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Adalimumab Versus Ustekinumab in Egyptian Patients with Moderate to Severe Inflammatory Bowel Disease: A Cohort Study

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ABSTRACT

Inflammatory bowel disease (IBD) is a progressive, relapsing disorder. Biologics for patients with moderate-to-severe IBD have shown promising therapeutic outcomes. This research aims to compare the efficacy, safety and cost of adalimumab versus ustekinumab in a group of patients with IBD who failed treatment with infliximab. A prospective cohort study was performed on 108 patients, 53 of whom received adalimumab (Gp A) and 55 received ustekinumab (Gp U), followed up for 24 weeks. Clinical response, clinical remission and C-reactive protein (CRP) normalisation were assessed for efficacy; a cost-effectiveness analysis was conducted, and safety was evaluated. The clinical response was achieved by 86.8% of the patients in the Gp A and 92.7% of those in the Gp U group, respectively, without a significant statistical difference. The patients in the Gp A group experienced clinical remission and CRP normalisation in proportions of 47.1% and 37.3%, respectively. In contrast, the patients in the Gp U group experienced 69.8% and 58.5%, respectively, with significant statistical differences between the two groups. Adverse events were fewer in the Gp U than in the Gp A group, with a significant statistical difference. Ustekinumab was more costly than adalimumab, with a significant statistical difference between both groups. In conclusion, ustekinumab is considered more effective and safer than adalimumab in infliximab-experienced patients but with a higher cost in patients with moderate to severe IBD.

KEYWORDS

biologics, cost-effectiveness, Crohn's disease, Humira, Stelara, ulcerative colitis

CITATION

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1. Introduction

Inflammatory bowel disease (IBD), which involves Crohn's disease (CD) and ulcerative colitis (UC), is a chronic inflammatory relapsing disorder affecting the gastrointestinal system and is known for its progressive nature and unpredictable disease course. Although UC affects only the colon mucosa, CD can affect any location from the mouth to the anus and all layers of the gut (Roda *et al.*, 2020).

Cases of IBD have increased globally over time to reach 6.8 million in 2017 (Alatab *et al.*, 2020). Although the greatest percentages of IBD cases have been documented in Western nations, the occurrence of IBD in the Middle East considerably increased in the twentieth century because its countries became more Westernised (Shamkh *et al.*, 2022). In 2021, the incidence rate of UC in Arab regions, including Egypt, was 2.33 per 100,000 people per year, while that of CD was 1.46 per 100,000 people per year (Mosli *et al.*, 2021).

Inflammatory bowel disease typically develops in adolescence and often affects both males and females equally (Sauer and Kugathasan, 2009). The IBD aetiology is still largely ambiguous; however, the complex interaction between genetic and environmental factors that affect immune responses may be the cause of the disease (Karthikeyan *et al.*, 2021). The most reported symptoms of IBD are weight loss, diarrhoea and abdominal pain, as are extraintestinal manifestations, including dermatological and musculoskeletal symptoms. Rectal bleeding is more frequent in UC, while fistulas and anal lesions are typically linked to CD (Seyedian *et al.*, 2019).

An IBD diagnosis is usually dependent on the assessment of clinical manifestations, laboratory findings such as faecal calprotectin (FCP), C-reactive protein (CRP), erythrocyte sedimentation rate (ESR) and complete blood count (CBC) and radiologic, endoscopic and histopathologic findings (Flynn and Eisenstein, 2019). Achieving and maintaining remission and minimising the negative health impacts of the disease itself are the major treatment goals of IBD. In addition, the therapies used to manage it aim to reduce the rate of hospitalisations, surgeries and disability (Cai *et al.*, 2021).

Although conventional therapy for IBD, like corticosteroids, aminosalicylates and immunomodulators provide symptomatic improvement, their use can also result in negative impacts and some patients fail to respond to these therapies. More targeted pharmacological therapies, called biologics, including infliximab, adalimumab and ustekinumab, have altered how IBD is treated (Moreno *et al.*, 2021). Unfortunately, the use of biologics can put a significant financial strain on the global health system.

