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ORIGINAL ARTICLE

Effectiveness and safety of adalimumab biosimilar in inflammatory bowel disease: A multicenter study

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Abstract

Background Adalimumab has emerged as a useful drug for treating patients with Crohn's disease (CD) and ulcerative colitis (UC), not responding to conventional therapy. There is limited data on effectiveness and safety of adalimumab biosimilar in patients with inflammatory bowel disease (IBD).

Methods Patients with IBD who received at least one dose of adalimumab biosimilar from October 2015 to February 2018 were retrospectively included in this multicenter data analysis. Its effectiveness in inducing and maintaining clinical remission at 8, 26, and 52 weeks for CD and UC and safety profile of the drug was studied.

Results Seventy patients (49 CD; 21 UC) with a median age of 39 (range 13–73) years, male predominance (64.3%), and median (IQR) disease duration of 72 (33–104) months were included. Adalimumab biosimilar was effective in inducing remission (at 8 weeks) in 46.9% and 52.4% patients with CD and UC, respectively, of whom 32.7% and 33.3% (three fourths of remitters) maintained remission over 1 year, respectively. Twenty (28.6%) patients experienced adverse events; seven (10%) were serious of whom three had developed tuberculosis.

Conclusions Adalimumab biosimilar in usual clinical practice is safe and effective in inducing and maintaining remission in Indian patients with IBD. Steroid-free clinical remission was observed in one third of patients with UC and CD at 1 year of therapy.

Bullet points of the study highlights

What is already known?

- Adalimumab is effective for the induction and maintenance treatment of patients with inflammatory bowel disease (IBD).
- It reduces the need for frequent hospitalizations and improves the quality of life in these patients.
- The literature on the efficacy and safety of adalimumab biosimilar in real-world setting is lacking.

What is new in this study?

- Adalimumab biosimilar had reasonable efficacy in patients with Crohn's disease as well as ulcerative colitis from major tertiary care centers of India.
- The safety profile of adalimumab biosimilar was acceptable in Indian setting.

What are the future clinical and research implications of the study findings?

- Adalimumab biosimilar can be a reasonable and relatively affordable option for patients with IBD in India.
- For optimal efficacy, further research into the development of low-cost therapeutic drug monitoring for adalimumab is warranted.

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Keywords Adalimumab · Biosimilar · Efficacy · Inflammatory bowel disease · Safety

Introduction

Inflammatory bowel disease (IBD) is a chronic inflammatory disorder of the intestine, which is characterized by periods of remission and relapses [1]. The incidence, prevalence, and overall burden of IBD are increasing in India, and as per recent reports, India has very high disease burdens of IBD in the world [2, 3]. It affects patients' quality of life (QOL) and poses substantial financial burden [4]. Maintaining the disease in remission, preventing relapses, and motivating patient to continue treatment and appropriate education are essential in managing IBD [5, 6]. Adalimumab is a tumor necrosis factor-alpha (TNFα) antagonist, a biological agent, which has been found to be effective in treating IBD [7]. In spite of its proven efficacy in IBD around the world [8, 9], doctors in Asia Pacific countries in general and in India, in particular, are reluctant to use the biological agents due to its high cost. Biosimilar has been recently introduced but sparse data exist on its use in real life for managing IBD. There has been only one study available over the years in India since its availability [10]. Hence, this multicenter data analysis was carried out to study the effectiveness and safety of adalimumab biosimilar (Exemptia) in Indian patients with IBD.

Methods

Study setting and population

This study included patients with IBD seen at four medical institutes in northern India (Department of Gastroenterology, All India Institute of Medical Sciences [AIIMS] New Delhi, Sanjay Gandhi Postgraduate Institute of Medical Sciences, Lucknow, Fortis Memorial Research Institute [FMRI], Gurugram and Dayanand Medical College and Hospital, Ludhiana) from October 2015 to February 2018. This study was conducted in accordance with Good Clinical Practice and in a manner to conform with the Helsinki Declaration of 1975, as revised in 2000 and 2008 concerning human rights. The study protocol was approved by the institutional ethics committee of the coordinating center.

Study design and data extraction

This was a retrospective analysis of patients with IBD who had received adalimumab biosimilar at least once during their visit from October 2015 to February 2018. Patient details were extracted into a standard proforma. The following parameters were extracted from the database: demographic features, disease characteristics including location, extent, severity and behavior, presence and number of extraintestinal manifestations (EIMs), complete blood count and liver and renal functions prior to adalimumab, history of smoking or alcohol intake, past history of tuberculosis (TB), any history of receiving anti-tuberculosis therapy (ATT) prior to the diagnosis of Crohn's disease, prior steroids and immunomodulator use, indication for the use of adalimumab, information on screening and presence of latent TB, dose, duration, period of follow up from the initiation of adalimumab biosimilar treatment, reason for loss to follow up, response, loss of response, and adverse events (AE) related to adalimumab biosimilar therapy. The frequency of development of active TB after adalimumab biosimilar treatment and its site was also recorded. Any missing data was confirmed by interviewing the patient in person. Patients' data were entered from the date of first dose of adalimumab biosimilar at the study center till the date of switching to therapy or February 28, 2018, whichever was earlier.

