Efficacy And Safety Of Adalimumab Biosimilar (Exemptia) In Moderate-To-Severe Steroid-Refractory Ulcerative Colitis Patients: Real-Life Outcomes In Resource-Constrained Setting At 24-Weeks Follow-Up

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ORIGINAL RESEARCH

Efficacy And Safety Of Adalimumab Biosimilar (Exemptia) In Moderate-To-Severe Steroid-Refractory Ulcerative Colitis Patients: Real-Life Outcomes In Resource-Constrained Setting At 24-Weeks Follow-Up

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Background: Adalimumab (ADA) is approved for the management of lcerative colitis (UC) not responding to conventional therapy. Use of biologics in resource-constrained settings is very challenging. Currently, real-life data on the safety and efficacy of ADA biosimilar (Exemptia) in steroid-refractory UC patients are limited.

Aim and objectives: To assess the efficacy and safety of ADA biosimilar (Exemptia) to treat steroid-refractory difficult-to-treat UC patients in a resource-constrained Indian setting at 24-weeks follow-up.

Materials and methods: This was a retrospective single-center study to evaluate the efficacy and safety of ADA biosimilar (Exemptia) in steroid-refractory UC patients. All the eligible patients who received induction dose of 160 mg at week 0, 80 mg at week 2 and 40 mg at week 4 and 40 mg every 4 weeks as maintenance regimen from 01 September 2017 to 31 Jan 2019 were retrospectively included in this single-center analysis. Those patients who had shown sub-optimal response at 12 weeks received 40 mg every 2 weeks as maintenance therapy. Outcomes in terms of clinical remission, clinical response and mucosal healing were evaluated in the short term at 12 weeks and 24 weeks.

Results: Twenty-five patients were retrospectively included between the time period of 1 September 2017 to 31 July 2018 with a mean age of 35 years. ADA biosimilar was effective in inducing clinical remission in 16% patients at 12 and 24 weeks, clinical response was seen in 48% at week 12 and 44% at week 24. The mean baseline total Mayo score (TMS) for all patients was 10.16 which decreased to a mean score of 5.72 at 12 weeks and 5.52 at 24 weeks with therapy with the decrease of the score being statistically significant both at 12 and 24 weeks ($p < 0.05$). Two patients (8%) developed pulmonary tuberculosis (TB). ADA biosimilar frequency was accelerated to once in 2 weeks in 14 (56%) patients who did not show an optimal response at 12 weeks. Of these 14 patients, 5 were responders and 9 were non-responders at 12 weeks. At 24 weeks, 6 patients showed clinical response and 7 were non-responders, while one patient had developed TB.

Conclusion: ADA biosimilar (Exemptia) therapy is a safe and cost-effective alternative to original biologics in difficult-to-treat UC patients in resource-constrained Indian setting with comparable efficacy. Maintenance therapy at four weekly intervals can be considered in those patients who have shown an early clinical response at 12 weeks to minimize costs, but more studies are needed to confirm the same.

Keywords: ulcerative colitis, steroid refractory, adalimumab, biosimilar, exemptia

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Introduction

Ulcerative colitis (UC) is a chronic inflammatory disease of the large intestine. Its exact cause is believed to be multi-factorial, with complex interaction between genetic and environmental factors that result in uncontrolled activation of the intestinal mucosal immune system and resulting inflammation that affects the gut mucosa.[1,2] Initially, treatment strategies focused mainly on the suppression of immune response leading to clinical remission and it had little or no effect on natural disease course.[3,4] Multiple studies have shown that active mucosal inflammation leads to further mucosal damage and increased risk of colorectal cancer, even if the patients are in clinical remission, so the concept of mucosal healing has come into vogue and has become the current standard of care in UC.[5,6]

Tumor necrosis factor-Alfa (TNF-α) is a pro-inflammatory cytokine that plays a key role in the initiation and amplification of mucosal inflammatory cascade in UC leading to mucosal injury.[7] TNF-α antagonists are the main therapeutic option in patients who have not responded adequately to conventional treatment with steroids and immunomodulatory agents. Over the last 15 years, Infliximab (IFX) and ADA have been the main biological therapies used for the treatment of UC, as they have been shown to induce and subsequently maintain both clinical and endoscopic remission.[6,8] The effectiveness of ADA in the treatment of UC was shown in landmark trials ULTRA 1 and 2.[9,10] Subsequent to these 2 randomized placebo-controlled trials, multiple real-time studies have also reinforced the efficacy of ADA in moderate-to-severely active UC.[11–16] ADA has benefits in terms of ease of administration via subcutaneous route, and hospitalization is not required with ADA. Treatment of UC, especially in difficult-to-treat steroid-refractory patients, is always a challenge in developing countries like India. Use of biologics in Inflammatory bowel disease (IBD) in developing countries poses various challenges including higher cost and risk of various infections, especially TB in developing countries.[17]

