Tumor necrosis factor-α (TNF-α) is a naturally occurring conventional treatment options for many patients with UC [1,2]. Thus, there is a need for new therapies beyond control the disease in a substantial proportion of patients and can lead on patient quality of life and places a substantial financial burden on healthcare systems, with direct cost estimates exceeding $3.4 billion in the USA and €5.4 billion in Europe. Goals of therapy include induction and maintenance of remission, improved quality of life and avoidance of disease- and treatment-related complications [2].

Methods: A total of 50 patients with moderate to severe UC, who were refractory to concurrent treatment with oral corticosteroids and/or immune suppressants, were randomly assigned in 1:1 ratio to receive either ADA (160/80 mg, subcutaneous) or IFX (5 mg/kg, intravenous) during the induction phase (8 weeks). Primary efficacy endpoint was clinical remission at week 8. Secondary efficacy endpoints were the clinical response, mucosal healing, subscores indicative of mild disease (rectal bleeding subscore [RBS], physician’s global assessment [PGA] subscore, and stool frequency subscore [SFS]). Partial Mayo score was also evaluated in addition to the inflammatory bowel disease questionnaire (IBDQ). Additional subgroup analysis was based on the Mayo score, extensive colitis, concomitant medications, high sensitivity C-reactive protein (hs-CRP) level, and patient weight at baseline. The safety profile was assessed in all enrolled patients.

Results: At week 8, 24% of patients receiving ADA were in clinical remission, compared with 28% on IFX (p=0.05). Clinical response was achieved in 48% of patients receiving ADA and 52% of patients on IFX (p=0.05). Mucosal healing was achieved in 40% of patients receiving either ADA or IFX (p=0.05). For the subscores indicative of mild disease (<1), the patients % of RBS and PGA was significantly higher within IFX group (p<0.05) while the patients % of SFS was significantly higher within ADA group (p=0.05). The proportion of patients achieving clinical remission based on the partial Mayo score, in addition to IBDQ response index, was not differ significantly between the two groups from week 2 and throughout the study (p>0.05). The patients with higher Mayo score (≥10), higher hs-CRP (≥10 mg/L), and higher weight (≥70 kg) at baseline were associated with reduced remission rates. ADA and IFX treatment were generally well-tolerated and the overall safety profile matched.

Conclusion: ADA and IFX were comparable in their effectiveness for inducing clinical remission and response in patients with moderate to severe UC. Both of the biologic agents were well tolerated with an approach safety profile.

Keywords: Ulcerative colitis, Adalimumab, Infliximab, Clinical remission, Safety profile.

INTRODUCTION

Ulcerative colitis (UC) is an idiopathic, chronic inflammatory disease of the large intestine, usually involving the rectum, characterized by a continuous pattern of inflammation and ulceration of the intestinal mucosa and submucosa. Presenting symptoms include rectal bleeding, diarrhea, urgency, and abdominal pain [1]. UC has a significant negative impact on patient quality of life and places a substantial financial burden on healthcare systems, with direct cost estimates exceeding $3.4 billion in the USA and €5.4 billion in Europe. Goals of therapy include induction and maintenance of remission, improved quality of life and avoidance of disease- and treatment-related complications [2].

Conventional medical therapies include 5-aminosalicylic acid, corticosteroids, and oral immunosuppressants (azathioprine, 6-mercaptopurine, and cyclosporine). However, these agents inadequately control the disease in a substantial proportion of patients and can lead to adverse events (AEs). Thus, there is a need for new therapies beyond conventional treatment options for many patients with UC [1,2].

Tumor necrosis factor-α (TNF-α) is a naturally occurring proinflammatory cytokine that appears to play a key role in the inflammatory processes of UC [3]. TNF-α expression and secretion are increased in mucosal macrophages isolated from IBD lesions and it is found in increased concentrations in the blood, mucosal tissue, and stools of patients with UC [4-6].

During the last decade, a randomized controlled trials have shown the anti-TNF biological therapy infliximab (IFX, a chimeric IgG1 monoclonal antibody) and adalimumab (ADA, a fully human IgG1 monoclonal antibody) to be efficacious in inducing and maintaining remission of UC [7,8], in addition to Crohn’s disease and other autoimmune disorders [9,10]. These anti-TNF medications work by inducing apoptosis of the TNF-α-expressing inflammatory cells; neutralizing soluble TNF, as well as deplete the number of immune cells through antibody-dependent cell-mediated and complement-dependent cytotoxicity. Anti-TNF therapies, IFX or ADA, are generally reserved for the treatment of moderate to severe inflammatory bowel diseases (IBD) that have not responded to corticosteroids and/or immunosuppressive agents, or when the patient experiences an AE or becomes unable to tolerate corticosteroids and/or immunosuppressive agents [11].