Both infliximab and adalimumab target and inhibit human tumour necrosis factor-alpha (TNFα), while the p40 subunit of interleukin (IL-12 and IL-23) may be inhibited by ustekinumab (Holmer and Singh, 2019). About one-third of patients are non-responsive to anti-TNF induction therapy due to primary failure, while some patients who initially respond discontinue treatment due to secondary failure or an intolerable adverse event (Singh *et al.*, 2018). Secondary failure will be considered if, following an initial response, the effectiveness is lost over time, the cause of which may be the development of anti-drug antibodies, which can neutralise the drug or result in sub-therapeutic levels. Primary failure will be considered if the drug is ineffective, with no clinical response within the initial treatment period and that may be due to a mechanistic failure (Vallejo-Yague *et al.*, 2021). To date, there is no definite proof for second-line biologics of choice in case of failure of the first anti-TNF drug; as such, the choice between a second anti-TNF drug or a

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different class of biologics is based on physician experience, drug availability and cost (Gisbert and Chaparro, 2021).

The induction and maintenance of remission using adalimumab and ustekinumab in patients suffering from IBD are well reported. Their use as second-line therapies has also been documented for non-responders or patients who are intolerant to infliximab (Ahmed *et al.*, 2019).

A recent study compared only the efficacy of second-line biologics after exposure to anti-TNF agents in patients with IBD from two electronic health records-based cohorts; the study found that patients with CD had better clinical outcomes with second-line ustekinumab compared to second-line vedolizumab or an alternative anti-TNF agent, while no difference in the efficacy was observed when comparing second-line vedolizumab with an alternate anti-TNF agent in patients with UC (Ibing *et al.*, 2023). Due to a lack of research comparing ustekinumab versus adalimumab in patients with IBD, particularly in the Egyptian population, this research was carried out to assess the efficacy, safety and cost of both drugs, in addition to determining factors related to clinical remission in patients with IBD.

2. Materials and Methods

2.1. Study Population

The research was carried out on adult patients with moderate to severe IBD, either UC or CD, who failed on infliximab therapy. Patients were eligible for the study if they were 18 years or older and had a history of infliximab therapy failure. Clinical scores of disease activity defined the severity of the disease according to either the Harvey Bradshaw Index (HBI) as ≥8 points for moderate to severe CD and based on a partial Mayo score (PMS) ≥5 points for moderate to severe UC (Mentella *et al.*, 2019; Zittan *et al.*, 2017).

Patients were excluded if they had indeterminate colitis or malignancy, were biological therapy-naive, had mild disease activity, were pregnant women, lacked adherence (missing 1 dose or more of the prescribed biologic agent), refused to sign the informed consent form or failed to be followed up (patient with non-complete data at week 24).

2.2. Study Design and Methodology

In a comparative, prospective and observational cohort study, patients were selected from the IBD clinics of El-Demerdash Hospital, Cairo, Egypt, and the National Hepatology and Tropical Medicine Research Institute, Cairo, Egypt and recruited by the physicians in both hospitals. The study period was from July 2021 until January 2023, and the follow-up period was 24 weeks for each patient. The institutional review boards of both hospitals approved the research protocol and ethical approval was granted by the Ethical Committee of the Faculty of Pharmacy, Helwan University, Cairo, Egypt (ethical committee approval number: 02H2021).

A total of 108 patients were eligible for inclusion, 53 of whom received adalimumab (HUMIRA®, AbbVie, North Chicago, USA, Batch Number: 28203XH04, EXP: 3-2023) (Gp A) and 55 received ustekinumab (STELARA®, Janssen, Beerse, Belgium, Batch Number: KJ53FMJ, EXP: 9-2023) (Gp U) based on physician experience and drug availability and followed up for 24 weeks. Regarding the assessment of patients' adherence, a double-check process was implemented to ensure the administration of the biologics to each patient; the first of these was through regular follow-up and direct communication with the patients in the IBD clinics during the physical visits and the second through regular review of the hospitals' electronic medical records, in which patients' medical data was entered and updated on a regular and continuous basis (Date of biologics' administration, either HUMIRA® or STELARA®, was recorded for each patient).

2.3. Treatment Protocol and Drug Use

According to the treatment protocols of both hospitals, a subcutaneous dose of 160 mg adalimumab was given initially on Day 0, followed by 80 mg two weeks later for induction and then 40 mg every two weeks for maintenance. Ustekinumab was given through intravenous infusion with a weight-based single dose for induction (for body weight ≤55 kg: 260 mg; >55 kg to 85 kg: 390 mg; and >85 kg: 520 mg), followed by a subcutaneous dose of 90 mg for maintenance every 2 months. Adjuvant medications, such as immunomodulators, corticosteroids, mesalazine and multivitamins were used concurrently with adalimumab or ustekinumab as part of the treatment protocol.

