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Clinical and Endoscopic Remission Among patients with Inflammatory Bowel Diseases Treated with Infliximab and Its Biosimilar

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Summary

Background: Inflammatory bowel diseases (IBD) include ulcerative colitis (UC) and Crohn's disease (CD) are chronic, progressive, immunomodulated inflammatory diseases of the gastrointestinal tract. Treatment goals in IBD have evolved greatly.

Aim of the study: to assess clinical and endoscopic remission rates in IBD patients treated with infliximab, infliximab biosimilar for more than 1year and assessing the correlation of scoring systems used to assess clinical remission in association with endoscopic disease activity.

Patients and methods: Observational cross-sectional study involved 50 patients diagnosed with IBD (27 CD,23 UC) who responded to infliximab/ infliximab biosimilar induction therapy and subsequently received scheduled maintenance therapy and adherent to therapy for more than 1year. Ileo-colonoscopy done, endoscopic healing assessed and clinical scoring systems were used to assess correlation to endoscopic activity. Demographic, clinical and treatment variables that may affect the proportion of mucosal healing were selected and assessed if they have significant associations.

Results: The clinical remission rate was 65.2% in UC, 74.1% in CD, endoscopic remission rate was 60.9% in UC, 48.1% in CD. Endoscopic healing with infliximab biosimilar was higher in CD, than those treated with infliximab (85.5% vs. 25%) with statistical significance. Endoscopic remission rates were higher in old, male, shorter treatment durations and concomitant use of azathioprine.

Conclusions: Long-term remission can be achieved by treatment with infliximab and its biosimilar, especially UC. Clinical scoring systems in UC are well correlated with endoscopic activity, while clinical indices in CD are poorly correlated. Loss of response to infliximab was higher in young, female and longer duration of treatment.

EDN: OZLOKW

Keywords: Inflammatory bowel diseases, Crohn's disease, Infliximab, Biosimilar, Ulcerative colitis

Conflict of interests. The authors declare no conflict of interest.

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Клиническая и эндоскопическая ремиссия у пациентов с воспалительными заболеваниями кишечника, получавших инфликсимаб и его биоаналог

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Резюме

Актуальность. Воспалительные заболевания кишечника (ВЗК), включая язвенный колит (ЯК) и болезнь Крона (БК), представляют собой хронические, прогрессирующие, иммуномодулированные воспалительные заболевания желудочно-кишечного тракта. Подходы к лечению ВЗК значительно эволюционировали, и целью терапии стало достижение стойкой клинико-эндоскопической ремиссии.

Цель исследования: оценить частоту достижения клинической и эндоскопической ремиссии у пациентов с ВЗК, получавших инфликсимаб и его биоаналог в течение более одного года, а также проанализировать взаимосвязь между клиническими шкалами оценки ремиссии и активностью заболевания по данным эндоскопии.

Материалы и методы. Обсервационное поперечное исследование включало 50 пациентов с подтверждённым диагнозом ВЗК (27 – с болезнью Крона, 23 – с язвенным колитом), ответивших на индукционную терапию инфликсимабом или его биоаналогом и получавших плановое поддерживающее лечение на протяжении более одного года. Всем пациентам проведена илеоколоноскопия с оценкой эндоскопического заживления слизистой оболочки; также использовались клинические шкалы для сопоставления с эндоскопической активностью. Были проанализированы демографические, клинические и терапевтические факторы, которые могут влиять на частоту мукозального заживления.

Результаты. Клиническая ремиссия достигнута у 65,2% пациентов с ЯК и у 74,1% с БК; эндоскопическая ремиссия – у 60,9% пациентов с ЯК и 48,1% с БК. Частота эндоскопического заживления слизистой была выше у пациентов с БК, получавших биоаналог инфликсимаба, по сравнению с оригинальным препаратом (85,5% против 25%; $p<0,05$). Более высокие показатели эндоскопической ремиссии наблюдались у пожилых мужчин с меньшей продолжительностью терапии и при сопутствующем приёме азатиоприна.

Выводы. Длительная ремиссия может быть достигнута как при использовании оригинального инфликсимаба, так и его биоаналога, особенно у пациентов с язвенным колитом. Клинические шкалы при ЯК хорошо коррелируют с эндоскопической активностью заболевания, тогда как при БК такая корреляция выражена слабо. Утрата ответа на инфликсимаб чаще наблюдается у молодых женщин и при более длительной терапии.