The purpose of this study was to compare the efficacy and safety of ADA and IFX for induction remission in Iraqi patients with moderately to severely active UC by a "real-life" clinical practice environment.

EFFECTIVE AND SAFETY OF ADALIMUMAB VERSUS INFLIXIMAB IN PATIENTS SUFFERED FROM MODERATE TO SEVERE ACTIVE ULCERATIVE COLITIS

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EFFECTIVE AND SAFETY OF ADALIMUMAB VERSUS INFLIXIMAB IN PATIENTS SUFFERED FROM MODERATE TO SEVERE ACTIVE ULCERATIVE COLITIS

ABSTRACT

Objective: Ulcerative colitis (UC) is an idiopathic, chronic inflammatory disease of the large intestine, usually involving the rectum. During the last decade, clinical trials have shown adalimumab (ADA) and infliximab (IFX) to be efficacious in inducing and maintaining remission for moderate to severe UC refractory to the conventional therapies. The purpose of this study was to compare the efficacy and safety of ADA and IFX for induction remission in Iraqi patients with moderately to severely active UC.

Methods: A total of 50 patients with moderate to severe UC, who were refractory to concurrent treatment with oral corticosteroids and/or immune suppressants, were randomly assigned in 1:1 ratio to receive either ADA (160/80 mg, subcutaneous) or IFX (5 mg/kg, intravenous) during the induction phase (8 weeks). Primary efficacy endpoint was clinical remission at week 8. Secondary efficacy endpoints were the clinical response, mucosal healing, subscores indicative of mild disease (rectal bleeding subscore [RBS], physician’s global assessment [PGA] subscore, and stool frequency subscore [SFS]). Partial Mayo score was also evaluated in addition to the inflammatory bowel disease questionnaire (IBDQ). Additional subgroup analysis was based on the Mayo score, extensive colitis, concomitant medications, high sensitivity C-reactive protein (hs-CRP) level, and patient weight at baseline. The safety profile was assessed in all enrolled patients.

Results: At week 8, 24% of patients receiving ADA were in clinical remission, compared with 28% on IFX (p=0.05). Clinical response was achieved in 48% of patients receiving ADA and 52% of patients on IFX (p=0.05). Mucosal healing was achieved in 40% of patients receiving either ADA or IFX (p=0.05). For the subscores indicative of mild disease (<1), the patients % of RBS and PGA was significantly higher within IFX group (p<0.05) while the patients % of SFS was significantly higher within ADA group (p=0.05). The proportion of patients achieving clinical remission based on the partial Mayo score, in addition to IBDQ response index, was not differ significantly between the two groups from week 2 and throughout the study (p=0.05). The patients with higher Mayo score (≥10), higher hs-CRP (≥10 mg/L), and higher weight (≥70 kg) at baseline were associated with reduced remission rates. ADA and IFX treatment were generally well-tolerated and the overall safety profile matched.

Conclusion: ADA and IFX were comparable in their effectiveness for inducing clinical remission and response in patients with moderate to severe UC. Both of the biologic agents were well tolerated with an approach safety profile.

Keywords: Ulcerative colitis, Adalimumab, Infliximab, Clinical remission, Safety profile.

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METHODS

Patient’s selection

This randomized double-blind comparative study was conducted at Baghdad Centers of gastrointestinal and liver disorders between April and November 2016. The protocol was achieved under the supervision of specialist physicians and approved by the ethical committee of the College of Pharmacy/University of Al-Mustansiriyah. All patients gave oral and written consent.

Eligible patients were ambulatory adults with moderate to severely active UC for at least 3 months with a Mayo score of (7-12) points and partial Mayo score of ≥2, despite concurrent therapy with steroids and/or azathioprine or 6-mercaptopurine. The Mayo score is a composite score of 4 items (i.e., rectal bleeding score [RBS], stool frequency score [SFS], physician’s global assessment [PGA], and mucosal appearance) (Table 1) [12]. For the scoring of the rectal bleeding and stool frequency items, the worst score from the previous 3 days before the study visit was used. The diagnosis of UC was confirmed by biopsy obtained at the screening colonoscopy or flexible sigmoidoscopy. The patients concurrently treated with oral corticosteroids were to receive a stable dose (prednisone ≥20 mg/day for at least 2 weeks, or <20 mg/day for at least 40 days) before baseline. Patients treated with immunomodulators were to receive at least a consecutive 3-month course of azathioprine (1.5 mg/kg/day, or highest tolerated dosage) or 6-mercaptopurine (1 mg/kg/day, or highest tolerated dosage) before baseline (with stable dosage for at least 4 weeks). Concurrent therapy was not required for patients who failed to respond to or could not tolerate previous corticosteroid or immunomodulator treatment. Patients were allowed stable dosages of 5-aminosalicylates as concurrent therapy, but 5-aminosalicylate use was not an entry criterion for the trial. The previous use of anti-TNF agents was not precluded. Female patients were postmenopausal, surgically sterile or using an approved method of birth control.

