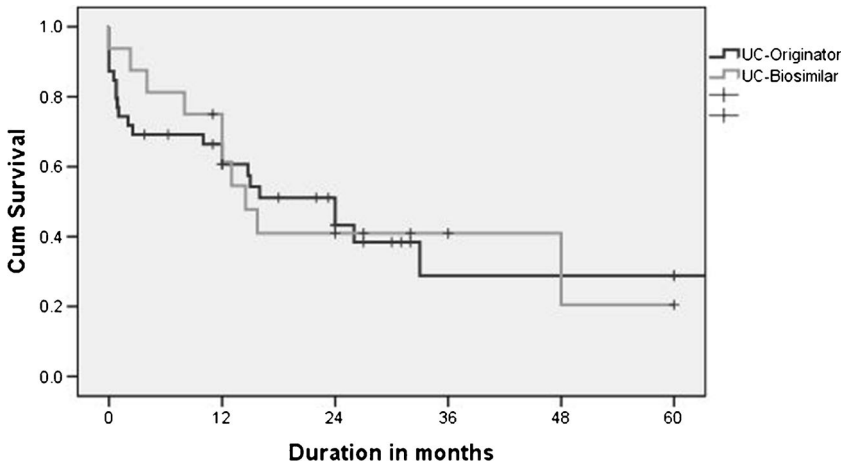


**Fig. 2** Kaplan-Meier survival graph comparing the proportion of patients maintaining response with originator vs. biosimilar in patients with ulcerative colitis

respectively (OR: 1.62 [0.547–4.825], $p$=0.380). Similarly, 43% ($n$=27) in originator group and 52.6% ($n$=10) in biosimilar group remained in clinical remission at 52 weeks (OR: 1.48 [0.52–4.14], $p$=0.454) (Table 2). Overall median duration of response with originator and biosimilar was similar in both groups (12 vs. 18 months) ($p$ value=0.128) (Fig. 1). The cumulative probability of maintaining response without discontinuation at 1 and 3 years is similar between both groups (56% vs. 79%; 26% vs. 40%).

## Originator vs. biosimilar in ulcerative colitis

### Baseline clinical and demographic features

Among 55 patients with UC, 39 were managed with an originator and 16 were managed with biosimilar anti-TNF. Median disease duration at biological initiation was comparable in the originator and biosimilar group (50 vs. 45 months, $p$=0.181). Similarly, other parameters like age at onset, disease activity, extent, and laboratory parameters like hemoglobin, albumin, C-reactive protein (CRP), and ESR were comparable between both groups. The median duration of infliximab therapy was also similar between both groups (13 vs. 14.5 months, [$p$=0.701]) (Table 3).

### Comparison of response

Nineteen percent ($n$=3) in the biosimilar group and 28% ($n$=11) in the originator group had primary non-response at 14 weeks, whereas 14% ($n$=4) had a secondary loss of response with originator compared to 15% ($n$=2) with biosimilar at 52 weeks.

After induction therapy (at 14 weeks), both clinical response (72% vs. 81.2%, OR: 1.7 [0.404–7.157], $p$=0.521) and remission (64.1% vs. 56.2%, OR: 0.720 [0.220–2.354], $p$=0.583) were comparable between originator anti-TNF vs. biosimilar group (Table 4). At 52 weeks, 66.7% ($n$=26) patients maintained clinical response with originator compared to 68.7% ($n$=11) with biosimilar ($p$=0.88). Similarly, 56.4% ($n$=22) in originator group and 62.5% ($n$=10) in biosimilar group remained in clinical remission at 52 weeks (OR: 1.28 [0.39–4.24], $p$=0.68) (Table 4). The overall median duration of response with originator and biosimilar was comparable (12 vs. 13.7 months) ($p$ value- 0.97) (Fig. 2). The cumulative probability of maintaining response without discontinuation at 1 and 3 years was similar between both the groups (65% vs. 74%; 30% vs. 40%).

Among the overall cohort, in the originator group, 51 (50%) patients discontinued treatment before 52 weeks, of whom 28.4% ($n$=29) patients experienced a loss of response, 16.6% ($n$=17) developed adverse effects, and 5% ($n$=5) had financial constraints. Of 35 patients on biosimilar, 13 (37%) discontinued treatment before 52 weeks of therapy and 11 discontinued treatment due to loss of response and two due to drug-related adverse effects. A median number of doses in originator and biosimilar groups are 9 and 10.5, respectively, and the median durations of therapy in originator and biosimilar groups are 12 and 18 months, respectively.