2.4. Data Collection

Patient characteristics such as sex, age and body mass index (BMI), were assessed at the baseline. In addition, a detailed medical history (age at diagnosis, disease extent, perianal behaviour, behaviour of disease, location of disease), comorbidities and co-medications were collected. Colonoscopy and laboratory investigations, which included virology testing (hepatitis C virus, hepatitis B virus and human immunodeficiency virus), were performed at baseline. Measurements were taken for CBC, CRP and ESR at baseline and at week 24. The scores for the HBI and the PMS were calculated at baseline, week 16 and week 24.

2.5. Clinical Evaluation and Assessment

Efficacy was assessed by: 1) achievement of clinical response after 16 weeks of treatment initiation, which was described as a decrease of at least 3 points in the HBI from baseline for CD and a reduction of at least 2 points in the PMS from baseline for UC; 2) achievement of clinical remission after 24 weeks of treatment initiation, which was described as an HBI score <5 points for CD and a PMS <2 points for UC; and 3) achievement of CRP normalisation (CRP <5 mg/L) after 24 weeks of treatment initiation (Allegretti *et al.*, 2017; Castiglione *et al.*, 2022; Zacharias *et al.*, 2017). To identify factors associated with clinical remission, patients were classified into 2 groups depending on their IBD type (either CD or UC).

Safety was evaluated by recording any adverse events that occurred among the patients during the period of 24 weeks. Adverse events were considered serious if they resulted in a life-threatening complication or required inpatient hospitalisation.

For cost assessment, a cost-effectiveness analysis was conducted from a healthcare system perspective, calculating the incremental cost-effectiveness ratio (ICER) as follows: ICER = (direct medical costs of the ustekinumab group − direct medical costs of the adalimumab group) / (effectiveness of the ustekinumab group − effectiveness of the adalimumab group) (Dos-Santos *et al.*, 2021). Costs were collected in Egyptian pounds, and only direct medical costs were considered in the analysis, such as the costs of the biological agent, co-medications, investigations and adverse drug events, including the need for hospitalisation, investigations and medications. The effectiveness was calculated using the clinical remission percentage at week 24, and the results of the ICER were plotted on a cost-effectiveness plane.

2.6. Statistical Analysis

All statistical analyses and graphs were conducted using the Statistical Package for the Social Sciences (SPSS) version 26. Continuous data were summarised as mean ± standard deviation (SD), while discrete

variables were described as counts and percentages. The Kolmogorov–Smirnov test assessed normal distribution. To test for significant differences in the mean values of the continuous variables, an independent samples t-test was performed. In comparison, the Mann–Whitney test was applied to data that were not normally distributed. The significance of differences between the mean values of two related samples that were normally distributed was assessed using a paired sample t-test. In contrast, the non-normally distributed samples were tested by a Wilcoxon signed-rank test.

Friedman's analysis of variance (ANOVA) for non-normally distributed data was conducted to test the significant difference in clinical scores within each treatment group during the follow-up period. The chi-square test and Fisher's exact test were both used to compare categorical data. To determine the association between variables, Spearman's correlation was used. A binary logistic regression analysis was carried out to detect factors related to clinical remission and to evaluate the risk of confounding factors. A two-sided $p < 0.05$ was used to determine significance.

2.7. Sample Size Calculation

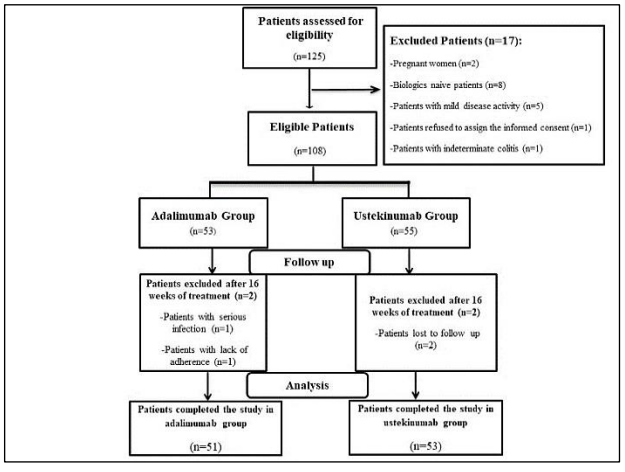
According to evidence from a similar study and considering ustekinumab's effectiveness in inducing clinical remission in patients with IBD as a primary outcome (Cerpa-Arencibia *et al.*, 2020), the sample size was calculated using the EpiCalc 2000 version1.02 software, assuming 80% power and a significance level of 0.05. Finally, the sample size was computed as 51 patients in each group, considering an extra 5% of the estimated sample size was added to account for the loss of follow-up in our study.