Patients were excluded if they had the following: History of subtotal colectomy with ileorectostomy for UC or planned bowel surgery; previous treatment with anti-TNF agents; receipt of intravenous (IV) immunomodulator treatment. Patients were allowed s

Efficacy evaluation

Primary and secondary variables

The primary efficacy variable was the proportion of remission patients in each treatment group per Mayo score at week 8 (remission defined as Mayo score ≤2 with no individual subscore >1).

Secondary variables were assessed at week 8 in each group and included: Proportion of patients with clinical response per Mayo score (Response: Decrease in Mayo score ≥3 points and ≥50% from baseline plus a decrease in the RBS ≤1 or an absolute RBS of 0 or 1); proportion of patients with mucosal healing (endoscopy subscore of 0 or 1); proportion of patients with subscores indicative of mild disease (RBS ≤1, SFS ≤1, and PGA subscore ≤1).

Partial Mayo score represents a Mayo score without endoscopy, and the proportion of patients in remission per partial Mayo score (defined as partial Mayo score ≤2 with no subscore >1) was determined in both groups at weeks 0, 2, 4, 6 and 8. Health-related quality of life, as measured by the IBDQ questionnaire (IBDQ), was also determined at weeks 0, 2, 4, 6, and 8. The IBDQ response was defined as an increase from baseline of ≥16 points [13].

Additional analyses

The proportion of patients in remission per Mayo score at week 8 was assessed after stratification by baseline Mayo scores (7-9 vs. 10-12), extent of disease, high sensitivity C-reactive protein level (hs-CRP <10 mg/L vs. ≥10 mg/L), patients weight (<70 kg vs. ≥70 kg), and by concomitant medication use (corticosteroid and/or immunomodulators, and aminosalicylates).

Safety evaluation

At each visit, from week 0 through week 8, patients underwent a physical examination, vital signs assessment, and recording previous or concomitant medications. AEs were recorded and general laboratory tests, including C-reactive protein and urinalysis, were performed.

Statistical analysis

Demographics and baseline characteristics were summarized using descriptive statistics. Continuous variables were expressed as mean ± standard deviation, while categorical variables were expressed as frequencies and percentages. Continuous variables were compared using analysis of variance test, discrete variables using the X² test. Efficacy variables (primary and secondary) and partial Mayo scores were assessed in the two population groups. Results for the ADA and IFX groups were compared using the X² test for the evaluated endpoints; remission rates were analyzed using the same method. The subgroup analyses and incidence of adverse effects in the ADA group was compared with that of IFX group using Fisher’s exact test. All of the analyses were performed using SPSS program and p<0.05 was considered statistically significant.

Table 1: Ulcerative colitis disease activity index [12]

| Stool frequency score (SFS) | Mucosal appearance |
|----------------------------|-------------------|
| Normal=0                   | Normal=0          |
| 1-2 stools/day > Normal=1  | Mild friability=1 |
| 3-4 stools/day > Normal=2  | Moderate friability=2 |
| >4 stools/day > Normal=3   | Exudation, spontaneous bleeding=3 |

| Rectal bleeding score (RBS) | Physician’s global assessment (PGA) |
|-----------------------------|----------------------------------|
| None=0                      | Normal=0                         |
| Streaks of blood=1          | Mild=1                           |
| Obvious blood=2             | Moderate=2                       |
| Mostly blood=3              | Severe=3                         |

Each variable is scored from 0-3, so the total index score ranges from 0-12. 0-2: remission; 3-6: mild; 7-10: moderate; >10: severe ulcerative colitis.
RESULTS

Patients flow
Of 64 patients enrolled in this study (33 on ADA and 31 on IFX), 50 completed 8 weeks (25 on ADA and 25 on IFX). Reasons for discontinuation were summarized in Table 2.

Baseline characteristics
The baseline demographic and clinical characteristics of patients were comparable across the two treatment groups (Table 3). The study participants were predominantly male with a mean duration of moderate to severe UC of approximately 6 years and a baseline Mayo score about 9. Patients in the IFX group had a numerically longer duration of disease, a higher percentage of pancolitis, a higher mean Mayo score, and higher mean hs-CRP levels at baseline, but the differences were not statistically significant (p > 0.05).

At baseline, total patients in both groups were taking UC-related medications with 50% on steroids, 16% receiving immunomodulators, 14% on steroids plus immunomodulators, and 82% receiving aminosalicylates. The highest rate of baseline steroid users was in the IFX arm, while the percentage of patients used immunomodulators was same for both arms.