The relatively high cost of therapy with biological agents and the recent expiry of the patent of some of these biological agents have led to the development of "biosimilar agents", which may be broadly defined as biotherapeutic products with quality, safety, and efficacy that are similar and comparable to the licensed reference biological agents.[18] Exemptia (ZRC-3197) is the first ADA biosimilar drug that was commercialized by Zydus Cadila (India) in 2014 and is currently licensed for use in India and Nepal and awaiting approval in other countries.[19] Exemptia is a fully human-recombinant monoclonal IgG1 antibody having a molecular weight of approximately 148 kDa with 2 copies each of heavy chains and light chains in the heterodimeric form. When evaluated against the originator ADA molecule (Humira) using analysis by cell-based assays and plasma resonance techniques, Exemptia demonstrated similar key structural and functional properties and showed a comparable level of heterogenicity and purity.[20] Few clinical studies exist on the comparative efficacy of ADA biosimilar (Exemptia) against the original ADA molecule (Humira) and none in patients with IBD. One study comparing efficacy of Exemptia against Humira in patients with Rheumatoid Arthritis demonstrated a high degree of biosimilarity with respect to efficacy, tolerability and safety of test ADA (Exemptia) and the reference ADA (Humira).[21]

In a recent study by Midha et al, ADA biosimilar (Exemptia) showed poor efficacy as salvage therapy in inducing remission at 8 weeks in steroid-refractory active UC patients (those with acute colitis who did not respond to 5 days of therapy with intravenous steroids).[22] However, another recently published multicenter study from India by Kamat et al, using ADA biosimilar (Exemptia) in IBD patients (including Crohns disease and UC), showed reasonable efficacy and safety at 26 and 52 weeks using simple clinical activity indices to assess response.[23]

In this retrospective study, we report on the real-time effectiveness of ADA biosimilar (Exemptia) in severe UC refractory to steroids at 24-weeks follow-up in a resource-constrained setting. In India, the use of biologics as therapy has been limited by the high costs that must be borne by patients and the introduction of biosimilars has been a welcome change primarily in view of the cost aspect. We have used once-in-4-week maintenance regimen in those patients who have shown good response to induction therapy with close follow-up/monitoring and scaling up to once in 2 weeks standard maintenance therapy in those with inadequate response at 12 weeks, with the primary aim of reducing the cost of therapy, improving patient compliance and reducing the risk of TB and other infections.

Aim And Objectives

The principal aim of this retrospective study was to assess the efficacy and safety of ADA biosimilar (Exemptia) to

treat steroid-refractory moderate-to-severe UC patients in resource-constrained Indian setting with once a 4-week regimen at 24-weeks follow-up.

Materials And Methods

This was a retrospective single-center study to evaluate the efficacy and safety of ADA biosimilar (Exemptia) in patients with steroid-refractory moderate-to-severe UC. This study was done from 1 September 2017 to 31 January 2019 and retrospectively included patients with steroid-refractory UC fulfilling inclusion and exclusion criteria who received induction dose of 160 mg at week 0, 80 mg at week 2 and 40 mg at week 4 and 40 mg every 4 or 2 weeks as a maintenance regimen. The study was approved by Institutional ethics committee of Base hospital (IEC BHDC/06 of 2017). The entire study was done as per the principles of the Declaration of Helsinki and according to good clinical practice. Written informed consent was taken from all the subjects.

Patients

A total of 25 patients who met inclusion and exclusion criteria were included in the study.