3. Results

3.1. Patient Demographics and Distribution

A total of 125 patients were evaluated for study eligibility and among them, 17 were excluded. A total of 108 patients met the study's eligibility requirements. Among them, 53 received adalimumab and 55 received ustekinumab. During the 24-week follow-up period, 4 patients dropped out of the study after 16 weeks. A total of 104 patients completed the study, of which 51 and 53 were in Gp A and Gp U groups, respectively (Figure 1).

Figure 1: Flowchart of Patients' Enrolment and Follow-up



3.2. Baseline Characteristics

The Gp A and Gp U groups shared comparable baseline characteristics without significant differences in age, BMI, gender, IBD type, age at diagnosis for CD and location of the disease, Montreal classification and endoscopic activity using the simple endoscopic score for CD (SES-CD) and the endoscopic Mayo score for UC ($p > 0.05$). Regarding co-medications, all patients were taking multivitamins; 58.3% of patients were on steroids, calcium and vitamin D; 45.4% of patients were on mesalazine; and 62% of patients were on azathioprine (Table 1 and 2).

Table 1. Baseline Characteristics of the Eligible Patients

Variable	Adalimumab group (N = 53)	Ustekinumab group (N = 55)	*p*
Age (Year), mean ± SD	32 ± 9	29.2 ± 9.2	0.06[M]
BMI (kg/m^2), mean ± SD	24.8 ± 3.7	24.2 ± 5.7	0.11[M]
BMI < 18 (kg/m^2), N (%)	1 (1.9%)	5 (9.1%)	0.21[F]
Female: Male, N (%)	35 (66%): 18 (34%)	30 (54.5%): 25 (45.5%)	0.22[C]
UC: CD, N (%)	33 (62.3%): 20 (37.7%)	31(56.4%): 24 (43.6%)	0.53[C]
Type of infliximab failure N (%)			
Primary failure	1 (1.9%)	5 (9.1%)	0.16[F]
Secondary failure	42 (79.2%)	44 (80%)	
Drug intolerance	10 (18.9%)	6 (10.9%)	
Endoscopic activity (SES-CD/Mayo score), N (%)			
Moderate	35 (66%)	34 (61.8%)	0.84[F]
Severe	17 (32.1%)	20 (36.4%)	
Not applicable (L4)	1 (1.9%)	1 (1.8%)	
Co-medications, N (%)			
Prednisolone (Solupred ORO)®	35 (66%)	28 (50.9%)	0.11[C]
Mesalazine (Marsalaz)®	29 (54.7%)	20 (36.4%)	0.06[C]
Azathioprine (Azathioprine)®	47 (88.7%)	20 (36.4%)	<0.001*[C]
Calcium and vit. D (Osteocare)®	35 (66%)	28 (50.9%)	0.11[C]
Multivitamins (Vitayami)®	53 (100%)	55 (100%)	

[M]Mann-Whitney test, [C]Chi-square, [F]Fisher exact test, *statistically significant, statistical significance at $p < 0.05$. SD, standard deviation; BMI, body mass index; UC, ulcerative colitis; CD, Crohn's disease; SES-CD, simple endoscopic score for Crohn's disease; vit.-vitamin

Table 2: Baseline Montreal Classification of the Eligible Patients

Variable	Adalimumab group	Ustekinumab group	P
Montreal classification for CD, N (%)	N = 20	N = 24	
A1 (≤16 years)	4 (20%)	4 (16.7%)	>0.99F
A2 (17–40 years)	16 (80%)	19 (79.2%)	
A3 (>40 years)	0 (0%)	1 (4.2%)	
L1 (Terminal ileum)	7 (35%)	7 (29.2%)	0.95F
L2 (Colon)	2 (10%)	2 (8.3%)	
L3 (Ileocolon)	10 (50%)	14 (58.3%)	
L4 (Upper GI)	1 (5%)	1 (4.2%)	
B1 (Inflammatory)	11 (55%)	11 (45.8%)	0.16F
B2 (Stricturing)	2 (10%)	8 (33.3%)	
B3 (Penetrating)	7 (35%)	5 (20.8%)	
Perianal behaviour (P), N (%)	3 (15%)	5 (20.8%)	0.71F
Montreal classification for UC, N (%)	N = 33	N = 31	
E1 (Ulcerative proctitis)	0 (0%)	0 (0%)	0.14C
E2 (Left sided UC)	21 (63.6%)	14 (45.2%)	
E3 (Pancolitis)	12 (36.4%)	17 (54.8%)	