Efficacy

Primary and secondary endpoints
The primary remission of patients in clinical remission in the ADA and IFX groups was approach (p > 0.05). At week 8, 24% of patients who received ADA versus 28% of patients who received IFX were in clinical remission (Table 4, Fig. 1).

Clinical response was achieved at week 8 in 48% of patients receiving ADA and 52% of patients on IFX (p > 0.05) (Fig. 1). Considering mucosal healing, it was achieved at week 8 in 40% of patients receiving either ADA or IFX (p > 0.05) (Fig. 1). For the subscores indicative of mild disease ≤11, the percentage of patients using Aza/6-MP and AZA was significantly higher within IFX group (p > 0.05), while the percentage of patients using Aza/6-MP was significantly lower within ADA group (p > 0.05) (Table 4).

The proportion of patients achieving clinical remission based on the partial Mayo score for both groups are shown in Fig. 2. Partial Mayo scores were used to gauge induction of remission over time. The proportion of patients based on this remission (partial Mayo score ≤2 with no subscore >1) increased over time in both groups, with no significant separation between the two biologic agents from week 2 through week 8, reaching a maximum at week 8 (p > 0.05). Same results were observed for IBDDQ response index (p > 0.05) (Fig. 3). No patient achieved steroid-free remission for both groups during the study period; also, no patient underwent colectomy for both agents.

Additional analyses
Patients with Mayo score >10 at baseline had lower rates of remission compared with those having Mayo score ≤10 in both groups although it was more pronounced in the IFX group (Table 5). The treatment effect was comparable in patients with or without extensive colitis, while higher hs-CRP levels (≥10 mg/L) and higher patient’s weight (≥70 kg) at baseline were associated with reduced remission rates. However, treatment effects were more pronounced in patients treated with corticosteroids plus immunosuppressants, and in those who received aminosalicylates at baseline.

Safety analysis
ADA and IFX treatment was generally well-tolerated and the overall safety profile matched. A comparable proportion of patients in each study group experienced treatment-emergent AEs (Table 6). Most of these AEs were not serious, mild or moderate in severity, and were considered “not related” or “probably not related” to the study drugs.

Table 2: Reasons for discontinuation of treatment

| Reason of withdrawal       | ADA group (n=33) | IFX group (n=31) |
|----------------------------|-----------------|-----------------|
| Consent withdrawn          | 2 (6)           | 1 (3)           |
| Lack of efficacy           | 1 (3)           | 0               |
| AEs                       | 2 (6)           | 2 (6)           |
| Protocol violation         | 2 (6)           | 1 (3)           |
| Lost to follow-up          | 1 (3)           | 2 (6)           |
| Death                     | 0               | 0               |

Table 3: Baseline demographics and clinical characteristics of studied groups

| Characteristics                        | ADA group (n=25) | IFX group (n=25) | Total (n=50) |
|----------------------------------------|-----------------|-----------------|--------------|
| Age, y, mean±SD                        | 42±12.22        | 40±14.47        | 41±13.86     |
| Male, n (%)                            | 18 (72)         | 16 (64)         | 34 (68)      |
| Weight, kg, mean±SD                    | 76±16.31        | 74±18.71        | 75±17.52     |
| Smokers, n (%)                         | 7 (28)          | 9 (36)          | 16 (32)      |
| Disease duration, y, mean±SD           | 6.1±5.37        | 6.5±5.09        | 6.3±5.23     |
| No. previous relapse, mean±SD          | 3.2±1.06        | 3.3±1.02        | 3.25±1.04    |
| Site of ulcerative colitis, n (%)      | 14 (56)         | 16 (64)         | 30 (60)      |
| Pancolitis                              | 10 (40)         | 8 (32)          | 18 (36)      |
| Other                                   | 1 (4)           | 3 (12)          | 4 (8)        |
| Extra-intestinal findings              | 6 (24)          | 8 (32)          | 14 (28)      |
| Mayo score, mean±SD                    | 8.8±1.50        | 9.0±2.10        | 8.90±1.75    |
| Endoscopy score                         | 2.4±0.50        | 2.5±0.50        | 2.45±0.50    |
| Rectal bleeding subscore               | 1.7±0.85        | 1.6±0.95        | 1.65±0.90    |
| Physician global subscore              | 2.2±0.75        | 2.3±0.25        | 2.25±0.50    |
| Stool frequency subscore               | 2.5±0.70        | 2.6±0.60        | 2.55±0.65    |
| Partial Mayo score                     | 6.5±1.35        | 6.5±1.55        | 6.5±1.45     |
| IBDDQ index, mean±SD                   | 150±26.9        | 146±28.7        | 148±27.8     |
| hs-CRP, mg/L, mean±SD                  | 13.7±38.78      | 14.3±30.07      | 14.0±34.48   |
| Concomitant medication, n (%)           | 12 (48)         | 13 (52)         | 25 (50)      |
| Steroids                               | 4 (16)          | 4 (16)          | 8 (16)       |
| IMM (Aza/6-MP)                         | 12 (48)         | 13 (52)         | 25 (50)      |
| Steroids+IMM (Aza/6-MP)                | 4 (16)          | 3 (12)          | 7 (14)       |
| No steroids, no IMM (Aza/6-MP)         | 4 (16)          | 5 (20)          | 10 (20)      |
| Aminosalicylates (5-ASA)               | 12 (48)         | 13 (52)         | 25 (50)      |

