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Adalimumab (Humira) for Treatment of Ulcerative Colitis

A project submitted to the council of College of Medicine / University of Diyala in Partial fulfillment of the Requirements for the Degree of bachelor in medicine and General surgery

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الاهداء

الاهداء أولا الى نور وجه الله سبحانه وتعالى...

والى والدي و والدتي العزيزين اللذان صرفا ورود عمرهم لأجلنا ...

والى جميع الاخوة والاحبة و الأصدقاء اللذين وقفوا بجانبي بكل صغيرة و كبيرة و لا زالوا معنا و رحمة الله تعالى على اللذين فارقونا في هذه الدنيا...

والى جميع اساتذتي الكرام بوجه عام والى **الأستاذ الدكتور عادل حسن الحسيني** بوجه خاص المشرف على بحثي هذا و الذي كان له دور كبير بأعطائي المعلومات القيمة...

اهدي لكم بحثي هذا وأسال الله ان يوفقني به في ما يحبه و يرضاه..

الشكر والتقدير

الحمد لله والشكر والفضل كله لله..

نتقدم بالشكر والتقدير الى ابي وامي اطال الله بعمرهما والى الاهل والأصدقاء والى كل من ساعدنا ولو بشيء قليل او كلام جميل..

وكذلك الى اساتذتنا الكرام اللذين بذلوا جهدا كبيرا في بناء جيل الغد والى كل من ساعد في إتمام هذا البحث وقدم لنا العون والمساعدة وزودنا بالمعلومات **الأستاذ الدكتور عادل حسن الحسيني..**

الباحث الطالب احمد فائق عمر
مرحلة سادسة \ طب ديالى

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Abstract

Adalimumab has been shown to induce and maintain clinical remission in patients with moderate to severe ulcerative colitis (UC). However, no large-scale population-based studies have been performed in Iraq. This study review from mainly two studies in Iraq and studies in other countries were conducted to evaluate the safety and effectiveness of adalimumab in clinical practice in patients with UC.

Introduction

Ulcerative colitis is a chronic, idiopathic disease-causing inflammation restricted to the colonic mucosa. The pathogenesis is not fully elucidated, but there is evidence of an inappropriate immune response in the gut mucosa targeted at commensal organisms in the gut in predisposed individuals (*Ungaro et al., 2017*).

Ulcerative colitis refers to an inflammatory bowel disease (IBD) that results in persistent inflammation and ulcers (lesions) in the large bowel. Ulcerative colitis affects the colon and the rectum. Symptoms appear over a long period (*Wanderas et al., 2016*). There is no real reason for the occurrence of ulcerative colitis, although there is linkage to the immunity of the body (*Mohammed et al., 2020*). Typically, ulceration starts in the rectum and extends upward through part of, or the entire, colon. Characteristic symptoms of UC include bloody diarrhea, urgency, tenesmus, abdominal pain, and, occasionally, fever. The clinical course of UC is unpredictable, marked by alternating cycles of relapse and remission (*Ogata et al., 2020*). Ulcerative colitis mainly begins in the rectum. It may stay in the rectum (ulcerative proctitis) or exceed contiguously, occasionally spreading wholly to the colon. Patients suffer from diarrhea, rectal bleeding, lower abdominal pain, and tenesmus (*Mohammed et al., 2020*).

Background

Adalimumab is a monoclonal antibody, tumor necrosis factor-alpha (TNFα) inhibitor that has efficacy for inducing and maintaining remission in moderate-to-severe ulcerative colitis. Real world studies with adalimumab in Latin American ulcerative colitis patients are scarce (*Zacharias et al., 2017*).

Humira (adalimumab) is a recombinant human IgG1 monoclonal antibody that acts by inhibiting tumor necrosis factor alpha, an inflammatory protein that, when produced in excess,

plays a key role in the inflammatory responses of some autoimmune diseases. On September 28, 2012, the FDA approved adalimumab for the treatment of moderate-to-severe ulcerative colitis in adults. The approval was based on findings of 2 clinical studies showing the safety and effectiveness of adalimumab for ulcerative colitis (*Page A.A., 2016*).

The FDA approval of adalimumab for ulcerative colitis did not come easy. The agency turned down Abbott's application for this indication in November 2011, citing inconclusive evidence of the drug's ability to stop symptoms such as diarrhea, rectal bleeding, and abdominal pain.