Inclusion Criteria

Eligible patients included men and women of at least 18 years of age with an established diagnosis of UC according to standard criteria of European Crohn's & Colitis guidelines.[24] All the patients were diagnosed with colonoscopy and histopathology before enrolling into the study. All the patients included in the study had moderate-to-severe UC defined as total Mayo score (TMS) of 6–12 points and Mayo endoscopic sub-score (MESS) >2 points in spite of concomitant therapy with immunosuppressive agents. All patients were steroid refractory (defined as those who had active disease despite prednisolone at a dose of 0.75mg/kg/day for a period of 04 weeks). Most patients had a relapse while on immunosuppressive therapy with Azathioprine (AZA) and 5-Aminosalicylic acid (5-ASA) at optimal doses requiring repeat therapy with prednisolone and despite the same still had active disease. These steroid-refractory patients were treated with ADA biosimilar.

Exclusion Criteria

Patients with hepatitis B, hepatitis C, human immunodeficiency virus, indeterminate colitis/Crohn's colitis, Clostridium difficile (CD) infection, TB and cytomegalovirus (CMV) infection were excluded from the study. Patients were screened for CD infection by glutamate dehydrogenase and CD toxin A/B test of stool samples. All the patients were screened for TB with chest X-ray, contrast enhanced CT scan, physical examination, tuberculin skin test and interferon-γ release assays (QuantiFERON TB gold). Patients with latent TB (positive tuberculin test or positive interferon-γ assay) and those with sequelae of past TB were excluded. All females with childbearing potential were screened for pregnancy by a urine test at baseline and at frequent intervals during the study, and all pregnant females were excluded from the study. Infection with CMV was excluded by blood tests for CMV DNA by PCR and the histopathological examination of biopsy for owl's eye inclusion bodies. Patients with neurological, renal, cardiac diseases, malignancies or any other systemic illness were also excluded.

Study Design

This was a retrospective study and all the patients included in the study from 01 September 2017 to 31 July 2018 were given ADA biosimilar (Exemptia) induction dose of 160 mg (4 injections of 40 mg each) at week 0, 80 mg (2 injections of 40 mg) at week 2 and 40 mg at week 4. All patient data including demographic characteristics, diagnosis, disease duration, past treatment given, past history of TB, duration and frequency of ADA biosimilar, concomitant medications, disease activity scores (TMS and MESS) and adverse events were noted in a standardized format on an Excel sheet.

Diagnosis And Management

Patients were diagnosed based on colonoscopy and histology as per standard ECCO guidelines, disease extent was assessed as per Montreal classification and severity was evaluated based on Mayo score.[24,25] After induction therapy at week 0, 2 and 4, all patients were given maintenance dose at 40 mg every 4 weeks till 12 weeks. After 12 weeks, we have used once-in-4-week maintenance regimen in those patients who have shown good response to induction therapy and shortened the maintenance dose interval to 2 weekly in those with inadequate clinical or endoscopic response at 12 weeks, the primary aim being to reduce the cost of therapy with close monitoring for any loss in efficacy, improving patient compliance due to affordability/cost factors and also to reduce the risk of opportunistic infections especially TB which is always a

threat in Indian setting. The dose of concomitant medications such as 5-ASA and AZA remained constant or was optimized based on clinical factors, and corticosteroids, if being used, were gradually tapered over 4 to 6 weeks. All the patients were evaluated at weeks 12 and 24 for clinical response, calculation of TMS and also underwent colonoscopy to assess mucosal healing and calculation of MESS (Table 1).

Efficacy Evaluation And Endpoints

The principal objective was to assess for efficacy in terms of clinical outcomes (clinical/endoscopic response and remission) of ADA biosimilar therapy in patients with UC and the development of any side effects. All patients were monitored for daily stool frequency, the number of bloody stools, abdominal pain and lab tests including complete blood count, ESR, C-reactive protein, liver function tests, albumin, urea/creatinine, electrolytes, and stool examination were done at baseline, 12 weeks and 24 weeks. Clinical remission was defined as TMS of ≤2 points, with no individual score >1 point. Decrease in the TMS by at least 3 points from the baseline and decrease in rectal bleeding score by at least 1 point and an absolute rectal bleeding score of 0 or 1 were defined as clinical response. Endoscopic remission was defined as a MESS of ≤1. No response to induction therapy (lack of improvement of clinical signs and symptoms with a decrease of <3 points from baseline in TMS) was defined as primary non-response. Secondary non-response was defined as an initial response to therapy after induction regimen with subsequent loss of response during remission maintenance treatment.

Clinical assessment during follow-up included monitoring for the occurrence of any adverse events, need of dose escalation in order to obtain/maintain remission and response, and need to discontinue treatment because of any adverse events or primary failure (defined as a failure in reaching remission/clinical response after induction therapy).