[C]Chi-square, [F]Fisher exact test, *statistically significant, statistical significance at $p < 0.05$. UC, ulcerative colitis; CD, Crohn's disease; GI, gastrointestinal

3.3. Clinical treatment

3.3.1. Efficacy

All laboratory parameters and clinical scores were significantly improved after treatment in both treatment groups ($p < 0.001$) as shown in (Tables 3 and 4).

Table 3: Clinical Scores Measured Before and After Treatment

Mean ± SD	Adalimumab group		Ustekinumab group	
	HBI	PMS	HBI	PMS
At Baseline	11.1 ± 3.7	7.6 ± 1.5	12.7 ± 3.7	7.8 ± 1.4
At Week 16	5.9 ± 3.2	3.5 ± 1.8	5.7 ± 2.6	2.4 ± 1.9
At Week 24	6.2 ± 4.5	3.3 ± 2.9	5.7 ± 3.2	1.8 ± 1.5
P	<0.001[F]	<0.001[F]	<0.001[F]	<0.001[F]

[F]Friedman ANOVA test, statistical significance at $p < 0.05$. SD, standard deviation; HBI, Harvey Bradshaw Index, PMS, partial Mayo score

Table 4: Laboratory Parameters Measured Before and After Treatment

Variable Mean ± SD	Adalimumab group			Ustekinumab group		
	At baseline	At week 24	*p*	At baseline	At week 24	*p*
CRP (mg/L)	24.6 ± 19.8	9.4 ± 10.6	<0.001[W]	31.9 ± 21.1	8.2 ± 9.2	<0.001[W]
ESR (mm/h)	43.9 ± 30.7	29.2 ± 45.1	<0.001[W]	53.9 ± 27.7	27.9 ± 42.7	<0.001[W]
Hgb (gm/dL)	10.5 ± 1.9	11.6 ± 1.8	<0.001[P]	10.2 ± 1.8	12 ± 1.5	<0.001[P]
HCT (%)	32.7 ± 5.1	35.5 ± 4.3	<0.001[P]	33.4 ± 4.7	37.2 ± 4	<0.001[P]
Plt (x10^3/mcL)	363.1 ± 132.2	314.5 ± 88.2	<0.001[W]	380.5 ± 111.7	332.6 ± 68	<0.001[W]

[P]Paired sample-t-test, [W]Wilcoxon signed-rank test, statistical significance at $p < 0.05$. SD, standard deviation; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; Hg, haemoglobin; HCT, haematocrit; Plt, platelets

At week 16, the clinical response was found in 86.8% of the Gp A and 92.7% of Gp U group patients, with a non-significant statistical difference ($p = 0.36$). At week 24, the Gp A group experienced clinical remission and CRP normalisation in proportions of 47.1% and 37.3%, respectively. In contrast, the Gp U group experienced these results as 69.8% and 58.5%, respectively, with a statistically significant difference between both groups ($p < 0.05$). (Table 5).

Table 5: Achievement of Clinical Response, Clinical Remission and CRP Normalisation after Treatment

Outcome	Adalimumab group	Ustekinumab group	P
Clinical response at week 16, N (%)			
IBD	46 (86.8%)	51 (92.7%)	0.36F
UC	31(93.9%)	31 (100%)	0.49F
CD	15 (75%)	20 (83.3%)	0.71F

Clinical remission at week 24, N (%)			
IBD	24 (47.1%)	37 (69.8%)	0.02*C
UC	16 (48.5%)	23 (76.7%)	0.02*C
CD	8 (44.4%)	14 (60.9%)	0.30C
CRP normalisation (<5 mg/L) at week 24, N (%)			
IBD	19 (37.3%)	31 (58.5%)	0.03*C
UC	11 (33.3%)	18 (60%)	0.03*C
CD	8 (44.4%)	13 (56.5%)	0.44C

[T]Fisher exact test, [C]Chi-square, * statistically significant, statistical significance at $p < 0.05$. IBD, inflammatory bowel disease; UC, ulcerative colitis; CD, Crohn's disease; CRP, C reactive protein.