IBDDQ: Inflammatory Bowel Disease Questionnaire, hs-CRP: High sensitivity C-reactive protein, IMM: Immunosuppressants, Aza: Azathioprine, 6-MP: 6-mercaptopurine.

Data expressed by mean±SD, or n (%). No significant differences (p>0.05)
There were no statistically significant differences between treatment groups for most of the emergent AEs (p>0.05). However, the incidence of severe and serious AEs tended to be numerically higher in one biologic agent over the other.

The proportion of patients who discontinued the study because of AEs was low and similar across the study groups. One patient in ADA group suffered worsening or flare of UC.

All injection site reactions were mild and most were managed without study drug interruption or discontinuation. The incidence of injection site pain was significantly higher in the IFX group (p<0.05).

Serious infections were reported in one patient of the ADA group (wound infection) and one patient in the IFX group (pneumonia), while just one patient in the IFX group experienced an opportunistic infection (esophageal candidiasis).

One case of tuberculosis was reported shortly after the last dose of ADA in a 70-years old patient receiving prednisone 20 mg/day; this patient had presented with a negative purified protein derivative test and chest X-ray at baseline. The patient was referred for treatment.

A significant proportion of IFX -treated patients reported hematologic-related AEs compared with ADA -treated patients (p<0.05). The latter AEs (mostly leukopenia) were reported in the IFX -treated patients who were receiving concomitant immunosuppressants at baseline. All events were resolved by the end of the study.

DISCUSSION

This study had similar inclusion and exclusion criteria to that of previously published Western studies of IFX and ADA [7,14]. Because UC is less common in Iraq than in the West countries, it has been difficult to enroll a large number of Iraqi patients. Currently, only limited data are available on the "real-life" clinical practice outcomes of

| Subgroups                  | ADA group (n=25) | IFX group (n=25) |
|----------------------------|-----------------|------------------|
| Mayo≤10, N                 | 16              | 17               |
| Remission, n (%)           | 5 (31.3)        | 7 (41.2)         |
| Mayo>10, N                 | 9               | 8                |
| Remission, n (%)           | 1 (11.1)*       | 2 (25)*          |
| Extensive colitis, N       | 13              | 12               |
| Remission, n (%)           | 3 (23)          | 4 (33.3)         |
| No extensive colitis, N    | 12              | 13               |
| Remission, n (%)           | 4 (33.3)        | 3 (23)           |
| hs-CRP<10 mg/L, N          | 20              | 19               |
| Remission, n (%)           | 7 (35)          | 6 (31.5)         |
| hs-CRP>10 mg/L, N          | 5               | 6                |
| Remission, n (%)           | 1 (20)*         | 1 (16.7)*        |
| Weight<7.0 kg, N           | 15              | 16               |
| Remission, n (%)           | 6 (40)          | 6 (37.5)         |
| Weight≥7.0 kg, N           | 10              | 9                |
| Remission, n (%)           | 2 (20)*         | 1 (11.1)*        |
| Corticosteroid (without IMM), N | 12 | 13 |
| Remission, n (%)           | 3 (25)          | 4 (30.7)         |
| IMM (without corticosteroid), N | 4 | 4 |
| Remission, n (%)           | 2 (50)          | 2 (50)           |
| Corticosteroid+IMM, N      | 4               | 3                |
| Remission, n (%)           | 3 (75)          | 2 (66.7)         |
| No corticosteroid+no IMM, N | 5 | 5 |
| Remission, n (%)           | 0               | 0                |
| Aminosalicylates, N        | 21              | 20               |
| Remission, n (%)           | 5 (24)          | 6 (30)           |
| No aminosalicylates, N     | 4               | 5                |
| Remission, n (%)           | 0               | 0                |

hs-CRP: High sensitivity C-reactive protein, IMM: Immunomodulators.