Safety Evaluation

All the patients were closely monitored for any adverse events and infection (eg hepatitis B, hepatitis C, human immunodeficiency virus, Tuberculosis, CMV infection, and other opportunistic infections) during the therapy with ADA biosimilar.

Statistical Analysis

Statistical analysis was done using Prism software. Descriptive statistics were used. p-Value, mean and standard deviation were calculated. Wherever appropriate, frequency, number, and percentage are mentioned. P-values < 0.05 were considered significant. One-way ANOVA was used to calculate the p-value at 12- and 24-weeks analysis.

Results
Baseline Patient Characteristics

The demographic and baseline characteristics of 25 patients are as shown in Table 2. Patients included those who received induction therapy with ADA biosimilar (Exemptia) between the time period of 1 September 2017 and 31 July 2018.

The mean age was 35 years and 66% of patients were female while 44% were male. Biopsy was done for all the subjects at baseline which confirmed UC in the active phase. Twelve patients had pan-colitis while 11 had left-sided colitis and 2 had proctitis. ADA biosimilar was used as therapy in those UC patients who were non-responders to AZA and 5-ASA and did not respond to repeated prednisolone therapy at a dose of 0.75mg/kg/day for a period of 04 weeks. Two patients were previously given IFX of which one was a primary non-responder and other had a secondary failure and these patients subsequently received ADA biosimilar therapy. Twenty-three patients (92%) patients were naive to anti-TNF therapy. All the patients were previously treated with 5-ASA and steroids, while 24

Table 1 Mayo Scoring System

| Variable	0 Points	1 Points	2 Points	3 Points
Bowel Movement (BM) Frequency	Normal	1–2 BM >normal	3–4 BM >normal	5 or more BM> normal
Rectal Bleeding	None	Streaks on stool < 50% BMs	Obvious fresh blood with most BM's	BM's with fresh blood
Mayo Endoscopy Sub-score (MESS)	Normal	Mild erythema, decreased vascularity, mild friability	Marked erythema, loss of vascular pattern, friability, erosions	Spontaneous bleeding, ulceration
Physician Global Assessment (PGA)	Normal	Mild	Moderate	Severe

Table 2 Baseline And Demographic Patient Characteristics

Characteristic	Value
Number of patients	25
Age	35.64 ± 12.58
Sex Male: Female Male Female	11:14 11 (44%) 14 (66%)

Disease extent
    Proctitis (E 1)
    Distal colitis (E2)
    Pancolitis (E3)
	
	2 (8%)
	11 (44%)
	12 (48%)

Disease duration
    Hemoglobin (g/dL)
    Albumin (g/dL)
    ESR
    Weight
    Mayo score, mean
	
	10.1 ± 1.99
	3.21 ± 0.39
	31 ± 12.0
	55.84± 5.92
	10.16 ± 0.90

Prior exposure
    5-Aminosalicylates
    Azathioprine
    Corticosteroids
    Infliximab
	
	25 (100%)
	24 (96%)
	25 (100%)
	2 (8%)

patients were treated previously with AZA. Concomitant medications included AZA in 24 (96%) patients and 5-ASA in all the patients.

The average weight of subjects at the baseline was 55.84 ± 5.92 kg. Mean TMS at baseline was 10.16 ± 0.90 with no significant differences between IFX-naive and IFX-exposed patients. Sixteen (64%) patients had UC of moderate intensity (TMS of 6–10) while the disease was severe (TMS of 11–12) in 9 (36%) patients. The mean MESS at baseline was 2.8 ± 0.41.