Diagnosis and management

Subtypes of IBD were diagnosed on the basis of standard European Crohn's and Colitis Organization (ECCO) guidelines [11, 12]. Disease extent was classified on the basis of the Montreal classification [13]. Except for one center (FMRI, Gurugram) which had used American College of Gastroenterology guidelines for definition of remission and relapse, other centers used simple clinical colitis activity index (SCCAI) for UC and Crohn's disease activity index (CDAI) for CD [14, 15]. At baseline and at each visit, patients were clinically assessed according to above criteria. All patients were screened for latent TB at entry, and those positive received chemoprophylaxis with isoniazid (5 mg/kg) for 9 months. Patients were started on adalimumab (Exemptia, Zydus Cadila, India) injection (four injections of 40 mg each, total of 160 mg at baseline, 80 mg [40 mg each × 2] at 14 days, and then 40 mg every other week). The steroids were tapered, and the dose of other concomitant medications remained constant. The patients were evaluated at weeks 8, 26, and 52 for clinical response and remission. Patients with anemia received iron supplements, antihypertensive and antidiabetic were used in patients who had these comorbid illnesses. AE, if any, were recorded. Treatment-related AE was defined as new events that began during or following the first and within 2 months after the last dose of adalimumab biosimilar. Patients who had previously failed infliximab and were switched over to adalimumab biosimilar were also included in the analysis.

Definitions

The treatment with adalimumab biosimilar was considered efficacious if patients had clinical remission at 8 weeks, while maintenance was assessed at 26 and 52 weeks.

Remission Remission for UC was defined as SCCAI ≤ 2. For CD, remission was defined as CDAI < 150 [16].

Response Response for UC was defined as decrease in SCCAI by 3 points. Response in CD was defined as decrease in CDAI by 100 points [16].

Relapse Disease associated with need for steroids and/or hospitalization for flares of disease despite optimal treatment with biologics.

Primary non-response Lack of response to induction dose of adalimumab.

Secondary loss of response Loss of response with maintenance dose of adalimumab (after an initial response to induction dose).

- Partial: Overcome by increasing the dose/frequency of adalimumab
- Complete: No response to increasing the dose/frequency of the drug needing switching of the therapy

Steroid-refractory disease As per ECCO guidelines, active disease despite prednisolone medication up to 0.75 mg/kg/day over a period of 4 weeks was defined steroid-refractory disease [11, 12].

Steroid-dependent disease Patients who were unable to reduce steroids below the equivalent of prednisolone 10 mg/day within 3 months of starting without recurrent active disease or who had a relapse within 3 months of stopping steroids [11, 12].

Partial healing can be "endoscopic improvement" or "absence of ulcerations" to a more quantified endoscopic Mayo score of 1 or a prespecified decrease in Simple Endoscopic Score for CD or Crohn's Disease Endoscopic Index of Severity [17].

Latent tuberculosis Diagnosed on the basis of positive Mantoux (> 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 as latent TB [20].

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 acid-fast bacillus (AFB) on the sputum smear examination [21]. Extrapulmonary TB was diagnosed on the basis of 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 a high levels of protein along with a adenosine deaminase (> 40 IU/mL) and lymphocytic predominance [21]. Patients with evidence of TB at more than one sites were diagnosed as disseminated disease.

Statistics Statistical analysis was done by SPSS (v.20) for Windows. Descriptive statistics were used. The median and interquartile ranges are given. Wherever appropriate, frequency, number, and percentage are mentioned. Categorical data were analyzed using the Chi-square test. Kaplan–Meier survival analysis was performed, and the log-rank test was used to compare remission and response rates among CD and UC patients; p values < 0.05 were considered significant.

Results

Baseline demographic and clinical features

A total of 70 patients (49 CD; 21 UC) who received adalimumab biosimilar were included. The age of onset was comparable between patients with UC and CD (28 years, IQR 21–51 vs. 35 years, 23–51, $p < 0.727$). At study entry, 42 (85.7%) patients with CD had moderate disease, while 7 (14.3%) had severe disease. Among patients with UC, 19 (90.4%) had moderate disease while 2 (9.5%) had severe disease. Baseline characteristics and clinical details of the patients are given in Table 1.

Remission and response in CD

Four patients with CD had a primary non-response. At 8 weeks, 23 (46.9%) patients with CD went into remission, and 5 had partial response (Fig. 1). At 26 and 52 weeks, 20 (40.8%) and 16 (32.6%) patients, respectively maintained clinical remission. Therefore, of 49 patients with CD who received adalumimab at baseline, 32.6% maintained clinical remission at end of 1 year (Table 2). The details on discontinuation due to loss of response and adverse events have been mentioned in Fig. 1.

Table 1 Baseline clinical, demographic features and disease characteristics of patients treated with adalumimab