Ключевые слова: воспалительные заболевания кишечника, болезнь Крона, инфликсимаб, биоаналог, язвенный колит

Конфликт интересов. Авторы заявляют об отсутствии конфликта интересов.

Introduction

Inflammatory bowel diseases (IBD) are chronic, progressive, immune-mediated inflammatory diseases of the gastrointestinal tract. Crohn's disease (CD) and ulcerative colitis (UC) are the two major forms of IBD. Numerous clinical and epidemiologic traits are shared by both, indicating that comparable underlying causes may exist. About 10% of cases lack sufficient clinical evidence to differentiate CD from UC, despite the fact that both conditions are typically regarded as unique syndromes with different prognosis and courses of treatment [1].

Although a diagnosis of IBD can be made at any age, it is most frequently made in early adulthood and adolescence. IBD cannot be diagnosed based on a single symptom, indicator, or diagnostic test. A thorough evaluation of the clinical presentation is used to establish the diagnosis, and pathologic, radiologic, and endoscopic findings are used as supporting evidence. Crohn's disease (CD) is a chronic inflammatory disorder that may include any region of the alimentary tract from the mouth to the anus, but with a tendency for the distal small intestine and proximal colon. On the other hand, UC solely impacts the colon and the rectum. The way that CD and UC express themselves might vary greatly and be rather subtle. The location of the illness, the degree of inflammation, and the existence of particular intestinal and extra-intestinal problems are some of the variables influencing this variability [2].

The objectives of IBD treatment have changed significantly over the past few decades. Instead of concentrating just on the clinical response, there is now a greater emphasis on improving outcomes related to mucosal lesion repair and looking beyond symptoms. Under these circumstances, managing inflammatory bowel disease (IBD) is difficult, with high expectations for both patients and physicians.

Treat to target approach:

Preventing unfavorable long-term outcomes requires early therapy utilizing a treat-to-target (T2T) method, which entails identifying a predetermined objective, followed by optimization of therapy and frequent monitoring until the goal is achieved. As a result, doctors and patients should talk about these goals and try to reach them by implementing therapeutic adjustments within specific time frames ideally by adhering to therapeutic algorithms. This method has been applied to numerous medical specialties where treatment goals are established to enhance patient outcomes and lower the chance of end-organ damage.

Role of Biological Therapy in IBD

The treatment of IBD involves the use of corticosteroids, immunomodulators, and amino salicylate (5-ASA). But the biological therapy revolution altered the manner that IBD was treated.

The discovery of biological therapy has significantly advanced our knowledge of and ability to treat IBD. The FDA authorized Infliximab as the first biologic agent for treatment of IBD in 1998. Since then, biological treatments for the treatment of IBD have continued to progress, and many drugs are presently undergoing clinical trials [3]. As of right now, anti-TNF α medications (Infliximab, Adalimumab, Certolizumab pegol, and Golimumab), anti-integrin medications (Vedolizumab and Natalizumab), and anti-IL-12/23 p40 subunit medications (Ustekinumab) are the available biologic medicines for usage in IBD [4].

Anti-TNF therapy

One important proinflammatory cytokine that has been shown to contribute to a number of disease conditions, including IBD is TNF. Patients with CD and UC have been reported to have inflammatory intestines with elevated TNF concentrations, and it has been demonstrated that the clinical disease activity of IBD patients is correlated with TNF concentrations in their mucosa and stool [5].

With a quick start of action and the ability to change the disease, infliximab (Remicade®) is a chimeric monoclonal antibody that targets tumor necrosis factor (TNF)-α and has demonstrated effectiveness in treating ulcerative colitis and Crohn's disease. Intravenous infusions are often given on a schedule that includes initial infusions at 0, 2, and 6 weeks, with subsequent delivery occurring once every 8 weeks. According to available evidence, infliximab may be economical, particularly when considering long-term clinical outcomes and the burden of the diseases [6].

Biosimilars are biologic medicines that, in terms of safety, purity, and efficacy, are very similar to an originator biologic therapy that has already received approval. Global regulatory bodies are increasingly approving these drugs in an effort to lower treatment expenses.