At week 24, a positive association (r = 0.38, $p < 0.001$) was found between clinical remission and CRP normalisation in both groups; 78% of patients who achieved CRP <5 mg/L were in clinical remission, whereas 59.3% of patients who did not achieve CRP <5 mg/L were not in clinical remission.

In the univariate analysis of binary logistic regression for clinical remission, adalimumab use relative to ustekinumab use ($p = 0.02$), a high PMS at week 16 ($p < 0.001$) and severe endoscopic activity at baseline ($p = 0.03$) were significant negative factors of clinical remission in UC at week 24. In contrast, a high HBI score at week 16 ($p = 0.008$) was a significant negative factor of clinical remission in CD at week 24 (Table 6).

In multivariate analysis, a high PMS at week 16 (odds ratio [OR] = 0.36, 95% confidence interval [CI], 0.22–0.62) and severe endoscopic activity at baseline (OR = 0.16, 95% CI, 0.03–0.94) were negative factors of clinical remission in UC at week 24, while a high HBI score at week 16 (OR = 0.46, 95% CI, 0.24-0.88) was a negative factor of clinical remission in CD at week 24 (Table 6).

Table 6: Factors Associated with Clinical Remission at Week 24

Binary logistic regression analysis for clinical remission					
	For UC (N = 63)			For CD (N = 41)	
Variable	Univariate OR [CI] (p)	Multivariate OR [CI] (p)	Variable	Univariate OR [CI] (p)	Multivariate OR [CI] (p)
UST use	Reference		UST use	Reference	
ADM use	0.29 [0.09–0.85](**0.02**)		ADM use	0.51[0.15–1.80] (0.30)	
PMS at 16 weeks	0.37[0.24–0.58](<**0.001**)	0.36[0.22–0.62] (<**0.001**)	HBI at 16 weeks	0.48[0.27–0.83](**0.008**)	0.46[0.24–0.88](**0.02**)
Severe endoscopic activity at baseline	0.30[0.10–0.87](**0.03**)	0.16[0.03–0.94](**0.04**)	Male gender	0.27[0.07–1.06](0.06)	
Steroid use	0.48[0.17–1.36](0.17)		Steroid use	0.37[0.12–1.14](0.08)	
AZA use	0.53[0.16–1.73](0.29)		AZA use	0.75[0.22–2.57](0.65)	
CRP >10 at baseline	1.02[0.29–3.58](0.98)		CRP >10 at baseline	0.53[0.09–3.28](0.49)	
BMI <18 at baseline	0.18[0.02–1.88](0.15)		BMI <18 at baseline	0.86[0.05–14.71](0.92)	

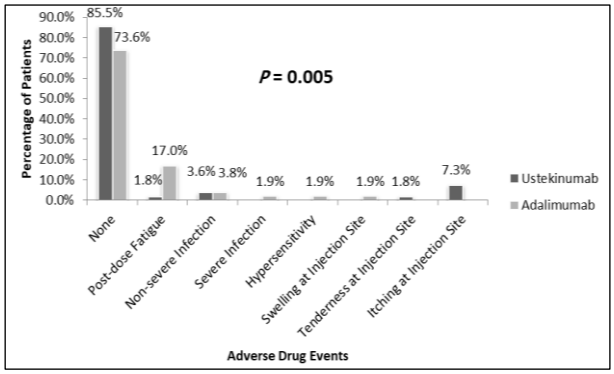
OR, odds ratio; CI, confidence interval; * statistically significant, statistical significance at $p < 0.05$. UC, ulcerative colitis; CD, Crohn's disease; ADM, adalimumab; UST, ustekinumab; PMS, partial Mayo score; HBI, Harvey Bradshaw Index; AZA, azathioprine; CRP, C-reactive protein; BMI, body mass index.

Univariate analyses of binary logistic regression for clinical response, clinical remission and CRP normalisation showed that azathioprine use was a non-significant factor of these outcomes (OR = 0.58, 95% CI, 0.15–2.33), (OR = 0.69, 95% CI, 0.31–1.57) and (OR = 0.59, 95% CI, 0.26–1.30), respectively.