Parameter	Crohn's disease ($n = 49$)	Ulcerative colitis ($n = 21$)	p-value
Median (IQR) age in years (at enrolment)	35 (23–51)	28 (21–51)	0.727
Gender—males (%)	33 (67.3)	12 (57.1)	0.414
M:F	2.06:1	1.3:1	
BMI, kg/m^2 median (IQR)	20 (16.4–22)	20.7 (19.6–23.2)	0.360
Duration between diagnosis and treatment with biologics (months) median (IQR)	54 (24–84)	60 (26.5–147.5)	0.435
Follow up from diagnosis (months)	69.5 (33–99.2)	72 (40–217.5)	0.224
Follow up duration after treatment with biologics (months) median (IQR)	26 (12–52)	18 (11.50–71.5)	0.140
Disease age, location, behavior (CD), *n* (%)*	A_1: 4 (8.2) A_2: 35 (71.4) A_3: 10 (20.4) B_1: 23 (46.9) B_2: 16 (32.7) B_3: 10 (20.4) Perianal: 11 (22.4) L_1: 5 (10.2), L_2: 7 (14.3) L_3: 14 (28.6) L_4: 1 (2) $L_1 + L_4$: 9 (18.4) $L_3 + L_4$: 13 (26.5)	Disease extent (UC) E1: 1 (4.8) E2: 13 (61.9) E3: 7 (33.3)	–
Median (IQR) CDAI for CD	390 (286.2–454.7)		–
Median (IQR) SCCAI for UC		8 (6.5–9)	
Smokers, *n* (%)	3 (6.1)	–	–
Extraintestinal manifestation *n* (%)	10 (20.4)	5 (23.8)	–
Prior treatment#, *n* (%)			
5-Aminosalicylates	29 (59.2)	21 (100)	–
Oral corticosteroids	45 (91.8)	18 (85.7)	
Intravenous steroids	7 (14.3)	6 (28.6)	
Azathioprine/6-mercaptopurine/methotrexate	40 (81.6)	15 (71.4)	
Tacrolimus/cyclosporine	0	2 (9.5)	
Antitubercular therapy	11 (22.4)	0	
Past exposure to infliximab	7 (14.3)	2 (9.5)	
Prior mean ± SD courses of steroid	1.97 ± 1.3	2.08 ± 1.3	–
Hb (g/dL) at enrolment	10.1 (9.1–11.4)	10.3 (9.9–12.9)	–
TLC (× 10^3/μL)	6.1 (5.3–7.4)	11 (6.4–11.8)	
Platelets (× 10^3/μL)	259 (196–359.5)	441 (236.5–476.5)	
Serum albumin (g/dL)	3.4 (2.8–4)	3.6 (2.9–4.1)	
CRP (mg/L)	1.7 (0.32–23.6)	3.5 (2–6.5)	
ESR (mm/h)	40 (29.5–66)	25 (11–43)	
Indications for treatment with biologics			
Top–down approach	5 (10.2%)	–	–
Postoperative recurrence	6 (12.2%)	–	
Fistulizing/stricturing disease	8 (16.3%)	–	
Steroid dependent/refractory	30 (61.2%)	20 (95.2%)	
Acute severe ulcerative colits		1 (4.7%)	

CD Crohn disease, *CDAI* Crohn disease activity index, *SCCAI* simple clinical colitis activity index, *TLC* total leukocyte count, *CRP* C-reactive protein, *ESR* erythrocyte sedimentation rate

*Twelve patients had overlap between perianal and other disease behavior

Patients may be on multiple medications at a time

Remission and response in UC

Five patients with UC had a primary non-response. At 8 weeks, 11 (52.4%) with UC went into clinical remission, and 2 had partial response (Fig. 2). At 26 and 52 weeks, nine (42.8%) and seven (33.3%) patients respectively maintained clinical remission. Therefore, of 21 patients with UC who received adalumimab at baseline, 33.3% maintained clinical