Data expressed by n (%). * Significant difference (p<0.05).
placebo response rates that were observed during ULTRA 1, whereas was effective for inducing clinical remission. In that study, significant Our results confirm the findings of ULTRA 1, an 8-week induction trial with ADA in patients with UC which demonstrated that ADA 160/80 mg was effective for inducing clinical remission. In that study, significant differences between the ADA and placebo group were only achieved for two of the secondary end points at week 8, RBS and PGA score [8]. In contrast, in ULTRA 2, significantly greater proportions of ADA- treated patients achieved almost all secondary endpoints at week 8 [14]. The discrepancy between the 2 trials might be due to the relatively high placebo response rates that were observed during ULTRA 1, whereas the placebo response rates observed in ULTRA 2 are generally similar to those reported in the two large placebo-controlled trials of IFX for UC (ACT 1 and ACT 2) [7]. It is possible that a high number of clinic visits (3-5 visits in 8 weeks) in the previous placebo-controlled trials may contribute to a placebo effect via the psychological factors and neurobiological mechanisms [22].

In contrast to the IFX studies, which demonstrated that for induction of remission of UC, 10 mg/kg of IFX do not provide higher efficacy than 5 mg/kg [7,23], dosing higher than 160/80 mg of ADA has not been tested. Dosing in the ADA induction trial in patients with UC was based on the doses of ADA known to be safe and effective in Crohn’s disease [24-26].

In the placebo groups within ACT1 and ACT2 trials, the clinical remission rates at week 8 were just 14.9% and 5.7%, respectively, while for IFX group (5 mg/kg) it was 38.8% and 33.9%, respectively [7]. In the present trial, the rate of remission to IFX was just 28%. Meanwhile, in the placebo groups within ACT1 and ACT2 trials, the clinical response rates at week 8 was just 37.2% and 29.3%, respectively, while for IFX group (5 mg/kg) it was 69.4% and 64.5%, respectively [7]. In the present trial, the rate of response to IFX was just 52%. Likewise, the proportion of patients achieving mucosal healing in the placebo groups at week 8 was 33.9% in ACT1 and 30.9% in ACT2, while for IFX group (5 mg/kg), it was 62.0% and 60.3% respectively [7]. In the present trial, the rate of mucosal healing to IFX was just 40%.

Although the main focus of treatment for patients with UC has traditionally been the alleviation of symptoms by inducing and maintaining symptomatic remission, there is increasing evidence to suggest that achieving mucosal healing and reduction in endoscopic disease activity may be as critical as improvement in symptoms in optimizing long-term outcomes [27]. Indeed, mucosal healing has been shown to correlate with better long-term remission rates, fewer disease-related complications, and better quality of life for patients [28-30]. The IFX group exhibited significantly higher rates of mucosal healing than the placebo group at weeks 8 and 30 in both ACT1 and ACT2 trials [7]. Similarly, during the ADA ULTRA2 trial, mucosal healing rates were higher in the treatment group than those in the placebo group both at week 8 and week 52 [14].

The previous studies have suggested that improvement in mucosal healing rates is associated with better long-term outcomes, improved quality of life, and reduced rates of colectomy [27,28,31]. Using data from ACT1 and ACT2 trials, a subsequent study demonstrated that patients treated with IFX had a significantly lower rate of colectomy and hospitalizations by week 54 than those treated with placebo [32]. Using data from ULTRA 2 trial, subsequent studies have indicated that ADA therapy is associated with significantly reduced risk of hospitalization and significantly greater improvement in health-related quality of life measures during 52 weeks than with placebo [33,34]. In our study, no patient underwent colectomy or hospitalizations throughout the follow-up period for both groups.

More recent observational study for comparison between ADA - and IFX-treated patients showed substantial improvements from baseline to follow-up in effectiveness measures; the results of these measures were similar between the ADA and IFX cohorts. Time to remission, no rectal bleeding, normal stool count and PGA score showed no significant differences between both agents in unadjusted and adjusted comparisons [35]. Authors concluded that ADA and IFX were similarly effective in the treatment of moderate to severe UC in the real-world clinical setting, and this was consistent with the findings of this study. Most of the secondary endpoint measures, in this study, were comparable between ADA and IFX group, a statistically significant difference was observed for the RBS, PGA, and SFS.

In this study and previous ADA trials, the Mayo score was calculated based on the worst score from the last 3 days for stool frequency and anti-TNF treatment for UC. A few studies have documented open-label experiences with both ADA and IFX [15-17]. Two large randomized controlled trials with IFX in the induction and maintenance of UC remission had been previously published (ACT1 and ACT2) [7] and two large randomized controlled trials with ADA in the induction and maintenance of UC remission had been achieved (ULTRA1 and ULTRA2) [8,14].