## Adverse events

Among patients with CD, adverse drug reactions were noted in 20 (31.7%) patients in the originator group and 3 (15.8%) in the biosimilar group. No patient in the biosimilar group developed TB. Thirteen (20.6%) patients in the originator group developed TB, of whom 8 (44.4%) developed disseminated TB. In the originator group, 2 (3.2%) patients had infusion reaction, 1 (1.6%) had life-threatening bronchospasm, 1 (1.6%) had an intra-abdominal abscess, 1 (1.6%) had chickenpox, and 1 (1.6%) patient each developed herpes zoster infection and in-grown toe-nail with recurrent infections. In the biosimilar group, 1 (5.3%) patient each developed herpes zoster infection, drug-induced lupus, and septic shock.

Among patients with UC, 7 (18%) and 3 (18.7%) patients had adverse drug reactions in the originator and biosimilar groups, respectively. Among patients treated with originator anti-TNF, four patients (10.2%) developed TB, 2 (5.2%) experienced infusion reaction, and 1 (2.6%) patient developed heart failure. Among patients who received biosimilar, 1 (6.3%) patient each developed TB, inflammatory arthritis, and infective vocal cord growth.

The period of use of originator and biosimilar was not the same. Originator molecule was being used at our centre since 2007, whereas biosimilar was introduced in 2014. Of the 18 patients who developed TB, baseline screening was done for all patients. Tubercular skin testing and chest X-ray were done in all TB patients, both in originator and biosimilar groups. IGRA was done in only 3 of 18 patients in the originator group and a single patient in the biosimilar group who developed TB did not have baseline IGRA testing done. Of 3 patients who underwent IGRA, none had any evidence of latent TB. Of 18 patients with TB, computed tomography (CT) was done in 14 patients and the single patient had minimal pleural effusion on the CT chest, the rest of all CTs were normal. None of the patients received latent TB prophylaxis. Eighteen patients had TB despite negative workup for latent TB. Of the 102 patients in the originator group, 52 (50.9%) had complete screening. Of the 35 patients in the biosimilar group, 21 (60%) had complete screening.

## Discussion

The present study adds to the existing literature on the efficacy of biosimilar molecules as compared to their originals in patients with IBD. This is particularly relevant for developing countries, where the prohibitive cost of these agents and lack of insurance coverage limit their use. The study demonstrates similar short-term and long-term treatment outcomes with infliximab biosimilar (BOW015) and originator molecule in Indian patients with IBD. There are many infliximab biosimilars available internationally, among which CT-P13 has the strongest evidence. In recent years, the use of biosimilar like CT-P13 has increased because of significant cost-saving and similar clinical efficacy to that of infliximab in the treatment of IBD [22].

The efficacy and tolerability of infliximab, the original biologic, have been established in multiple randomized clinical trials (RCTs) in IBD [23–26]. Regarding biosimilars, several observational cohort studies demonstrated similar efficacy of CT-P13 compared to the originator in biological naïve patients and also with switch in patients with IBD [8, 9, 27–29]. A large comparative equivalence cohort study of 5050 patients with CD from a French nationwide health administrative database demonstrated a similar composite endpoint of death, CD-related surgery, all-cause hospitalization, and use of another biologic therapy between CT-P13 and originator infliximab, along with similar safety outcomes [30]. Another study of 3000 UC patients from the same group demonstrated the equivalency of CT-P13 to the originator [31].

In our study, clinical response and remission rates with biosimilar at 14 weeks were 84.2% and 58%, respectively, in CD, and 81.2% and 56.2%, respectively, in UC patients. These findings were comparable to originator infliximab. These results are similar to previously published observational studies. In a prospective, multicentre, nationwide cohort study from Hungary [27], the clinical response and remission rates with biosimilar (CT-P13) were 86% and 49% at week 14, respectively, in CD, and 74% and 56% at week 14, respectively, in UC. However, a retrospective study from Korea [9] demonstrated a higher clinical response and remission rate with biosimilar CT-P13 (94% and 78%) in CD patients compared to our study at 14 weeks. Another study by Jung et al. [28] also showed a comparable clinical response of 87.2% but a higher remission rate of 69.2% in CD patients at 14 weeks with biosimilar CT-P13.

Our study also demonstrated comparable long-term clinical remission and response rates in CD and UC at 52 weeks. In the studies by Jung et al. [28] and Kim et al. [9], the clinical response rates in CD and UC were 87.8% and 100%, and 92.7% and 80%, respectively, at 52 weeks. In comparison to our study, the clinical remission rate in the study by Jung et al. was higher in CD (75%) and lower in UC (50%); however, the clinical remission rate in the study by Kim et al. was higher in CD (82.4%), but comparable in UC (59.8%). In contrast to our study, Kim et al. excluded patients who discontinued CT-P13 after 1 or 2 doses due to insufficient clinical response, and this must have led to an overestimation of the efficacy of CT-P13.