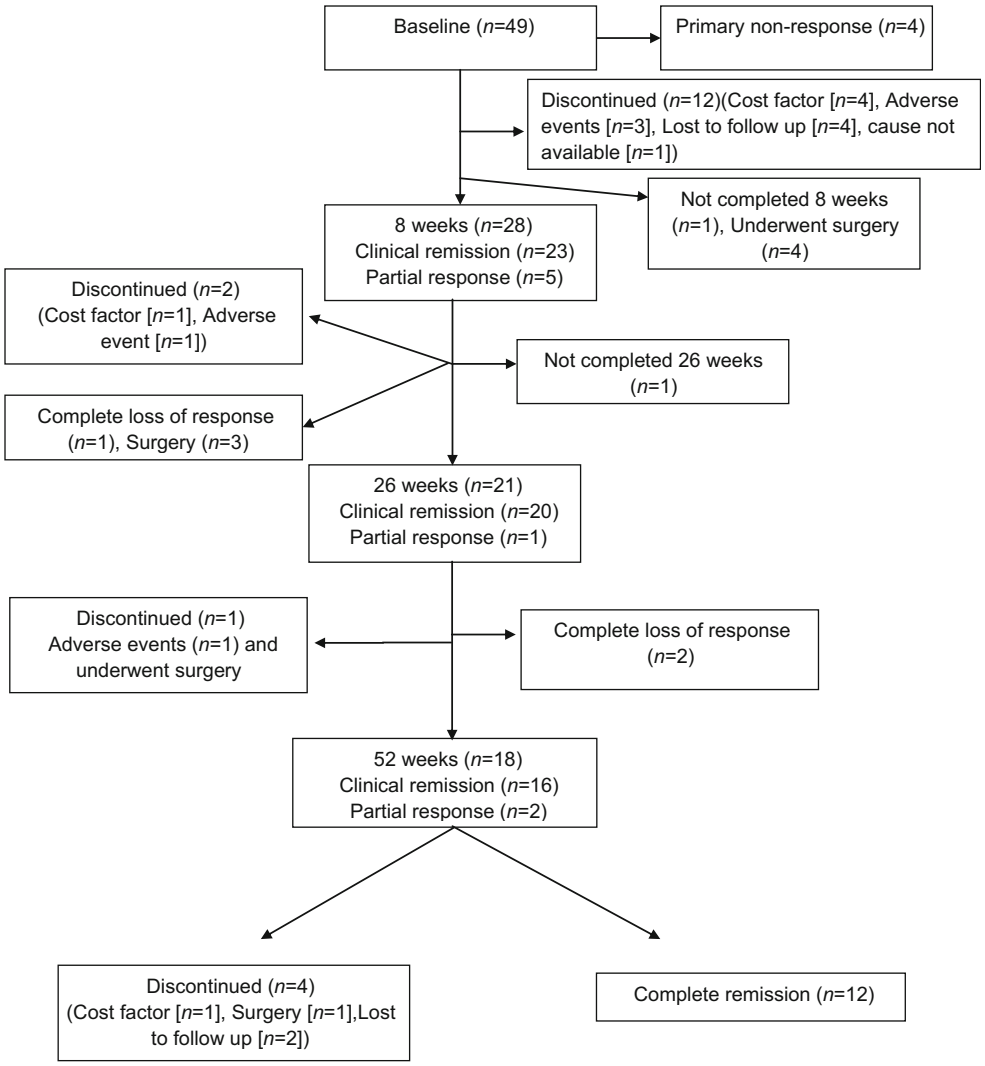

Fig. 1 Follow up of patients with Crohn's disease treated with adalimumab biosimilar

remission at the end of 1 year. The details on discontinuation due to loss of response and adverse events are mentioned in Fig. 2. Probability of short-term and long-term responses at 8, 26, and 52 weeks was not different between patients with CD and UC (Fig. 3a–c).

Only one center accessed mucosal healing during adalimumab biosimilar therapy. Three of 11 (27.3%) patients each with CD had partial and complete mucosal healing at 26 weeks while 4/11 (36.4%) had partial mucosal healing at 52 weeks.

Nine patients had previously received infliximab out of whom one third responded to adalimumab biosimilar therapy, one third lost response after 26 weeks, and the data of remaining were unavailable.

Adverse events of adalimumab

Characteristics of selected patients who developed AE during adalimumab biosimilar therapy are given in Table 3. Twelve (17.1%) patients underwent surgery, ten (14.2%) discontinued drug due to financial constraints, and seven (10%) had serious AE. Patients who had a low BMI (≤ 18.5) tended to develop AE though the difference was not statistically significant. Three patients developed pulmonary TB after starting adalimumab biosimilar, although all were negative for latent TB on appropriate screening; TB developed 8 months (median) later. Two of these patients (UC) received 6 months and one (CD) received 9 months ATT, and all of them responded. Two patients (CD), positive for latent TB on screening, received INH prophylaxis, none of whom developed TB.

Discussion

With the increasing disease burden of IBD in the developing world [22, 23] and with improving economy in these regions, more patients will receive anti-TNF agents; hence, we need

Table 2 Response and remission to treatment with adalimumab during follow up

Variables	Crohn's disease ($n = 49$)	Ulcerative colitis ($n = 21$)	p-value
Concomitant medications while starting biologics[#]			
Oral corticosteroids	12 (24.5%)	7 (33.3%)	–
5-ASA	8 (16.3%)	9 (42.8%)	
AZA	19 (38.7%)	6 (28.5%)	
MTX	5 (10.2%)	–	
Response CDAI[##] > 100, SCCAI < 3			
8 weeks	28 (57.1%)	13 (61.9%)	0.67
26 weeks	21 (42.8%)	10 (47.6%)	0.59
52 weeks	18 (36.7%)	8 (38.1%)	0.66
Remission CDAI < 150, SCCAI ≤ 2			
8 weeks	23 (46.9%)	11 (52.4%)	0.71
26 weeks	20 (40.8%)	9 (42.8%)	0.71
52 weeks	16 (32.6%)	7 (33.3%)	0.91
Adverse drug reaction			
Tuberculosis	1 (2%)	2 (9.5%)	–
Other infectious complications	3 (6.1%)	–	
Abdominal pain	2 (4%)	1 (4.8%)	
Nasopharyngitis	1 (2%)	–	
Skin rash	3 (6.1%)	2 (9.5%)	
Leukocytoclastic vasculitis	1 (2%)	1 (4.8%)	
Death	3 (6.1%)	–	
Reasons for adalumimab discontinuation			
Cost factor	6 (12.2%)	4 (19%)	–
Primary non-response	4 (8.2%)	5 (23.8%)	
Underwent surgery after adalumimab	9 (18.3%)	3 (14.3%)	
Developed serious adalumimab	5 (10.2%)	2 (9.5%)	

[#] Some patients may be on drugs from more than one class

[##] CDAI reduced by 100, SCCAI reduced by 3

5-ASA 5-aminosalicylic acid, *AZA* azathioprine, *MTx* methotrexate, *CDAI* Crohn disease activity index, *SCCAI* simple clinical colitis activity index

information on their efficacy and side effects, especially TB (as these areas are endemic for TB). We recently analyzed our data on the efficacy and side effects of infliximab [24] and reported a primary non-response at 8 weeks and secondary loss of response at 26 and 52 weeks as 14.5%, 6%, and 15%, respectively and TB reactivation rate of 11.6%. We similarly evaluated the efficacy and side effect profile of adalimumab biosimilar Exemptia in 70 patients in a multicenter study in northern India.

The clinical remission rates at 8 weeks in patients with UC and CD were 52.4% and 46.9%, respectively. The results for patients with CD are almost similar to that seen in the CHARM trial (40%) [7] but slightly higher than CLASSIC trial (36%) [25]. However, for patients with UC, the remission rates at 8 weeks are considerably higher than that seen in ULTRA 1 and 2 trials (16.5% and 18.5%) [26, 27], the only available recent Indian study (response 24.1%; remission 3.5%) [10], and a Japanese study (10%) [28]. The response rates at 8 weeks were similar between the present study and the Japanese study (59% vs. 50%). However, the real-world studies from Europe and North America [29], Belgium [30], and Brazil [31] reported 8-week remission rates of 48%, 44%, and 41.7%, respectively, which were quite similar to the present study. Better response rates in the present study, as compared to the other Indian study, could be because of difference in disease severity between the two studies, as patients in the other study were refractory to 5 days of intravenous corticosteroids [10].