The European Medicines Agency and the Food and Drug Administration approved CT-P13 (Remsima™) in 2013 for the treatment of CD [7]. Remsima shares the same molecular similarities as the original Infliximab and exhibits the same affinity for Fcγ receptors as well as monomeric and trimeric forms of TNF-α. The Mayo score and Crohn's disease activity index (CDAI) significantly decreased, and both UC and CD patients' CRP levels significantly decreased throughout therapy, according to research on the effectiveness and safety of CT-P13 for the induction of remission and maintenance of remission in UC and CD [8].

Aim of the Study

Is to assess the clinical and endoscopic remission rates of patients with IBD treated with Infliximab, Infliximab biosimilar for more than 1 year, in addition assessing the correlation of scoring systems used to assess clinical remission in association with those assessing endoscopic disease activity and predict the factors that may affect long-term endoscopic remission rates.

Patients and Methods

Study design and population

This is an observational cross-sectional, prospective single center study was conducted in the hospital of gastroenterology & Hepatology, Teaching and Clinical Centre, Baghdad, Iraq, between July 2020 and June 2021.

50 patients diagnosed with IBD (27 CD and 23 UC) were included in this study who responded to infliximab/ infliximab biosimilar (IFX-B) induction therapy and subsequently received scheduled maintenance therapy and adherent to treatment for more than 1 year (54 weeks and more) in the period between July 2015 and June 2021. Initiation of IFX/IFX-B was indicated if they had moderate to severe disease, had not responded to a full and adequate course of corticosteroid and/or immunosuppressant therapy, were intolerant to or had medical contraindications to such medications, and history of segmental bowel resection with high risk of recurrence or Rutgeerts score >= i1. This study was approved by the scientific council of Gastroenterology & Hepatology research committee guidelines and Basrah college of medicine ethical committee. Study was done in the period between July 2020 and June 2021.Informed written consents were taken from the patients.

Data collection

Demographic and clinical characteristics of the patients were recorded by means of direct questioning of patients at the outpatient visit for receiving IFX/ IFX-B. Age, Sex, gender, body weight, type of disease, disease duration, duration of biological therapy and adherence, clinical symptoms, steroids free period, concomitant therapy (5-ASA, Immunomodulators) were recorded. 23 patients of CD and 22 patients in UC were on Azathioprine (50 mg or 100 mg) while 13 patients of UC and 3 patients of CD were on Mesalamine. In CD, 20 patients on IFX and 7 patients on IFX-B, while in UC, 18 patients on IFX and 5 patients on IFX-B. Dose optimization considered if shortening of duration or on increment of the dose was done.

All ileo-colonoscopies were performed by gastroenterologists of this hospital using Olympus® and Pentax® endoscopes (Tokyo, Japan). Endoscopies considered eligible for inclusion if it were done within 3 months of clinical data collection.

Exclusion criteria

Patients were excluded from this study if they were less than 15 years old, primary non responders, gastroduodenal CD, proximal disease location, indeterminate IBD, had started anti-TNF therapy after July 2020, non-adherent to anti-TNF therapy, patients switched to another class of biological agents, admitted to hospital due to acute flares within the last 6 months, patients who developed serious side effects and discontinue therapy, those who refused endoscopic assessment, or having severe chronic comorbid illnesses (cardiac, renal, hepatic, neurologic disorders and malignancies).

Definitions and outcomes

Therapeutic outcomes of interest are clinical and endoscopic remission as targets of therapy and secondary loss of response to IFX.

Long term remission was defined as endoscopic healing after 1 year (54 weeks and more) of treatment with IFX/IFX-B.

Clinical assessment in UC:

The clinical assessment included evaluation of stool frequency (SF), rectal bleeding (RB) and physician's global assessment using Mayo Partial score (pMS). Patient considered in clinical remission if his/her Mayo partial score ≤1; if not have rectal bleeding. The physician's global assessment included the combination of the following three clinical features: normalization of bowel frequency, absence of blood with defecation, and the tapering of corticosteroids to zero.

The extent of disease was categorized using the Montreal classification [9]. E1 for proctitis, E2 for any extent beyond the rectosigmoid junction and does not cross splenic flexure, and E3 as any extension after splenic flexure.