In this study, the treatment with ADA and IFX demonstrated a substantial benefit in the rates of clinical remission at week 8 (24% vs. 28%, respectively) among patients who had previously failed or were currently failing steroids and/or immunosuppressive therapy. Substantial benefits were also seen for clinical response, partial Mayo score components, in addition to IBDQ index, compared to baseline data.

Two clinical practice papers describing ADA treatment for UC have been published. The first, which had a 13-patient cohort, showed the probability of an ADA induced response being maintained as 84.6% at 3 months and 60.6% at 6 months [17]. The second study reported that 67% of a nine-patient cohort had an improvement of their symptoms [18]. Similarly, the clinical practice use of IFX for UC treatment has been reported in three studies. In the first, 67% of patients had an initial clinical response and 68% of these initial responders experienced a sustained clinical response [19]; second study showed that, at week 8, the response rates were only 58% [20]; the third one reported clinical response rates of 56% [21]. The induction response rate in this “real-life” clinical practice study within 8 weeks was lower for IFX (52%) and ADA (48%) than those reported in the initial randomized placebo-controlled trials for IFX (ACT1=69.4%, ACT2=64.5%) [7] and ADA (ULTRA1=54.6%, ULTRA2=50.4%) [8,14].

Data expressed by n (%). *Significant difference (p<0.05). AE: Adverse events, ADA: Adalimumab, IFX: Infliximab

| AEs                                      | ADA group (n=25) | IFX group (n=25) |
|------------------------------------------|------------------|------------------|
| Any AE                                   | 20 (80)          | 21 (84)          |
| AE at least possibly drug-related        | 8 (32)           | 8 (32)           |
| Severe AE                                | 4 (16)           | 5 (20)           |
| Serious AE                               | 4 (16)           | 3 (12)           |
| AE leading to early discontinuation      | 2 (8)            | 2 (8)            |
| UC worsening/flare AE                    | 1 (4)            | 0                |
| Allergic reaction-related AE             | 1 (4)            | 1 (4)            |
| Injection site reaction-related AE       | 2 (8)            | 5 (20)*          |
| Serious infectious AE                    | 1 (4)            | 1 (4)            |
| Opportunistic infection-related AE       | 0                | 1 (4)            |
| AE (no TB)                               |                  |                  |
| Tuberculosis                             | 1 (4)            | 0                |
| Hematologic AE                           | 2 (8)            | 4 (16)*          |
| Hepatic AE                               | 0                | 0                |
| CHF-related AE                           | 0                | 0                |
| Demyelinating disease AE                 | 0                | 0                |
| Lupus-like syndrome AE                   | 0                | 0                |
| Malignant AE                             | 0                | 0                |
| Lymphomas AE                             | 0                | 0                |
| Fatality AE                              | 0                | 0                |
rectal bleeding [8,14]. In contrast, in the IFX trials and other UC trials, the average score for stool frequency and rectal bleeding from the last 3 days was used to calculate the Mayo score [7]. In addition, the patients in the current trial were anti-TNF-naïve patients, whereas 40% of patients in the ADA ULTRA2 trial had previously been exposed to anti-TNF agents [14]. These differences in clinical trial design and patient populations limit across-trial comparisons.

The partial Mayo score data in this study indicate that the plateau of efficacy for ADA and IFX had not yet been reached by week 8, suggesting a need for longer exposure to observe a maximum response. Results from open-label phase of the induction trial and double-blind maintenance trial may be required to improve our understanding of the peak period for induction of remission in patients with moderately to severely active UC treated with these biologic therapies.

Results from the baseline Mayo score, hs-CRP level, and patient weight subgroups demonstrated that patients with Mayo score ≥10, elevated hs-CRP level (≥10 mg/L) and higher weight (≥70 kg), may have an inflammatory disease burden that is not adequately addressed and giving an acceptable clinical remission by the ADA dose used in this study. Thus, our data suggest the possibility that a substantial proportion of patients with UC may require a higher dose of ADA to induce remission, compared with Crohn’s disease patients, though the biological rationale for this remains unclear. In addition to increased dose, patients with UC may require a longer exposure to high doses of ADA than patients with Crohn’s disease to achieve induction of remission.

Regarding the significant and dangerous side effects of corticosteroids over a long-term administration, steroid-sparing is an important aim for chronic UC treatment. In the ACT 1 study, 61% of the patients were on corticosteroids at baseline; of these, 21% of those treated with IFX were in steroid-free clinical remission at 54 weeks [7]. In ULTRA2 trial, ADA therapy was associated with meaningful rates of steroid discontinuation in patients taking steroids at baseline with approximately 40% of patients becoming steroid-free at week 52 [14]. In our study, no patient achieved steroid-free remission for both groups during the induction period, and we did not evaluate the effects of ADA and IFX during a maintenance long-term phase.