The study outline is given in Figure 1. All the patients received an induction dose of ADA biosimilar 160 mg at week 0, 80 mg at week 2 and 40 mg at week 4. After that, all the patients were continued on once-in-4-week maintenance regimen. At 12-weeks follow-up, 14 patients (66%) had their ADA biosimilar dose increased to once every 2 weeks due to a sub-optimal or poor clinical or endoscopic response. The frequency of ADA biosimilar was accelerated either in non-responders or in those patients who had a MESS of more than 2. Of these 14 patients, 9 were non-responders and 5 showed a clinical response at 12 weeks but had a MESS of more than 2.
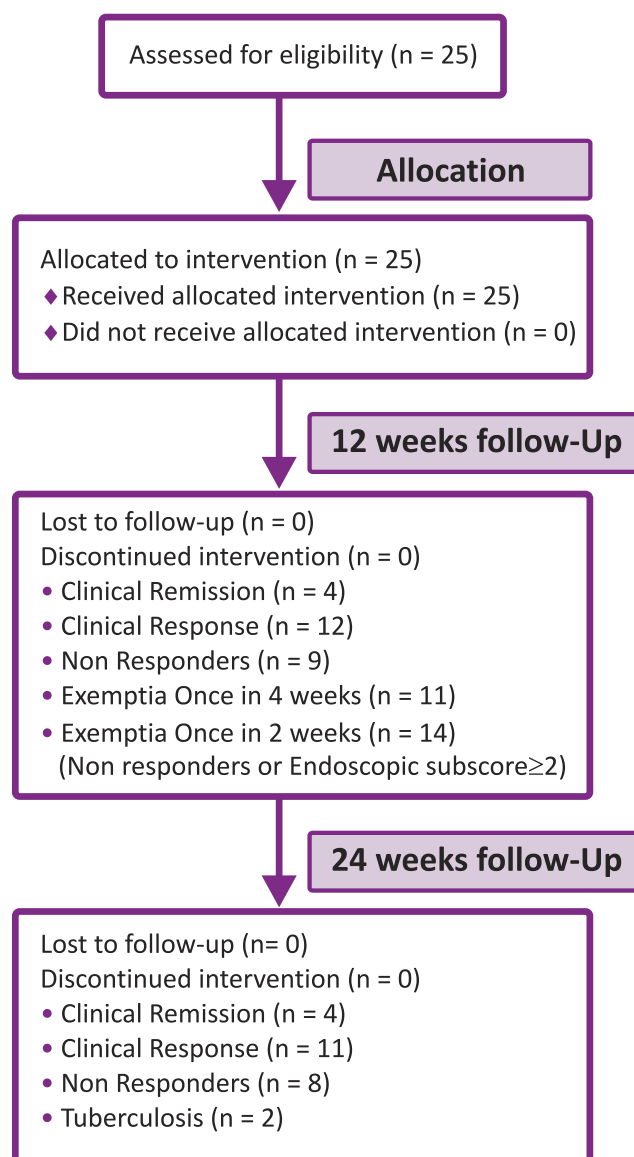
Figure 1 Study design in ulcerative colitis patients on ADA biosimilar and reasons for discontinuation.

Clinical Effectiveness

Clinical remission was achieved in 4 (16%) of 25 patients at week 12 while the clinical response was observed in 12 patients (48%) with a total of 16 patients (64%) showing clinical response and remission at week 12 (Figure 2). The rate of clinical remission at week 24 was the same at 16% (4 of 25 patients) while 11 (44%) of 25 patients had shown a clinical response at week 24 (Figure 3). Thus at week 24, a total of clinical response and remission was seen in 15 patients (60%). Two patients developed pulmonary TB. No response to therapy was noted in 9 patients (36%) and 8 patients (28%) at weeks 12 and 24, respectively.
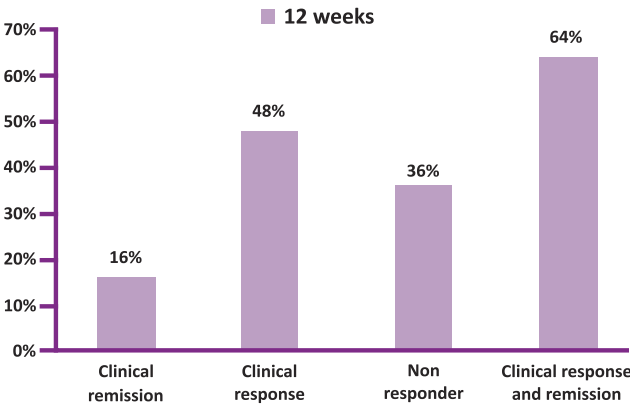
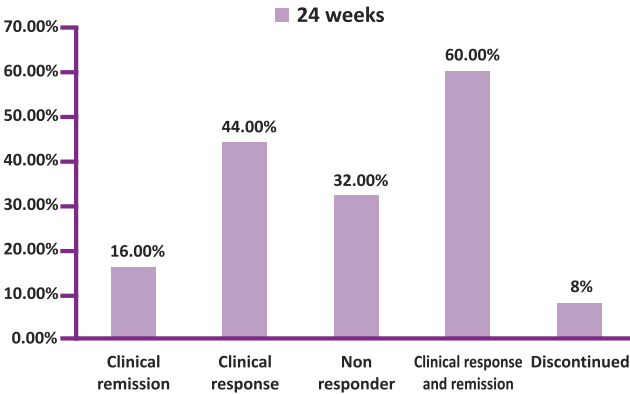**Figure 2** Clinical remission/response at 12-weeks follow-up.