Endoscopic activity assessed using Mayo Endoscopic Subscore (MES). Mucosal healing was defined as a mucosa subscore of ≤1. Active disease considered >1, as showed in table below:

Endoscopic scoring system for ulcerative colitis

Score 0	Normal or inactive colitis
Score 1	Mild disease(erythema, decreased vascular pattern, mild friability)
Score 2	Moderate disease(Marked erythema, absent vascular pattern, friability, erosions)
Score 3	Severe disease(spontaneous bleeding, ulceration)

VARIABLE	
Age of diagnosis (yr)	A1, ≤16
	A2, 17–39
	A3, ≥40
Location	L1, ileal
	L2, colonic
	L3, ileocolonoc
	L4, isolated upper disease[a]
Behavior	B1, non-stricturing, non-penetrating
	B2, stricturing
	B3, penetrating
	p, perianal disease modifier[b]

[a] L4 is a modifier that can be added to L1–L3 when concomitant upper gastrointestinal disease is present.
[b] p is added to B1–B3 when concomitant perianal disease is present.

Clinical assessment in CD:

Location of the disease, behavior and perianal disease involvement were categorized using Montreal classification for CD, as shown below [10].

The clinical assessment of CD patients was done using both Crohn's disease severity index (CDAI).CDAI remission is defined as score <150, mild disease as 150–220, moderate as 220–450, and severe if > 450, as shown in table below:

Clinical or laboratory variables
Number of liquid or soft stools each day for 7 days
Abdominal pain(graded from 0 to 3 based on severity) each day for 7 days
General wellbeing, subjectively assessed from 0(well) to 4(terrible) each day for 7 days
Complications*
Use of diphenoxylate or opiates for diarrhea
An abdominal mass (0 for none, 2 for questionable, 5 for definite)
Absolute deviation of haematocrit from 47% in men and 42% in women
Percentage deviation from normal weight

All patients subjected to endoscopy were graded using the Simple Endoscopic Score for Crohn's Disease (SES-CD) [11]. Mucosal healing (MH) is considered if SES-CD score ≤ 2 or if 'absence of ulcerations' or 'clear improvement of ulcerations compared to baseline endoscopy, as shown in table below:

Variable	Simple endoscopic score			
	0	1	2	3
Size of ulcers	None	Aphthous ulcers	Large ulcers	Very large ulcers
Ulcerated surface	None	<10%	10–30%	>30%
Affected surface	Unaffected segment	<50%	50–75%	>75%
Presence of narrowing	None	Single, scope passable	Multiple, scope passable	Scope impassable

Materials and method

We classified patients according to type of IBD (CD and UC), and further subdividing these categories according to the remission status depending on achievement of the clinical and endoscopic targets or not. We used clinical scoring systems (CDAI and pMS) to assess for clinical remission and SES-CD score and MES to assess for endoscopic healing. we correlate clinical to the endoscopic results and assess their reliability as markers of endoscopic remission.

Multiple demographic, clinical and treatment variables studied if may affect the proportion of mucosal healing and assessed if they have significant associations. These variables include Age, gender, disease duration, extent (UC), location, behavior, perianal disease (CD), treatment duration, concomitant therapy with Azathioprine and 5-ASA, type of biological agent (originator vs. biosimilar), and history of previous segmental bowel resection.

The terms (endoscopic healing), (endoscopic remission), and (mucosal healing) will be used interchangeably during this study.

Statistical analysis:

Data input, tabulation, handling and analysis was done using IBM® SPSS® version 23. Chi-square test and Fisher's Exact test were used for assessing the association between categorical data when applicable. Independent Samples T- test was used for assessing the difference in mean between two normally distributed data, and Mann Whitney U test was used assessing the difference in ranks between two variables that did not follow the normal distribution test. P- values of less or equal to 0.05 were considered significant throughout the results, Cohen's kappa (κ) calculates inter-observer agreement was used to test the agreement between the two methods of assessment, Value of κ Strength of agreement: < 0.20= Poor, 0.21–0.40= Fair, 0.41–0.60= Moderate, 0.61–0.80=Good, and 0.81–1.00= Very good.