3.3.2. Safety

Regarding safety, post-dose fatigue was experienced by 17% of Gp A and 1.8% of Gp U ($p = 0.008$) group patients. Non-severe infections (upper respiratory tract and urinary tract infections that did not require hospitalisation) were reported by 3.8% of Gp A and 3.6% of Gp U ($p > 0.99$) group patients. Severe infections, hypersensitivity and swelling at the injection site were found in 1.9% of Gp A ($p = 0.49$) group patients. In comparison, 7.3% and 1.8% of Gp U group patients had itching and tenderness at the injection site ($p = 0.12$ and > 0.99, respectively). Adalimumab adverse events as a whole were compared to ustekinumab adverse events and showed a significant statistical difference ($p = 0.005$) as shown in Figure 2.

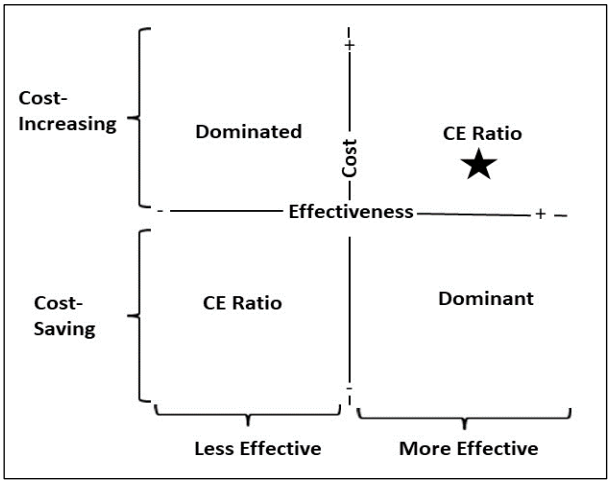
Figure 2. Adverse Drug Events Reported in Both Treatment Groups



3.3.3. Cost-Effectiveness Analysis

For Gp A group patients, the total direct medical costs, including the biologic agent, co-medications, investigations and adverse drug events, was estimated to be LE 977,534.71 with an average of LE 18,444.1/patient, whereas for Gp U group patients, this was estimated to be LE 3,581,167 with an average of LE 65,112.13/patient. This difference between the Gp A and Gp U groups was considered significant ($p < 0.001$). The calculated ICER was +LE 2,055.86/effectiveness, where ustekinumab is thought to be more effective but requires a higher cost than adalimumab as clarified in Figure 3 (Cohen and Reynolds, 2008).

Figure 3. Cost-Effectiveness Plane Showing Ustekinumab with a Higher Efficacy and Cost



4. Discussion

The introduction of biologics is undoubtedly the best therapeutic progress in managing IBD, especially in the last few decades, allowing targeted treatment with high efficacy and safety profiles. This research aimed to prospectively compare the efficacy, safety and cost of adalimumab (Humira®) versus ustekinumab (Stelara®) for managing moderate to severe IBD in a group of Egyptian patients who failed on infliximab therapy.

According to the hospitals' protocols, patients first started treatment with infliximab. They subsequently shifted to either adalimumab or ustekinumab as a second biological agent after infliximab failure due to primary failure, secondary failure or drug intolerance.

Baseline characteristics of the studied patients in the Gp A and Gp U groups were comparable with a non-statistically significant difference. However, we noticed a statistically significant difference in azathioprine use as a co-medication among the two groups ($p <$ 0.001). Owing to the high risk of antidrug antibodies developing

with adalimumab (0%—54%) compared to ustekinumab (1%—11%), an immunomodulator agent such as azathioprine could be used to reduce immunogenicity (Strand *et al.*, 2017; Vermeire *et al.*, 2018). The binary logistic regression analyses revealed that azathioprine use had no confounding effect on the outcomes achieved by the studied treatment groups.

The achievement of clinical response, clinical remission and CRP normalisation were the parameters used to measure adalimumab and ustekinumab efficacy in this study. Moreover, biochemical evaluation and clinical score changes were considered from baseline to the 24-week follow-up period. Both adalimumab and ustekinumab showed significant improvements in all laboratory parameters and clinical scores compared to baseline findings ($p < 0.001$), and the results were comparable with the previous studies from the literature (Afify *et al.*, 2021; Forss *et al.*, 2021; Kim *et al.*, 2021; Okuyucu *et al.*, 2022).