The efficacy of adalimumab in the present study are lower than that seen with infliximab at our center where at 8 weeks, the remission rates in patients with CD and UC were 80.8% and 77.3%, respectively [24]. Although there is no head to head comparison, these results are significant and are concordant with recent network meta-analyses, which reported better induction rates with infliximab than adalimumab [32]. Comparing the landmark registration trials of infliximab (IFX) (ACT 1 and ACT 2) [33] and adalumimab (ULTRA 1 and ULTRA 2) for UC, the 8-week induction rates for clinical remission, response, and mucosal healing were

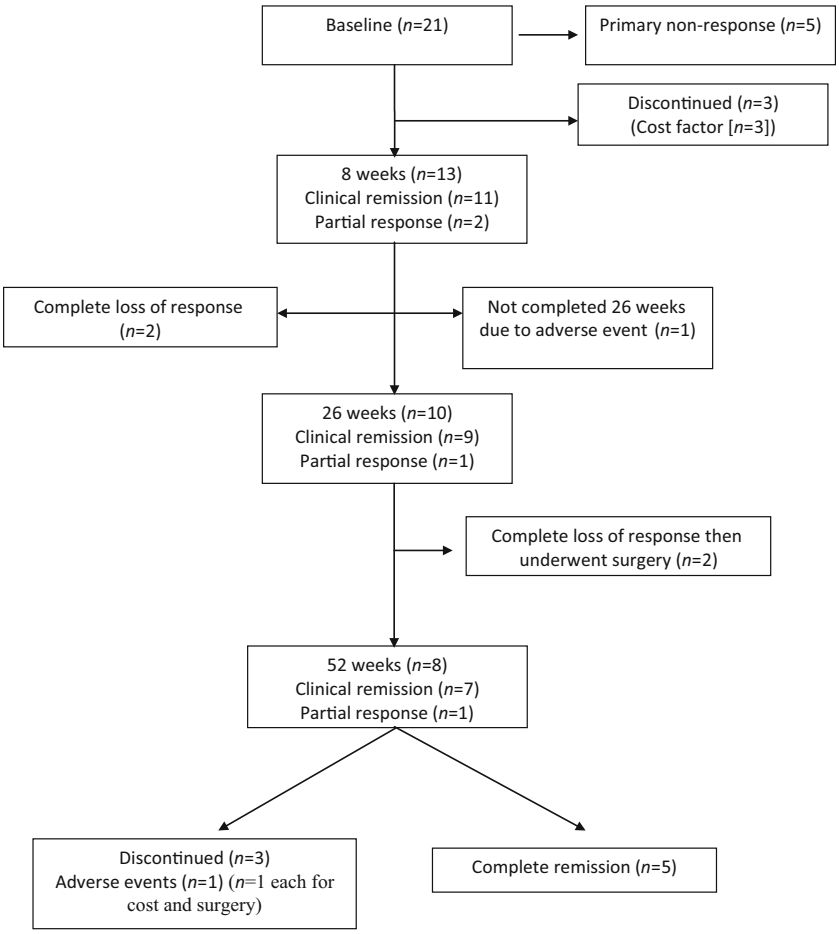

Fig. 2 Ulcerative colitis patients on adalimumab biosimilar in remission and reasons for discontinuation

approximately 16%, 18%, and 19% higher for infliximab than adalumimab. The results of retrospective cohort studies comparing adalumimab and infliximab are heterogeneous with a few reporting superiorities of infliximab over adalumimab and others reporting similar efficacy for both. Overall, the evidence supports similar efficacy of adalumimab and infliximab for CD, but for UC, infliximab may be slightly better than adalumimab for induction of remission.

Of patients who were in remission at 8 weeks, three quarter sustained remission by 52 weeks, which for CD was similar to the CLASSIC II trial (79%) and for UC was higher than the ULTRA 2 trial (17%). On comparing results of infliximab from our center, almost similar proportion of remitters maintained remission at 52 weeks. Similarly, most of the network meta-analyses have also reported similar efficacy of infliximab and adalimumab in the maintenance of remission. Comparison of registration (ACT 1 and ACT 2 [33] vs. ULTRA 2) trials revealed that for maintenance of remission, the differences between infliximab and adalimumab were less dramatic than that for induction of remission.

Patients with IBD who lose response or are intolerant to infliximab may benefit from switching to adalimumab. Of patients ($n = 9$) who lost response to infliximab and were switched to adalimumab, 44% (4/9) patients responded while one achieved remission by week 4. Although the numbers are small for any comparison, the literature suggests similar or lower response rates on adalimumab in infliximab-experienced patients [34]. In the study by Taxonera et al. [35], clinical response and remission at week 12 were achieved in 60% and 27% patients, respectively. In the ULTRA 2 trial, 9% and 10% of infliximab experienced patients with UC achieved clinical remission at week 8 and 52, respectively. In the GAIN trial, 21% infliximab experienced patients with CD achieved clinical remission at week 4 [36]. In patients who did not respond to adalimumab, there is an unmet need to do trough levels. If trough levels are low then dose needs to be optimized. If trough levels are adequate and autoantibodies are developed, then one needs to switch to the other drugs [37].