Results

During the study period, a total of 50 patients were enrolled, 23 (46%) of them had UC, and 27 (54%) had CD. The demographic data revealed that mean age of the total sample was 32.8±12.2 years, with equal gender distribution. The mean UC disease duration was 98.1±56.1 months, while it was 70.7± 41.6 months in patients with CD, and the treatment duration was 48.8± 23.9 months in patients with UC, and 46.4±20.5 months in patients with CD. 51.9% of cases with CD were located at ileum, and 40.7% behaved as non-stricturing, non-penetrating, while 47.8% of cases with UC were extensive (proximal to splenic flexure).Azathioprine use was almost 10% higher in UC (95.7%) compared to CD (85.2%), while 5-ASA use was much more in UC (56.5%) compared to CD (11.1%). Infliximab was used for 18(78.3%) patients with UC and 20 (74.1%) patients with CD, while Remsima was used for 5(21.7%) patients with UC and 7(25.9%) patients with CD (*Table 1 and 2*).

Table 1. Demographic and clinical characteristics of the study population

Variables			UC	CD
Age (yrs.)[1]			33.1± 12.8	32.6±11.9
Gender	Male N(%)		13 (56.5)	12(44.4)
	Female N(%)		10(43.5)	15(55.6)
Disease duration (months)			98.1±56.1	70.7± 41.6
Treatment duration (months)			48.8± 23.9	46.4±20.5
Median age at diagnosis (yrs.)[1]			23.0	26.0
Extent		E1	3(13.0)	N/A
		E2	9(39.1)	N/A
		E3	11(47.8)	N/A
Location		L1	N/A	14(51.9)
		L2	N/A	5(18.5)
		L3	N/A	8(29.6)
Behavior		B1	N/A	11(40.7)
		B2	N/A	9(33.3)
		B3	N/A	7(25.9)
Perianal disease			N/A	8(29.6)
Concomitant therapy		Azathioprine	22(95.7)	23(85.2)
		5-ASA	13 (56.5)	3(11.1)
Anti TNF agents		Infliximab	18(78.3)	20(74.1)
		Remsima	5(21.7)	7(25.9)
Previous surgery			N/A	8(29.6)

Table 2. Disease activity indices in patients with UC and CD

Disease activity		UC[a]	CD[b]
Remission	Clinical	15(65.2)	20(74.1)
	Endoscopic	6 (26)	13(48.1)
Mild	Clinical	4(17.4)	4(14.8)
	Endoscopic[c]	8(34.8)	7(25.9)
Moderate	Clinical	4(17.4)	3(11.1)
	Endoscopic	6(26)	5(18.5)
Severe	Clinical	0	0
	Endoscopic	3(13.0)	2(7.4)

Note: [a] pMS for clinical remission and MES for endoscopic remission.[b]CDAI for clinical remission, SES-CD for endoscopic remission.[c] Mild MES score considered endoscopic remission.

Figure 1.
Distribution of patients according to clinical & endoscopic remission.

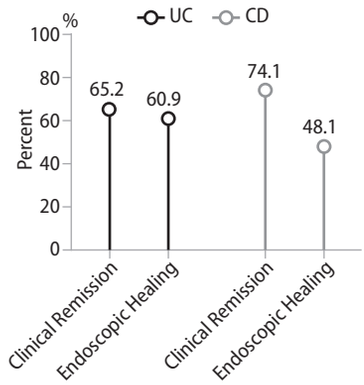
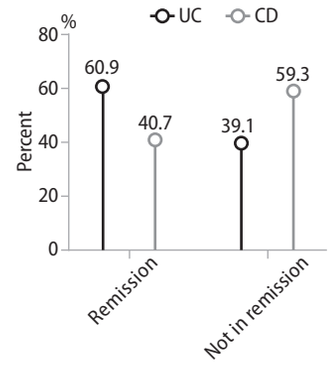


Figure 2.
Distribution of patients according to complete remission (clinical and endoscopic remission)



The clinical remission rate was 65.2% in cases with UC and 74.1% in cases with CD, while the endoscopic remission rate was 60.9% in cases with UC and 48.1% in cases with CD, as shown in (*Figure 1*).

Complete remission (combined clinical and endoscopic) rates were 60.9% in UC and 40.7% in CD (*Figure 2*).