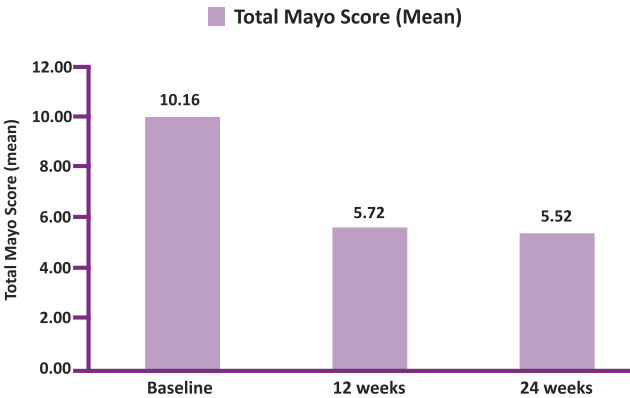**Figure 3** Clinical remission/response at 24-weeks follow-up.

Figure 4 Total Mayo Score (TMS) at Baseline, 12weeks and 24 weeks (N=25 at 12 weeks and N=23 at 24 weeks).

Mean values of TMS and MESS are given in Figures 4 and 5. The mean baseline TMS for all patients was 10.16 which decreased to a mean score of 5.72 at 12 weeks and 5.52 at 24 weeks with therapy with the decrease of the score being statistically significant both at 12 and 24 weeks (p<0.05). The mean MESS at baseline for all patients was 2.8 which corresponded to moderate-to-severe disease
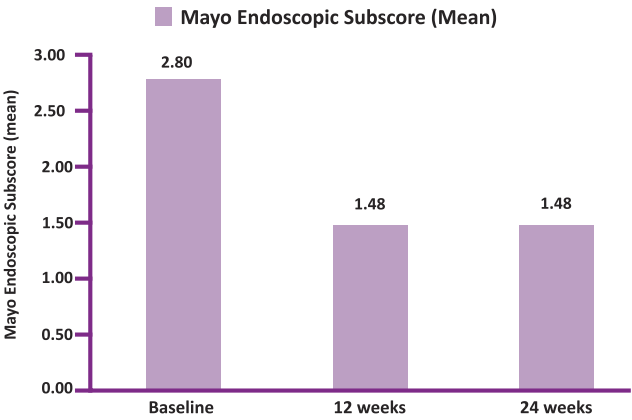

Figure 5 Mayo endoscopic sub-score (MESS) at Baseline, 12weeks and 24 weeks (N=25 at 12 weeks and N=23 at 24 weeks).

activity while the mean MESS at 12 and 24 weeks was 1.48 with therapy which was significant (p<0.05). Although there was a significant reduction in TMS and MESS from baseline to 12 weeks and 24 weeks with therapy, the reduction from 12 weeks to 24 weeks was non-significant in both TMS and MESS (Table 3).

Sustained clinical remission, defined as clinical remission at week 12 maintained through week 24, was achieved in all the 4 (16%) of 25 patients who achieved remission at 12 weeks. These 4 patients also showed complete mucosal healing (endoscopic sub-score of 0) at 12 and 24 weeks. Endoscopic remission (MESS of <_1) was achieved in 11 (44%) patients at weeks 12 and 24 (N=25). Of 25 patients, none of the patients required colectomy. No death was reported. Other pharmacological salvage measures including corticosteroids and IFX were used in non-responders.

ADA biosimilar frequency was accelerated to once in 2 weeks in 14 (56%) patients who had sub-optimal clinical or endoscopic response at 12 weeks. Of these 14 patients, 5 were clinical responders and 9 were non-responders at 12 weeks. The 5 patients who were clinical responders,

Table 3 Total Mayo Score (TMS) And Mayo Endoscopic Sub-Score (MESS) At Baseline, 12 Weeks And 24 Weeks (N= 25 At 12 Weeks And N=23 At 24 weeks)

	Total Mayo Score Significant (P < 0.05)	**Mayo Endoscopic Sub-Score Significant (P < 0.05)**
Baseline vs 12 Weeks	Yes	Yes
Baseline vs 24 Weeks	Yes	Yes
12 Weeks vs 24 Weeks	No	No

however, had a MESS of more than 2. Of these 14 patients, 6 patients showed clinical response while 7 were non-responders at 24 weeks and 1 patient developed TB (Table 3). Of 6 responders, MESS decreased by at least 1 point in 2 patients.