Patients on anti-TNF are at an increased risk of AE and opportunistic infections [38]. Twenty (28.6%) patients in our study experienced some form of AE during the treatment, of which 7 (10%) were serious AE. Though adalimumab is a humanized antibody (expected to be less immunogenic than infliximab), several studies reported varying rates of AE over a period of time. Of 70 patients, 3 (4.3%) developed

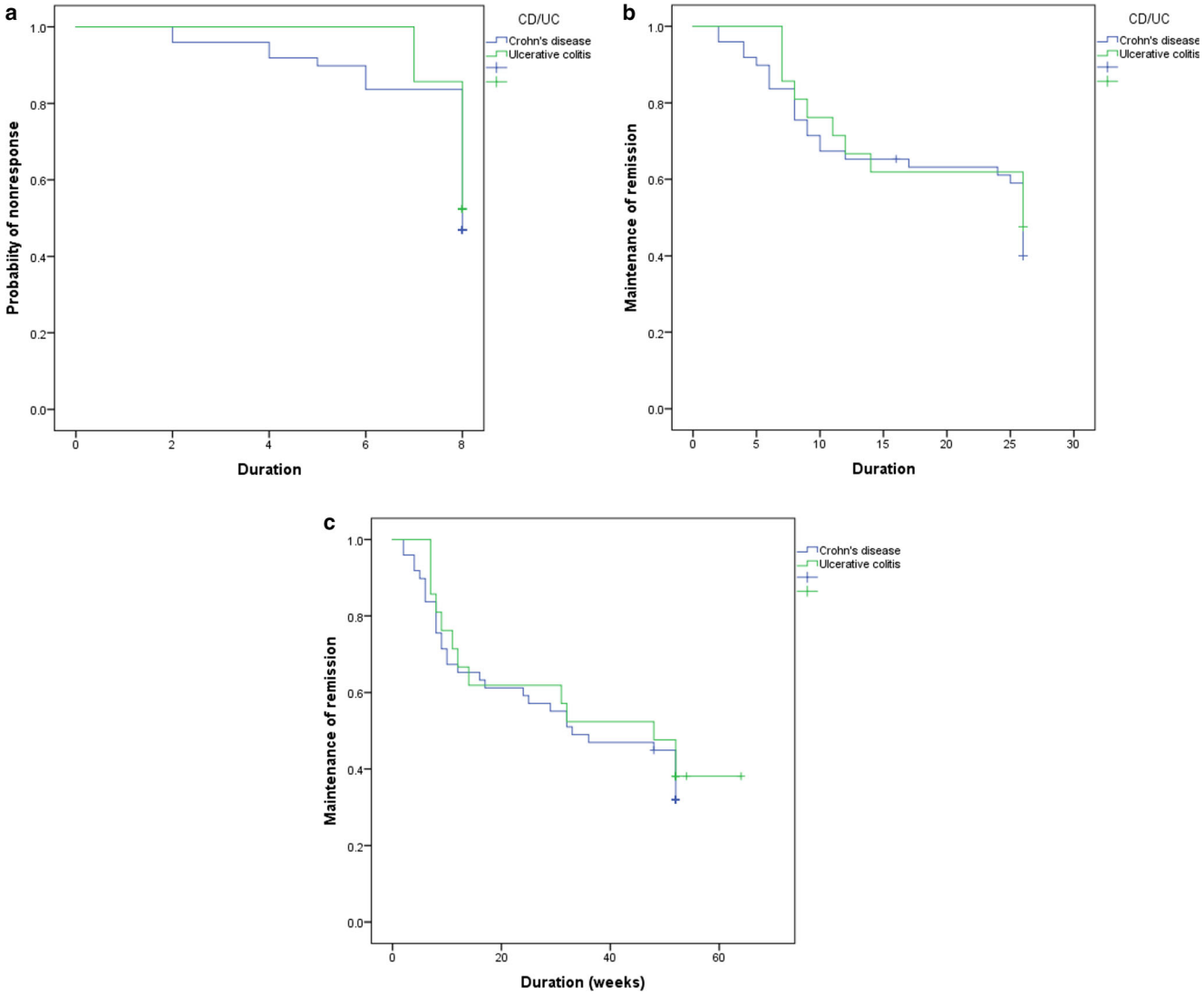

Fig. 3 **a** Kaplan–Meier curve showing clinical remission in UC and CD patients treated with adalimumab at 8 weeks. Log rank test, $P = 0.62$. **b** Kaplan–Meier curve showing clinical remission in UC and CD patients treated with adalimumab at 26 weeks. Log rank test, $P = 0.56$. **c** Kaplan–Meier curve showing clinical remission in UC and CD patients treated with adalimumab at 52 weeks. Log rank test, $P = 0.62$

pulmonary TB after adalimumab, and this risk was lower than that on infliximab as reported from a three-center Indian study (7.9%) and a recent report from our center (11.6%). However, the only Indian study [10] on adalimumab in UC reported a TB reactivation rate of 13.8% which is almost equal to that of TB reactivation on infliximab as reported from our center. Hence, the literature on TB reactivation risk between infliximab and adalimumab remains heterogeneous with the evidence suggesting possible higher risk associated with infliximab. In our study, 14.3% discontinued drug due to financial constraints due to high cost of therapy [39].