There were no statistically significant differences between cases with endoscopic remission in UC versus non-remission regarding the mean age (35.4± 14.6 years compared to 29.7± 9.1 years, p-value=0.66), mean disease duration (112.3±65.8 months compared to 76.0±26.8 months, p-value=0.09) and mean treatment duration (47.4± 24.4 months compared to 51± months, p-value=0.11).Regarding sex in UC patients, there was no statistical significance between male and females in remission (5(38.5) for males in remission compared to 4(40) for females in remission, p-value=0.07). In addition, in CD cases with remission compared to no remission, there was no statistically significant differences regarding mean age (33.4±11.3 months compared to 32.1±12.7 months, p-value= 0.1), mean disease duration (78 ± 55.2 months compared to 66 ± 31.2 months, p-value=0.09) and mean treatment duration (40.7±21.4 months compared to 50.4±19.5 months, p-value=0.08). Regarding sex in CD patients, there was also no statistical significance association between male and females in remission (6(50) for males in remission compared to 5(33.3) for females in remission, p-value=0.06), also this study showed that there was lower rate of remission in younger age group, longer treatment duration and female patients (*Table 3*).

Remission in patients on azathioprine was 63.6% in UC and 43.5% in CD, while the remission in patients on 5-ASA was 61.5% in UC and zero in CD. Remsima was significantly associated with higher remission rate (85.7%) compared to infliximab (25%) in patients with CD (p= 0.005), while in UC, infliximab showed better remission compared to Remsima (66.7% compared to 40%, respectively) and this was statistically significant (p-value=0.02), however, Remsima was more recently introduced to patients with IBD compared to infliximab with shorter durations of treatment. Dose optimization (increasing the dose or shortening the duration) did not seem to affect remission rates neither in UC nor CD. (*Table 4 and figure 3*).

Table 3.
Distribution of basic/clinical characteristics according to remission in UC and CD

Variables		Remission					
		UC			CD		
		Yes	No	P-value	Yes	No	p-value
Mean Age(years)		35.4± 14.6	29.7± 9.1	0.66	33.4±11.3	32.1±12.7	0.1
Sex	Male N(%)	5(38.5)	8(61.5)	0.07	6(50)	6(50)	0.06
	Female N(%)	4(40)	6(60)		5(33.3)	10(66.7)	
Disease duration(months)		112.3±65.8	76.0±26.8	0.09	78 ± 55.2	66 ± 31.2	0.09
Treatment duration (months)		47.4± 24.4	51± 24.3	0.11	40.7±21.4	50.4±19.5	0.08

Table 4.
Distribution of medication efficacy in maintaining endoscopic remission in cases with UC and CD.

Note:
*P-value=0.02,**P-value=0.005

Variables		Remission			
		UC		CD	
		Yes	No	Yes	No
Azathioprine		14(63.6)	8(36.4)	10(43.5)	13(56.5)
5-ASA		8(61.5)	5(38.5)	0	3(100.0)
Corticosteroids free period	≤ 1 year	5 (55.6)	4(44.4)	3(60.0)	2(40.0)
	> 1 year	6(66.7)	3(33.3)	5(31.3)	11(68.8)
Anti TNF agents	Infliximab	12(66.7)*	6(33.3)	5(25.0)	15(75.0)
	Remsima	2(40.0)	3(60.0)	6(85.7)**	1(14.3)
Dose optimization	Yes	1(50.0)	1(50.0)	3(37.5)	5(62.5)
	No	13(61.9)	6(38.1)	8(42.1)	11(57.9)

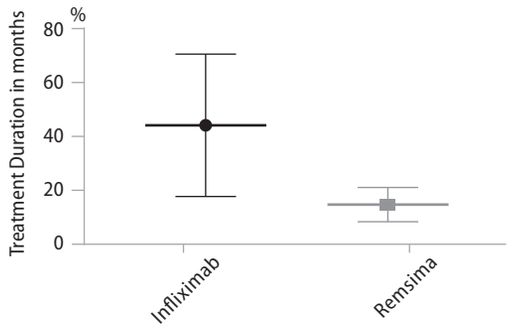


Figure 3. Distribution of treatment duration in months according to IFX/IFX-B in Crohn's disease.

The disease location showed no statistically significant influence on endoscopic healing (EH) in CD, however, remission was higher in ileal (50%), than colonic (40%), and the colonic was better than ileocolonic (25%).The extension of UC did not affect the remission rates as was seen in 66.7% E1 or E2, and 54.5% E3 which is statistically insignificant (p-value=0.846) (*Table 5*).