Safety Evaluation

Adverse effects were noted in 2 patients (8%) with both patients developing TB. One patient developed pulmonary parenchymal TB while the other developed TB pleural effusion. These 2 patients were discontinued from ADA biosimilar therapy and started on anti-TB therapy as per standard guidelines. None of the patients exhibited leucopenia or demyelination during the study.

Discussion

This is a retrospective single-center study of difficult-to-treat steroid-refractory UC patients treated with ADA biosimilar (Exemptia) to assess its short-term efficacy and safety over a period of 24 weeks in inducing clinical/endoscopic response and remission. All the included patients were difficult-to-treat subset with moderate-to-severe steroid-refractory UC having sub-optimal response while on immunomodulatory therapy. Two patients in this study were prior non-responders to IFX.

Despite difficult-to-treat patient profile, 16% of patients achieved clinical remission at week 12 with all of them having complete clinical and endoscopic remission. In the landmark ULTRA-1 trial, which first established the safety and efficacy of ADA in moderate-to-severe UC, 18.5% of patients achieved clinical remission at week 8.[9]

Various studies across the globe have also reported almost similar efficacy of ADA in UC patients.[16,26] Clinical response at week 12 was 48% and a total of 64% patients (including remission) responded to ADA biosimilar treatment. In ULTRA-2 landmark trial, 50.4% patients had shown a clinical response at week 8, whereas a prospective real-time Hungarian study by Szepes et al showed remission/response rates of 23.5% and 52.5% at week 12 in a similar subset of steroid-refractory patients while another study by Balint et al reported 49.3% (N=73) clinical response at week 12 in the Hungarian population.[10,27,28]

In the study by Midha et al, of 29 patients with steroid-refractory active UC treated with ADA biosimilar (Exemptia), clinical response was noted in only 7

patients (24.5%) at 8 weeks while 4 (14%) developed active TB.[22] In our opinion, this variation in clinical response in the study by Midha et al and present study may be due to differences in extent and severity of disease in the selected patient cohort, variation in definition of steroid-refractory active UC, absence of concomitant use of immunomodulatory therapy with AZA and early assessment of response at 8 weeks. In another recent multicenter study by Kamat et al using simple clinical parameters to assess remission, of 21 patients with UC, ADA biosimilar (Exemptia) was able to induce remission in 52.7% patients at 8 weeks with 33.3% of patients (three fourth of remitters) maintaining remission at 1 year.[23] These findings are similar to the current study, wherein 16% patients had clinical and endoscopic remission while 48% showed clinical response at 12 weeks.

At 24 weeks, clinical remission was achieved in 16% patients and clinical response was seen in 44% with a total of 60% patients responding to therapy. Afif et al, in 2009, reported 20% and 50% clinical remission and response at week 24 in US population (N=20) while an Italian study by Armuzzi et al reported higher clinical remission rates of 36.4% at week 24.[11,16] The strict criteria (MESS less than 1 and TMS <3) use of a biosimilar instead of originator ADA and difficult-to-treat steroid-refractory population in the current study might be the reason for slightly less remission as compared to other real-world observational studies.[11,27–29]

In the current study, a significant reduction in TMS and MESS from baseline to 12 weeks and 24 weeks was observed. Although a reduction from 12 weeks to 24 weeks was non-significant in both TMS and MESS, endoscopic remission was achieved in 44% (MESS of ≤1) patients at 12 and 24 weeks. Complete mucosal healing was achieved in 16% patients at 12 and 24 weeks (endoscopic sub-score of 0). Complete mucosal healing in the current study was higher than in the Italian study by Armuzzi et al.[16]

ADA biosimilar has also shown efficacy as a steroid-sparing drug in this patient population. Steroids were withdrawn in all the patients who showed clinical response and remission while 5-ASA and AZA were continued at optimal doses. Steroid-free remission/response was achieved in 60% of patients at 24 weeks which is comparatively higher than the steroid-free remission achieved in the Italian study (40% at 1 year).[16] No patient underwent colectomy in this current study.