Our results revealed that both adalimumab and ustekinumab achieved a clinical response in CD and UC patients at week 16. This result agreed with a previous study on adult patients with moderate to severe CD (Ahmed *et al.*, 2019). In addition, ustekinumab showed greater efficacy than adalimumab, as evaluated by clinical remission and CRP normalisation at week 24 ($p < 0.05$). Interestingly, this difference in efficacy resulted in UC but not CD patients, possibly due to the more complicated nature of CD compared to UC. These findings were consistent with those of existing studies (Cerpa-Arencibia *et al.*, 2020; Ahmed *et al.*, 2019; Sands *et al.*, 2022).

Cerpa-Arencibia *et al.*, 2020 compared ustekinumab and anti-TNF drugs as second biologics in patients with CD who were non-responsive to the first anti-TNF agent treatment, which was comparable with our finding that showed no significant statistical difference in CRP normalisation between CD patients in both groups. However, it showed that ustekinumab had higher efficacy in achieving clinical remission than adalimumab. This difference may have resulted from their study comparing ustekinumab-treated patients to anti-TNF-treated patients (Cerpa-Arencibia *et al.*, 2020).

The binary logistic regression analysis conducted in this research detected factors related to clinical remission at week 24 and evaluated the risk of confounding factors. The multivariate analysis revealed that severe endoscopic activity at baseline and a higher PMS at week 16 were considered negative factors of clinical remission in UC patients. In contrast, a higher HBI score at week 16 was considered a negative factor of clinical remission in CD patients.

The results of this study were comparable to similar studies of regression analyses on clinical remission in patients with IBD (Dalal *et al.*, 2021; Hassan *et al.*, 2017; Mühl *et al.*, 2021). Conversely, research by Liefferinckx *et al.* (2019), who studied CD patients on ustekinumab who had previously been exposed to several biologics, revealed that a baseline BMI <18 kg/m^2 was considered a negative factor of clinical remission in CD; the difference between this result and the findings of the present study may have resulted due to the few patients in our study who had a BMI <18 kg/m^2 at baseline (only 6 patients) (Liefferinckx *et al.*, 2019).

This study showed a positive but weak association ($r = 0.38$, $p < 0.001$) between clinical remission and CRP normalisation, and this finding was consistent with earlier researches. Their studies explained that although clinical remission was attained, the systemic inflammatory process could not be completely reduced in some patients, leading to higher CRP values. The remaining inflammatory process subsequently resulted in an early relapse (Hoekman *et al.*, 2016; Lin *et al.*, 2020; Murdoch *et al.*, 2015).

This study showed that ustekinumab was superior to adalimumab in terms of safety as evaluated by recorded adverse events during a 24-week follow-up. Post-dose fatigue was the most frequent side effect related to adalimumab, while injection site reactions were the most frequent adverse effect related to ustekinumab.

Overall, reported adverse events were consistent with previous studies without any additional serious events. In contrast, the SEAVUE trial showed similar safety profiles for adalimumab and ustekinumab. This may have been because this trial had been performed only on bio-naive non-Egyptian patients with CD and lasted 52 weeks as opposed to 24 weeks (Prieto-Perez *et al.*, 2016; Sands *et al.*, 2022).

The study findings showed ustekinumab was more effective in managing patients with moderate to severe IBD but at a higher cost than adalimumab, calculated based on the ICER equation. This matched a study conducted by Aliyev *et al* (2019), which revealed that ustekinumab was more expensive than adalimumab; however, the study was performed from a societal rather than a healthcare system perspective.

5. Conclusion

In conclusion, ustekinumab was found to have better efficacy and safety profiles than adalimumab in managing moderate to severe IBD in Egyptian patients. However, treatment comes at a higher cost compared to adalimumab. The study showed a positive but weak association between clinical remission and CRP normalisation in patients with IBD. In addition, higher clinical scores at week 16 and severe SES-CD at baseline were linked to lower clinical remission rates at week 24.

This study has several strengths as follows. 1) To the best of our knowledge, this is the first observational study to compare adalimumab versus ustekinumab in the management of patients with moderate to severe UC who failed treatment with infliximab; in addition, it is the first study to compare the two drugs in the management of moderate to severe CD in Egyptian patients with a history of infliximab failure. 2) The study's prospective design and head-to-head comparison of two promising biologic agents in the real world presents an actual reflection of their role in IBD management. 3) The research was carried out on patients with UC and CD. 4) The efficacy evaluation was performed clinically and biochemically. Conversely, the study limitations included 1) a relatively short follow-up period, preventing us from assessing the long-term efficacy and safety outcomes. 2) The FCP biomarker and endoscopic activity were not followed up.

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