When studying remission according to Montreal classification, & bowel resection in CD, this study showed that disease in L1 and L2 classes are equal in remission rate, while those patients with L3 class showed lower remission rate (25% compared to 75% non-remission) with no statistical significance regarding disease location (p-value=0.597) rate was 63.6% in non stricturing, non-penetrating CD (B1), 22.2% in stricturing (B2), and 28.6% in penetrating behavior (B3), with no significant association between them (p-value= 0.178), endoscopic remission rate was lower in CD patients with Perianal disease (37.5%), while it is equally distributed in patients with history of segmental bowel resection (*Table 6*).

Table 5. Distribution of EH according to Extension in UC.

Note: *: Fisher's Exact Test, E1: proctitis, E2: beyond rectosigmoid, E3: proximal to splenic flexure

Variables		Remission			
		Yes	No	Total	P-value
Extension	E1	2(66.7)	1(33.3)	3(13.0)	0.847*
	E2	6(66.7)	3(33.3)	9(39.1)	
	E3	6(54.5)	5(45.5)	11(47.8)	
Total		14(60.9)	9(39.1)	23(100)	

Table 6. Distribution of remission according to Montreal classification, & bowel resection in CD

Note: *: Fisher's Exact Test

Variables		Remission			
		Yes	No	Total	P-value
Location	L1	7(50)	7(50)	14(51.9)	0.597*
	L2	2(40)	3(60)	5(18.5)	
	L3	2(25)	6(75)	8(29.6)	
Behavior	B1	7(63.6)	4(36.4)	11(40.7)	0.178*
	B2	2(22.2)	7(77.8)	9(33.3)	
	B3	2(28.6)	5(71.4)	7(25.9)	
Perianal		3(37.5)	5(62.5)	8(29.6)	-
Segmental bowel resection		4(50%)	4(50%)	8(29.6)	-

Discussion

Clinical disease indices have long served as primary endpoints in research studies. However, mucosal healing offers an exciting possibility for gastroenterologists to predict future risk of endoscopic activity, clinical symptoms, and long-term outcomes. Mucosal healing (MH) in patients with IBD is an important treatment goal, leading to better long-term remission rates, better quality of life, lower need for hospitalization and surgeries, and lower rates of colorectal cancer [12].

Despite the large number of studies discussing clinical and endoscopic remission in inducing and maintaining mucosal healing up to 54 weeks, there is scarce data for maintenance remission for periods more than 12 months.

In this study, the mean age showed no significant statistical difference between the study groups, but remission was lower in younger age group (29.7 vs. 35.4y in UC and 32.1 vs. 33.4 in CD). these results are comparable to an Asian study done by Tia et al(2006) [13], which found that young patients underwent a more aggressive clinical course. Gender variation showed that male population had slightly higher rates of remission in comparison with female population (61.5% vs 60% for UC and 50% vs. 33% for CD), although statistically insignificant, which could be contributed to selection bias.

Treatment duration of biological therapy showed no significant statistical significance but disease

activity was higher in longer duration of treatment (51 months vs 47.4 months in UC, 50.4 months vs 40.7 months in CD). These results are consistent with a study done by Ma, Christopher, et al (2015) [14], which showed 59.1% of infliximab-treated patients experienced a secondary loss of response after 1 year of maintenance therapy. These outcomes support the data and many observational cohort studies which confirmed the efficacy of infliximab maintenance with an estimated 10% to 15% loss of response annually [15]. This study found that 61% of UC patients achieved MH versus 48% of CD patients. These results are incomparable with a study done by Farkas et al (2014) [16], in which mucosal healing was observed in 56% and 32% of CD and UC patients, respectively. These differences may be attributed to selection bias and study design.

This study also found that 93% of patients with UC who have mucosal healing achieved clinical remission using pMS. These results are consistent with the large meta-analysis study done by Turner, Dan, et al (2021) [17] which concluded that complete clinical remission using pMS is associated with EH or near EH (Mayo Endoscopic Subscore [MES] of 0 or 1 respectively) in approximately 80% to 90% of patients. While in CD patients, only 65% who had endoscopic healing achieved clinical remission with CDAI. These results are parallel with the study done by Peyrin-Biroulet, Laurent. et al(2014) [18] which showed that only 53% of patients in clinical remission displayed EH. This confirms the growing evidence that clinical indices, including CDAI, have been shown to be relatively poor markers of endoscopic inflammation in CD. The limitations of CDAI as a marker of intestinal inflammation in CD are highlighted by a study in which CDAI scores were similarly elevated in CD and IBS cohorts [19].