Table 4 Total Mayo Score (TMS) And Mayo Endoscopic Sub-Score (MESS) Of 14 Patients Whose Dose Has Been Accelerated At 12 Weeks From Once In 4 Weeks To Once In 2 Weeks

	Baseline	12 Weeks	24 Weeks
Total Mayo Score (Mean)	10.29 ± 0.61	7.86 ± 1.29	7.46 ± 2.44
Mayo Endoscopic Sub-Score (Mean)	2.93 ± 0.27	2.14 ± 0.36	2.08 ± 0.64
Clinical Response		5	6
Non-Responders		9	7
Adverse Events (TB)		0	1

This is comparable to a previous real-world study using ADA by Afif et al in 2009 that reported no colectomy in US population (N=20), while another study by Balint et al reported colectomy in 5.4% patients in Hungarian population (N=73).[11,28]

ADA biosimilar frequency was maintained at once in 4 weeks in 11 (44%) patients. Of these 11 patients, 4 were in clinical remission, 5 showed clinical response whereas 1 patient developed TB and 1 patient was non-responder at 24 weeks. This suggests that those patients with good early response post-induction therapy are likely to maintain response even with 4-weekly maintenance dose frequency. ADA biosimilar frequency was accelerated to once in 2 weeks in 14 (56%) patients at 12 weeks. Of these 14 patients, 5 were responders but had MESS of more than 2 while 9 were non-responders at 12 weeks. At 24 weeks, 6 patients showed clinical response with a mild decrease in cumulative MESS while 7 were non-responders and one patient developed TB (Table 4). Of 5 responders who had a MESS of more than 2 at 12 weeks, MESS decreased by 1 point in two patients at 24 weeks. However, the overall reduction was non-significant in both TMS and MESS from 12 weeks to 24 weeks.

In the present study, of 25 patients, only 2 patients (8%) developed side effects with both patients developing TB. In the study by Kamat et al, of total 70 patients with Crohns and UC, 28.6 % patients experienced adverse effects with 7 patients (10%) having serious adverse events and 3 patients developed TB.[23] In the study by Jani et al, both Exemptia and Humira were safe and well tolerated, while in the study by Midha et al, of 29 patients, 4 patients developed TB at 8 weeks.[21,22] The use of longer dosing interval of 4-weekly maintenance therapy in our study in comparison to recommended 2-weekly dosing interval may have contributed to lesser incidence of adverse events due to TB.

Apart from the efficacy of the drug, the cost of drug always matters in resource-constrained settings to maintain long-term remission. In the current study, 44% of patients remained on once-in-4-week therapy with good clinical response of which 16% showed sustained clinical remission at 24 weeks. This lesser frequency of biologic therapy will be economical and cost-effective when compared to different previous western studies using ADA (Table 5). No requirement of colectomy and lesser side effects further strengthen the role of ADA biosimilar as a cost-effective alternative in difficult-to-treat steroid-refractory UC patients.

Conclusion

ADA biosimilar (Exemptia) therapy is a safe and cost-effective alternative to original biologics in difficult-to-treat UC patients in resource-constrained Indian setting with comparable efficacy. Maintenance therapy at four weekly intervals can be considered in those patients who have shown an early clinical response at 12 weeks to

Table 5 Various Reported Real-Time Studies On Adalimumab In UC

S.No	Study	Country	N	Clinical Remission (12 Weeks)	Clinical Response (12 Weeks)	Clinical Remission (24 Weeks)	Clinical Response (24 Weeks)	Colectomy
1	Current study	India	25	16%	48%	16%	44%	0
2	Taxonera et al, 2011[15]	Spain	30	26.7%	60%	–	–	20%
3	Balint et al, 2016[28]	Hungary	73	26%	49.3%	–	–	5.4%
4	Afif et al, 2009[11]	USA	20	5% (8 weeks)	25% (8 weeks)	20%	50%	0
5	Armuzzi et al, 2013[16]	Italy	88	23.4%		36.4%		25%
6	Szepes et al, 2014[27]	Hungary	56	23.2 %	52%	54.5% (30 weeks)	27.5% (30 weeks)	–

minimize costs, but more studies are needed to confirm the same.

Disclosure

The authors report no conflicts of interest in this work.

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