On August 28, however, the FDA Gastrointestinal Drugs Advisory Committee voted overwhelmingly to recommend approval of the drug for ulcerative colitis. It based its decision on 2 clinical trials showing that 16.5% to 18.5% of patients treated with adalimumab experienced clinical remission after 8 weeks compared with 9.2% to 9.3% of patients who received a placebo. Shortly before the committee vote, FDA staff had questioned whether an efficacy difference of less than 10% between adalimumab and the placebo justified giving the drug to patients in lieu of already approved therapies. Ultimately, the committee decided that the modest benefit was clinically meaningful (*Lowes, 2012*).

Methods

Proceeding this study review according to multiple studies in different countries in the World, to perceive the efficacy and clinical remissions of adalimumab in severe to moderate ulcerative colitis patients. Also to assess the real-life efficacy and safety, assess the clinical remission rates in induction, and evaluate the short- and long-term outcomes of adalimumab in ulcerative colitis patients managing outpatients previously treated with infliximab in some studies.

Treatment protocol

Adalimumab (HUMIRA® brand name of Abbvie Company) subcutaneously with a recommended dose regimen of 160 mg initially on day 1 followed by 80 mg two weeks later than 40 mg every two weeks, according to the FDA (*Mohammed et al., 2020*). The drug should be discontinued in patients who have not shown evidence of clinical remission by 8 weeks. Infections, injection-site reactions, rash, and headache are common adverse reactions (*Lowes et al., 2012*).

Definitions

Clinical remission was defined as a partial Mayo score ≤ 2. Clinical response was defined as a reduction of partial Mayo score by 2 or more points between the beginning of treatment and certain periods of follow-up. Endoscopic remission or mucosal healing was defined as Mayo endoscopic sub-score ≤ 1. Primary loss of response was defined as lack of clinical improvement after the induction period. Secondary loss of response was defined as the need for one of the following outcomes during treatment: colectomy, dose optimization for weekly ADA or drug switching (*Zacharias et al., 2017*).

Mayo Endoscopic sub-score

Ileo-colonoscopy was performed in all the enrolled patients and classified according to Mayo subscore for endoscopy (*Sandborn et al., 2012*). This score was used to assess mucosal healing (MH), then recorded by specialists and compared to before and after 6 months of treatment, for severity grade (see Table below). Mucosal healing is defined as a score of 0 or 1 (*Mohammed et al., 2020*).

Table 1: Mayo endoscopic sub-scores

Grading	Disease Activity	Finding
0	Inactive	Normal
1	Mild	Mild friability, erythema and loose of vascular pattern
2	Moderate	Erosions, absent of vascular pattern, marked erythema and friability
3	Severe	Spontaneous bleeding and ulceration

End points

The primary end point was the induction of clinical remission in UC, defined as Mayo partial score ≤2, at 3 months, and maintenance of clinical remission, during the follow-up. Secondary end points were:

- ✓ Clinical response, defined as reduction of at least 2 point in the Mayo partial score during follow-up (if blood in stool is present, it must be reduced of at least one point).
- ✓ Reaching of mucosal healing (MH), defined as Mayo subscore for endoscopy ≤1, during follow-up.
- ✓ Prevention of colectomy (*Sandborn et al., 2012*).

Results

In the two studies in Iraq that discussed activity and toxicity of different TNF-alpha inhibitors in controlling patients with active ulcerative colitis (*mshimesh et al., 2019*) and Effectiveness of Infliximab and Adalimumab in Iraqi patients with ulcerative colitis (*Mohammed et al., 2020*) comprising the clinical remission, mucosal healing, and clinical response and that reported in other different studies.

This study review included many studies that observational, noninterventional, multicenter and retrospective study on a case series of patients with moderate-to-severe ulcerative colitis under adalimumab therapy.

In study (*Mshimesh et al., 2019*), treatment with adalimumab and infliximab demonstrated a substantial benefit in the clinical remission extent at week 8 (24% vs. 28%, respectively) among patients who were previously or currently not responded to steroids and/ or immunosuppressants. Substantial benefits were also seen for clinical response, partial Mayo score components, in addition to IBDQ index, compared with baseline data. considering mucosal healing, it was seen at week 8 in 40% of patients receiving either adalimumab or infliximab.