The relatively small sample size limits the generalizability of our findings. In patients showing loss of response to adalimumab, measurement of trough levels of the drug and autoantibodies could be useful. Other limitations include retrospective, uncontrolled, observational nature of the study. As only the initial few doses were administered at the hospital, it may not be surprising if patients would have missed a few doses. Due to retrospective design, QOL and patient-reported outcome could not be assessed. We assessed for clinical response and remission while mucosal healing was not assessed routinely in all the patients. Despite these shortcomings, this study indeed provides vital information on usefulness, safety, and effectiveness of adalimumab biosimilar in IBD in India.

To summarize, for a chronic, frequently fluctuating disease like IBD, adalimumab biosimilar appears as an effective drug in inducing and maintaining remission. Early response to adalimumab is a good predictor of long-term response. In a subset of patients who do not respond to adalimumab might need appropriate dose optimization prior to switching to the other drugs. This study has highlighted many important facts

Table 3 Characteristics of patients who developed serious adverse drug reaction on adalumimab

Parameters	Patient number						
	1	2	3	4	5	6	7
Baseline demographic and clinical characteristics							
Age	51	35	55	46	25	65	10
Gender	Male	Male	Male	Male	Male	Male	Male
BMI	–	18.5	23.5	19.5	16	–	15.4
Disease type	UC (E3)	UC (E3)	CD	CD	CD	CD	CD
Disease location (CD)	–	–	L3	L3 + 4	L3	L3	L1 + 4
Disease behavior (CD)	–	–	B1 + 2	B2	B1 + 2 + 3 + 4	B1	B2
EIM	+	–	+	–	+	–	–
Past history of TB	No	No	No	Yes	No	No	No
ATT before diagnosis of CD/UC	No	No	No	No	Yes	No	Yes
Indication for biologic	Acute severe ulcerative colitis	Steroid refractory and AZA intolerant	Steroid dependant, AZA intolerant	Steroid refractory, AZA intolerant, post hemicolectomy recurrence	Steroid dependent/AZA intolerant	Postoperative recurrence	Steroid dependent, MTX refractory, failed thalidomide and IFX
Adalumimab doses received	7	18	25	4	25	3	5
Result	Pulmonary TB treated with 6-month ATT	Pulmonary TB treated with 6-month ATT	Pulmonary TB treated with 9-month ATT	Cause of death unknown	Death due to sepsis + MODS + perianal abscess	Cause of death unknown	Leuocytoclastic vasculitis. Underwent surgery

BMI body mass index, *TB* tuberculosis, *ATT* anti-tubercular therapy, *EIM* extraintestinal manifestation, *AZA* azathioprine, *MTx* methotrexate, *IFX* Infliximab, *MODS* multiple organ dysfunction syndrome

which might prove useful in clinical decision making for adalimumab in IBD.

Compliance with ethical standards

Conflict of interest NK, SK, UCG, AN, GM, AS, VM, VG, GC and VA declare that they have no conflict of interest.

Ethics statement The study was performed in a manner to conform with the Helsinki Declaration of 1975, as revised in 2000 and 2008 concerning human and animal rights. The study protocol was approved by the institutional review board and ethics committee of the coordinating center.