A recently published RCT by Ye et al. is the first clinical trial to confirm the equivalent efficacy of CT-P13 relative to the originator in biologically naive patients with active CD [32]. In this multicentre, double-blind, phase 3 trial, patients were randomly assigned in four groups: CT-P13 followed by CT-P13, CT-P13 followed by infliximab, infliximab followed by infliximab, and infliximab followed by CT-P13, with the switch occurring at week 30. The primary endpoint (clinical improvement, defined as a decrease in the CDAI by 70 points at week 6) was similar for CT-P13 (69·4%) and originator (74·3%) anti-TNF. Even though this study also looked at the efficacy of the switch at 30 weeks, the study was underpowered for this outcome. Another important observation from this study was the 21% absolute difference of anti-drug antibodies between the CT-P13–infliximab (33%) and infliximab–CT-P13 groups (55%), which could be clinically relevant. However, the drug levels were similar between the two groups. Similarly, in SECURE, a phase 4 prospective open-label study, of 88 patients with IBD (CD 46 and UC 42) in clinical remission on infliximab, switch to CT-P13 at the same

dose was not associated with lower drug levels 16 weeks after switching as compared to those on originator infliximab at baseline [33]. However, in our study, we did not perform drug levels or anti-drug antibody levels.

The overall clinical response and remission rates for both originator (infliximab) and biosimilar (infimab) maintenance therapy in this study are somewhat higher than those reported in well-known RCTs (ACCENT I and ACT I) [23, 25]. In ACCENT I, the clinical response and remission rates for infliximab in anti-TNF-naïve CD patients were 50% and 39% at week 30, and 39% and 30% at week 54, respectively, while those in anti-TNF-naïve UC patients were 52% and 34% at week 30, and 46% and 35% at week 54, respectively, in ACT I. Different study designs and patient populations could be the main reason for this disparity in data. The retrospective design in the present study can overestimate the efficacy of anti-TNF compared with that in RCTs.

We recently reported a primary non-response at 8 weeks and secondary loss of response at 52 weeks as 14.5% and 15%, respectively, and TB reactivation rate of 11.6% in a cohort of patients on infliximab [34]. Recent data on adalimumab biosimilar (ZRC-3177) reported remission at 8 weeks in 46.9% and 52.4% patients with CD and UC, respectively, of whom 32.7% and 33.3% maintained remission over 1 year, respectively [35]. On similar lines, we evaluated the efficacy and side effect profile of infliximab biosimilar (infimab-BOW015) and compared it to the originator compound (Remicade).

Anti-TNF use in IBD is associated with an increased risk of adverse events (AE) and opportunistic infections [36]. In our study, 3 (15.8%) patients in CD and 3 (18.75%) in UC experienced some form of AE during the treatment with the biosimilar, of which only one patient in UC developed TB. However, in the originator group, 20 (31.7%) patients in CD and 7 (18%) in UC developed some form of AE and TB was documented in 13 (20.6%) and 4 (10.2%) patients in CD and UC, respectively. Lower rates of development of TB in biosimilar group could be due to improved latent TB (LTB) screening techniques over the years, as demonstrated in our recent data analysis (unpublished), where patients started on anti-TNF over the last 2 years had significantly lower TB reactivation as compared to patients started before that, and this correlated with higher LTB detection rates in the latter cohort.

Major limitations of our study include the retrospective design, small sample size, and disproportionate numbers in originator and biosimilar groups. Mucosal healing was not assessed in our study. Infliximab serum trough levels and anti-drug antibody levels were not measured. Among the originator group, 50% of patients discontinued therapy before 1 year and in the biosimilar group, 37% discontinued therapy before 52 weeks. This also affects the comparison of efficacy between the two groups. However, previous studies have already demonstrated similar immunogenicity of biosimilar compared to the originator. Even though all biosimilars are supposed to have similar efficacy, potency, and safety to the originator, the majority of the studies were done on CT-P13. Despite similar chemical structures, minor differences in the manufacturing process can be clinically relevant. There are no studies of BOW015 biosimilar in patients of IBD, and our study demonstrated both short-term and long-term efficacy of this biosimilar compared to infliximab biosimilar in the real-world scenario.

In conclusion, infliximab biosimilar is as effective and safe as its originator in both inducing and maintaining clinical remission in patients with IBD.

**Funding** Indian Council for Medical Research - Centre for Advanced Research and Excellence in Intestinal Diseases.

## Declarations

**Conflict of interest** PK, SKV, BK, SK, PS, MKR, SM, RG, MK, SV, AG, NY, GM, and VA declare no competing interests.

**Ethics statement** The study was performed conforming to the Helsinki declaration of 1975, as revised in 2000 and 2008 concerning human and animal rights, and the authors followed the policy concerning informed consent as shown on Springer.com.

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