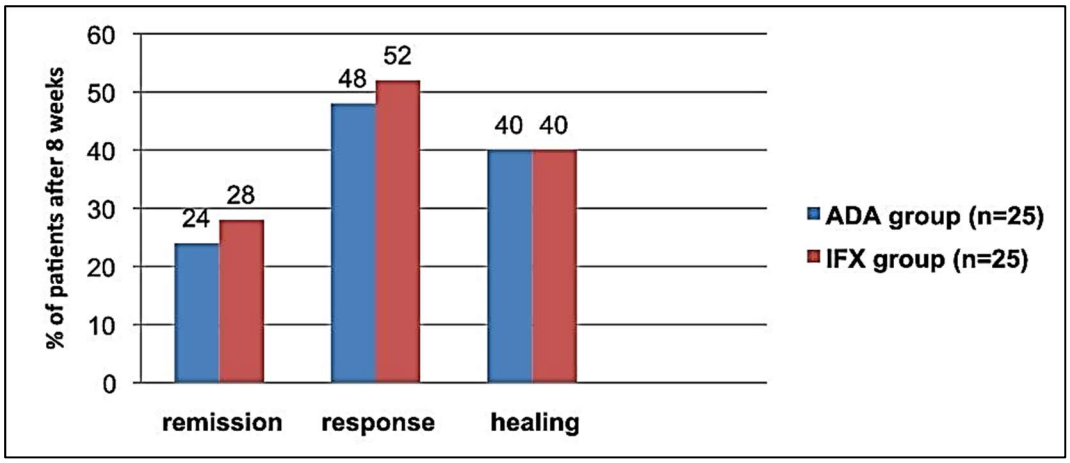

Figure 1. Fraction of patients with clinical remission, clinical response, and mucosal healing after 8 weeks of treatment with ADA(Adalimumab) or IFX(Infliximab) agents. n= no. of patients. $p > 0.05$ means no significant difference (*Mshimesh et al., 2019*).

The 100 ulcerative colitis patients in (*Mohammed et al., 2020*) study, 70% of them received Infliximab, and 30% received Adalimumab. At baseline, 45% of patients had endoscopy subscore 1, after 6 months only 26 (57.8%) remained with the same score, also 18 of them (40%) reduced their score to zero, and only 1 patient had increased to 3. Initially, 55% of patients had endoscopy subscore 2 and 3, after 6 months only 3 of them remained with the same score, the rest of them reduce at least one level.

Table 2: Assessment of the Mayo endoscopic sub-score

Baseline	After 6 months			
	Inactive	**Mild**	**Moderate**	**Severe**
		All patients		
Mild	18 (40%)	26 (57.8%)	0 (0%)	1 (2.2%)
Moderate	15 (60.0%)	8 (32.0%)	2 (8.0%)	0 (0%)
Severe	22 (73.3%)	6 (20.0%)	1 (3.3%)	1 (3.3%)
		Infliximab		
Mild	13 (39.4%)	20 (60.6%)	0 (0%)	0 (0%)
Moderate	12 (60.0%)	7 (35.0%)	1 (5.0%)	0 (0%)
Severe	12 (70.6%)	5 (29.4%)	0 (0%)	0 (0%)
		Adalimumab		
Mild	5 (41.7%)	6 (50.0%)	0 (0%)	1 (8.3%)
Moderate	3 (60.0%)	1 (20.0%)	1 (20.0%)	0 (0%)
Severe	10 (76.9%)	1 (7.7%)	1 (7.7%)	1 (7.7%)

Infliximab showed slightly better conversion from moderate-severe Mayo endoscopic sub-score to mucosal healing, 97.3%, compared with adalimumab (83.3%), however, the difference did not appear to be significant between the two drugs.

An indirect comparison between the main real world studies from the international literature regarding clinical remission and response, as well as colectomy rates, is shown in detail in Table 3.

Author	Reference	Country	Patient with ADA(n)	Clinical remission(%)		Clinical response(%)		Colectomy %
				Short-term	Long-term	Short-term	Long-term	
Mshimesh et al.,	1	Iraq	25	24% Week 8	-	48% Week 8	60.6% Week 24	0%
Zacharias et al.,	2	Brazil	36	41% Week8	47.2% Week 52	55.6% Week 8	61% Week 52	16.7%
Ogata et al.,	5	Japan	1593	49.7% Week 4	74.4% Week 52	18.2% Week 8	53.1% Week 52	0%
Toxonera et al.,	6	Spain	30	10% Week 4	26.7% Week 12	53.3% Week 4	60% Week 12	20%
Angelison et al.,	7	Sweden	118	-	32.2% Week 12	-	72% Week 12	0%
Tusi A. et al.,	10	Italy	107	85.1% Month 3	66.2% Month24	-	-	2.5%
William et al.,	11	USA	494	16.5% Week 8	17.3% Week 52	-	-	-
Abbvie lnc et al.,	13	USA	242	16.5% Week 8	8.5% Week 52	-	-	
Balint et al.,	19	Hungary	73	26% Week 12	58.3% Week 52	49.3% Week 12	33.3% Week 52	5.4%

Table 3. Indirect comparison of remission, response and colectomy rates between the some retrospective studies from different countries sample of patients.