The previous data demonstrated the similar efficacy of ADA in Japanese and Western patients with UC and Crohn’s disease [36]. However, in one study achieved on Japanese population, the patients on ADA who were taking steroids at baseline may not be truly steroid-resistant. This phenomenon was not noted at the end of the study, which is also consistent with the known lack of long-term efficacy noted with steroid therapy [37].

In the current study, a small percent of ADA- and IFX -treated patients were on concomitant immunosuppressive therapy. Whether the uses of immunosuppressants have a role in the induction and maintenance response rates for ADA or IFX remains to be determined. Future studies are needed to determine the exact ways concomitant immunosuppressive therapy might affect anti-TNF antibodies, serum levels, and sustained responses. Nevertheless, ACT and ACCENT trials have shown immunomodulator use to be related to less immunogenicity, fewer infusion reactions, but not to improved efficacy, as compared with anti-TNF therapy alone [38].

Important long-term outcomes, including improved quality of life, steroid discontinuation with the achievement of steroid-free remission, reduction in the rates of hospitalization and colectomy occurred more frequently during maintenance therapy with ADA. The decision to continue long-term therapy in patients with UC is generally based on response to induction therapy [39]. The greater efficacy over time coupled with a lower rate of overall AEs in week 8 responders relative to the overall population receiving biologic therapy, both support the favorable benefit/risk profile of maintenance therapy in patients exhibiting an early response to induction therapy.

How should the results of this trial be incorporated into clinical practice? ADA, given subcutaneously as a self-administration, has not been studied in hospitalized patients with severe UC who are failing IV steroids. It might offer an additional treatment option for outpatients who did not tolerate IFX or its infusion route that requires a special technique. Because of the subcutaneous route of administration, ADA can be self-administered by patients at home, thus avoiding the high cost and inconvenience of hospital visits due to IV infusion of IFX.

The overall safety profile of ADA and IFX observed in this study was similar to that seen in other trials of these drugs in patients with IBDs [8,40]. Notably, comparable incidence rates were observed for AEs, severe AEs, serious AEs, and serious infectious AEs in patients receiving ADA, compared with those on IFX.

The incidence of injection site reaction (mainly pain) and hematologic events (mainly leukopenia) was significantly higher in the IFX group and may attribute to the IV route of administration for this agent. These events were mild and not required discontinuation of any agent.

One patient who received ADA and developed tuberculosis in this study had other risk factors for this infection, including increased age [41] and concomitant high-dose corticosteroid use [42]. This patient had undergone standard screening for tuberculosis, purified protein derivative skin testing and chest X-ray, consistent with the guideline recommendations. Cases of tuberculosis have been observed in ADA -treated patients with negative screening tests [43] and may represent new-onset infections or false-negative testing, which may be more likely in patients taking concomitant corticosteroids or immunomodulators [41]. Clinicians initiating ADA in patients on combination immunosuppressive therapy or patients with other risk factors for infections should carefully monitor these patients for signs and symptoms and have a high index of suspicion of infection in patients with symptoms suggestive of tuberculosis (e.g., persistent cough, weight loss, and fever).

Biological agents are also associated with an increased risk of malignancies, especially lymphoma [44]. This is probably due to the inhibition of the apoptotic and tumor suppressive functions of TNF-α. In the current study, no patient suffered lymphoma within each group.

Limitations of this study were its relatively small sample size and its short-term course (just induction phase). In addition, this study did not evaluate the efficacy of ADA and IFX in patients who had previously received other biologic therapies.

Many of the biological agents are immunogenic and patients frequently develop antibodies against these drugs, which can interfere with their therapeutic effects and safety. This problem is more frequent with chimeric agents, like IFX, which is considered more immunogenic than with fully humanized agents, like ADA [45]. Even though, in certain report of ADA, response of patients with UC to immunosuppressants and lack of antibody against ADA - platelet complex suggests that this biological agent can induce destruction of platelets by the formation of antiplatelet antibodies (immune-mediated thrombocytopenia) [46,47]. Hence, future long-term, large-scale studies may be required to measure antibodies against ADA or IFX and their trough serum concentrations for the remitter and non-remitter patients, and for patients on concomitant immunosuppressive agents and those receiving just the biologic therapy. Furthermore, because of family history, genetic polymorphism, and variant human leukocyte antigens, studying the response rates of UC to the biologic therapy in different geographical regions may be required.

CONCLUSION

In conclusion, this real-life clinical trial demonstrated that ADA (160/80 mg) and IFX (5 mg/kg) were comparable in their effectiveness for inducing clinical remission and response in patients with moderate to severe ulcerative colitis.
severe UC who did not adequately respond or intolerant to conventional therapy with oral corticosteroids and/or immunosuppressive agents. Both of the biologic agents were well tolerated with an approach safety profile.

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