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References

1. Abraham C, Cho JH. Inflammatory bowel disease. N Engl J Med. 2009;361:2066–78.
2. Kedia S, Ahuja V. Epidemiology of inflammatory bowel disease in India: the Great Shift East. Inflamm Intest Dis. 2017;2:102–15.
3. Ahuja V, Tandon RK. Inflammatory bowel disease in the Asia-Pacific area: a comparison with developed countries and regional differences. J Dig Dis. 2010;11:134–47.
4. Singh P, Ananthakrishnan A, Ahuja V. Pivot to Asia: inflammatory bowel disease burden. Intest Res. 2017;15:138–41.
5. Panés J, O'Connor M, Peyrin-Biroulet L, Irving P, Petersson J, Colombel JF. Improving quality of care in inflammatory bowel disease: what changes can be made today? J Crohns Colitis. 2014;8:919–26.
6. Kamat N, Rajan Mallayasamy S, Sharma PSVN, Kamath A, Pai CG. Video assisted patient education improves compliance with follow up and depression scores in inflammatory bowel diseases. Postgrad Med. 2018;130:355–60.
7. Colombel J, Sandborn W, Rutgeerts P, Enns R. Adalimumab for maintenance of clinical response and remission in patients with Crohn's disease: the CHARM trial. Gastroenterology. 2007;132:52–65.
8. Wasan SK, Kane SV. Adalimumab for the treatment of inflammatory bowel disease. Expert Rev Gastroenterol Hepatol. 2011;5:679–84.
9. Colombel JF, Sandborn WJ, Ghosh S, et al. Four-year maintenance treatment with adalimumab in patients with moderately to severely active ulcerative colitis: data from ULTRA 1, 2, and 3. Am J Gastroenterol. 2014;109:1771–80.
10. Midha V, Mahajan R, Mehta V, et al. Efficacy and safety of the adalimumab biosimilar Exemptia as induction therapy in moderate-to-severe ulcerative colitis. Intest Res. 2018;16:83–9.
11. Dignass A, Eliakim R, Magro F, et al. Second European evidence-based consensus on the diagnosis and management of ulcerative colitis part 1: definitions and diagnosis. J Crohns Colitis. 2012;6:965–90.
12. Van Assche G, Dignass A, Panes J, et al. The second European evidence-based consensus on the diagnosis and management of Crohn's disease: definitions and diagnosis. J Crohns Colitis. 2010;4:7–27.
13. Silverberg MS, Satsangi J, Ahmad T, et al. Toward an integrated clinical, molecular and serological classification of inflammatory bowel disease: report of a Working Party of the 2005 Montreal World Congress of Gastroenterology. Can J Gastroenterol. 2005;19 Suppl A:5A–36A.
14. Walmsley RS, Ayres RC, Pounder RE, Allan RN. A simple clinical colitis activity index. Gut. 1998;43:29–32.
15. Best WR, Becktel JM, Singleton JW, Kern F. Development of a Crohn's disease activity index. National Cooperative Crohn's Disease Study. Gastroenterology. 1976;70:439–44.
16. Sandborn WJ, Feagan BG, Hanauer SB, et al. A review of activity indices and efficacy endpoints for clinical trials of medical therapy in adults with Crohn's disease. Gastroenterology. 2002;122:512–30.
17. Osterman MT. Mucosal healing in inflammatory bowel disease. J Clin Gastroenterol. 2013;47:212–21.
18. Schluger NW, Burzynski J. Recent advances in testing for latent TB. Chest. 2010;138:1456–63.
19. Pai M, Denkinger CM, Kik SV, et al. Gamma interferon release assays for detection of Mycobacterium tuberculosis infection. Clin Microbiol Rev. 2014;27:3–20.
20. WHO | Latent tuberculosis infection (LTBI) [Internet]. WHO. [cited 2018 Feb 5]. Available from: http://www.who.int/tb/areas-of-work/preventive-care/ltbi_faqs/en/.
21. Information NC for B, Pike USNL of M 8600 R, MD B, Usa 20894. Case definitions [Internet]. World Health Organization; 2010 [cited 2017 Dec 6]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK138741/.
22. Kedia S, Ahuja V. Is the emergence of inflammatory bowel disease a prime example of "the third epidemiological transition"? Indian J Gastroenterol. 2018;37:183–5.
23. Ahuja V, Tandon RK. Inflammatory bowel disease: the Indian augury. Indian J Gastroenterol. 2012;31:294–6.
24. Agarwal A, Kedia S, Jain S, et al. Very high rate of tuberculosis complicating infliximab therapy for inflammatory bowel disease despite tuberculosis screening in India. Intest Res. 2018;16:588–98.
25. Hanauer S, Sandborn W, Rutgeerts P, et al. Human anti-tumour necrosis factor monoclonal antibody (adalimumab) in Crohn's disease: the CLASSIC-I trial. Gastroenterology. 2006;130:323–33.
26. Reinisch W, Sandborn WJ, Hommes DW, et al. Adalimumab for induction of clinical remission in moderately to severely active ulcerative colitis: results of a randomised controlled trial. Gut. 2011;60:780–7.
27. Sandborn WJ, van Assche G, Reinisch W, et al. Adalimumab induces and maintains clinical remission in patients with moderate-to-severe ulcerative colitis. Gastroenterology. 2012;142:257–65.
28. Suzuki Y, Motoya S, Hanai H, et al. Efficacy and safety of adalimumab in Japanese patients with moderately to severely active ulcerative colitis. J Gastroenterol. 2014;49:283–94.
29. Travis S, Feagan BG, Peyrin-Biroulet L, et al. Effect of adalimumab on clinical outcomes and health-related quality of life among patients with ulcerative colitis in a clinical practice setting: results from InspirADA. J Crohns Colitis. 2017;11:1317–25.
30. Van de Vondel S, Baert F, Reenaers C, et al. Incidence and predictors of success of adalimumab dose escalation and De-escalation in ulcerative colitis: a real-world Belgian cohort study. Inflamm Bowel Dis. 2018;24:1099–105.
31. Zacharias P, Damião AOMC, Moraes AC, et al. Adalimumab for ulcerative colitis: results of a Brazilian multicenter observational study. Arq Gastroenterol. 2017;54:321–7.
32. Thorlund K, Druyts E, Mills EJ, Fedorak RN, Marshall JK. Adalimumab versus infliximab for the treatment of moderate to severe ulcerative colitis in adult patients naive to anti-TNF therapy: an indirect treatment comparison meta-analysis. J Crohns Colitis. 2014;8:571–81.

33. Rutgeerts P, Sandborn WJ, Feagan BG, et al. Infliximab for induction and maintenance therapy for ulcerative coliti. N Engl J Med. 2005;353:2462–76.
34. Song WJ, Kang B, Choi SY, Choe YH. Adalimumab treatment in pediatric-onset Crohn's disease patients after infliximab failure: a single center study. Pediatr Gastroenterol Hepatol Nutr. 2016;19: 116–22.
35. Taxonera C, Estelles J, Fernandez-Blanco I, et al. Adalimumab induction and maintenance therapy for patients with ulcerative colitis previously treated with infliximab. Aliment Pharmacol Ther. 2011;33:340–8.
36. Rutgeerts P, Sandborn WJ, Enns R, et al. Adalimumab rapidly induces clinical response and remission in patients with moderate to severe Crohn's disease who had secondary failure to infliximab therapy: results of the GAIN study. Gut. 2006;55 Suppl:A20.
37. Mazor Y, Almog R, Kopylov U, et al. Adalimumab drug and antibody levels as predictors of clinical and laboratory response in patients with Crohn's disease. Aliment Pharmacol Ther. 2014;40: 620–8.
38. Hindryckx P, Novak G, Bonovas S, Peyrin-Biroulet L, Danese S. Infection risk with biologic therapy in patients with inflammatory bowel disease. Clin Pharmacol Ther. 2017;102:633–41.
39. Kamat N, Ganesh Pai C, Surulivel Rajan M, Kamath A. Cost of illness in inflammatory bowel disease. Dig Dis Sci. 2017;62:2318–26.