Discussion

Anti-TNF therapy is one of the most effective agents for ulcerative colitis. They are used when the other treatment fails to improve the signs and symptoms of the disease, by blocking the activity of TNF, a substance that causes immune-system diseases and inflammation.

In (*Mohammed et al., 2020*) study, after 6 months of treatment, most ulcerative colitis patients achieved or maintained 95% mucosal healing. Infliximab showed slightly better conversion from moderate-severe Mayo endoscopic sub-score to mucosal healing (MH), 97.3%, compared with adalimumab (83.3%), however, the difference between the two drugs did not appear to be significant.

In (*Zacharias et al., 2017*) study, half of the patients lost clinical response during follow-up, with dose optimization to ADA weekly being required in eight cases. On the other hand, in (*Balint et al., 2016*) observed lower loss of response rates, 9.1% at week 30. Among those who remained in response (34.1%), 8.3% lost response at week 52. The drug was optimized in 17.8% of the cases.

Partial Mayo score information in this research show that the steady state level of response for adalimumab and infliximab had not yet been achieved at the end of week 8, proposing a requirement for a longer period to give the greatest efficacy. Data from open-label and double-blind trials may be required to enhance our comprehension of the time frame for the remitted induction in those with moderate-severe active UC controlled with these agents (*Mshimesh et al., 2019*).

The main adverse events described in the (*Zacharias et al., 2017*) study are detailed in **Table 4**. Most of the adverse events were related to infections. There was no mortality in the present study, and only one patient presented malignancy (a basal cell skin carcinoma), which was locally excised without significant clinical consequences.

Adverse events	Overall (n=36)
Most common infections (n/%)	17 (47.2%)
Urinary tract infection	6 (16.7%)
Sinusitis	5 (13.9%)
Pneumonia	4 (11.1%)
Other infections (n/%)	5 (13.9%)
Herpes zoster	1 (2.8%)
Perianal abscess	1 (2.8%)
Gastroenteritis	1 (2.8%)
Tonsillitis	1 (2.8%)
Parotitis	1 (2.8%)
Local injection reaction (n/%)	2 (3.6%)
Skin reaction (n/%)	3 (8.3%)
Other (basal cell carcinoma)	1 (2.8%)

There is some limitation of the study in Iraq represented in present two studies that found to this studying review, limitations of the *(Mshimesh et al.,2019*) study were its relatively small sample sizes and short-term course. Since ulcerative colitis is uncommon in Iraq compared to the Western nations, it has been hard to select a large sample of patients. Also, the design of this study was restricted by extensive inclusion/exclusion criteria, and some patients were withdrawn from the study by different reasons. Moreover, this research did not assess the adequacy of adalimumab and infliximab in patients who had beforehand gotten other biologic treatments.

In (*Mohammed et al., 2020*) study limitation the small sample size of this study is a potential bias, in addition, the short duration of prospective follow-up (i.e. six months) also limits the number of events observed by the researcher.

Conclusion

Occasionally the adalimumab (ADA) is effective and safe in ulcerative colitis outpatients in real life, including patients with prior exposure to anti-TNFα. As this is a retrospective study, prospective studies are needed to confirm these results that confirmed by these studies around the world. The clinical trial demonstrated that adalimumab (160/80 mg) and infliximab (5 mg/kg) were comparable in their effectiveness for inducing clinical remission and response in patients with moderate-severe ulcerative colitis who inadequately respond or intolerant to traditional management with oral corticosteroids and/or immunosuppressants. Both of the biologic agents were well tolerated, with an approach safety profile.

In this real-world studies, there was no significant difference between the most commonly used anti-TNF medications for the treatment of ulcerative colitis, namely infliximab and adalimumab, in their effect on decreasing relapse rate and mucosal healing after 6 months of follow-up.

Present studies also found that adalimumab (ADA) is effective in reaching the secondary end points. The most important secondary end point was the impressive rate of mucosal healing. This rate was significantly higher than the one reported in both pivotal and real-life studies, which never overcomes 50%. In addition, adalimumab treatment led to long-term response, remission, and mucosal healing.

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