Concomitant use of azathioprine showed higher rates of remission in UC patients (63.6% vs. 36.4), although statistically insignificant. These results supported by the Italian study done by Panaccione R, et al [20], which found that patients receiving combination therapy had higher rates of steroid-free remission (40%) compared with those receiving monotherapy (22% for infliximab alone). Rates of mucosal healing were also significantly higher in the combination group.

While in CD patients, concomitant therapy with azathioprine showed lower remission rates (43.5% vs. 56%). These results are inconsistent with a comparable study done by Colombel JF et al [21], which revealed that combination therapy was more effective than others in inducing MH, achieving it in 44% of patients at maintenance phase, compared to 30% of patients treated with only IFX.

The study results also found that UC patients with concomitant use of 5- ASA has no significant statistical difference related endoscopic remission. These results are consistent with a large study done by Singh R, et al(2018) [22], which concluded that concomitant use of 5-ASA was not associated with odds of achieving clinical remission, clinical response or mucosal healing. Also, most patients who are taking 5-ASA therapy are already on AZA therapy, which makes statistical analysis inconvenient.

While in CD, patients who receive 5-ASA showed no benefit of remission (100%). Although sample size is small in this study (3 patients), these results confirm the solid evidence in the last years about the role of 5-ASA in CD patients, where mesalamine-based products have been excluded from recent evidence-based treatment algorithms as maintenance therapy [23].

CD patients who are treated with IFX-B (Remsima) had higher rate of EH than those who are treated with IFX (85.5% vs. 25% in CD) with significant statistical difference. These findings mostly attributed to the length of duration of treatment for patients who are treated with IFX, as our study shown that patients with longer duration of treatment are more likely to develop loss of response. On further reviewing our data, we found that only 30% of CD patients who are treated with Infliximab had dose optimization, which could be elicited as another cause for this variability in remission rates.

In UC patients, only 2 patients treated with IFX-B (versus 12 treated with IFX) showed remission, while 3 patients (vs. 11) have endoscopic disease activity. These variabilities in sample size makes assessing these results statistically unfeasible.

Our study did not elicit a significant statistical difference for patients with dose intensification for both CD and UC regarding endoscopic healing. These results are inconsistent with the study done by Taxonera, Carlos, et al (2015) [24] which showed 70% of patients with UC recaptured remission after dose intensification. This discrepancy may be contributed to difference in sample size, study designs and number of centers included in these studies.

Disease behavior, location, history of bowel segmental resection in CD patients did not show any statistical significance in remission rates. These results were inconsistent with a Belgian study done by billet et. Al(2016) [25] which showed ileal (L1), penetrating (B3) CD carries a higher rate of IFX treatment failure.

The limitations in this study can be summarized by being it is a single center study with a limited sample size.

mucosal healing cannot be assessed precisely because of the availabilities of different therapies that affect mucosal healing in IBD, beside the effect size of different therapies is difficult to assess because of different definitions of mucosal healing, different study designs, and different timing of endoscopic evaluation.

Although endoscopic healing became widely needed as an endpoint of long-term remission, colonoscopy is still an invasive procedure and has a low acceptance rate in asymptomatic IBD patients. Also, there were limited data about the clinical and endoscopic scores for patients at time of diagnosis and induction of biologic agents, which makes assessing clinical response inapplicable.

Unavailability of IFX drug level and drug anti-body levels make identifying the causes of loss of response to anti-TNF therapy a matter of challenge.

Conclusions

Results in this study supports the growing evidence that scheduled IFX treatment has proven to be an effective strategy in IBD patients for long-term remission especially in UC patients. This study also confirmed that clinical scoring systems in UC are well correlated with the endoscopic degree of inflammation, while poorly correlated in CD. Our study also founded that remission rates were lower in younger age group, female gender, longer duration of treatment, although statistically insignificant.

DECLARATIONS:

Ethics approval and consent to participate statement: The study was approved by the Ethics Committee of the Arab scientific council of Gastroenterology & Hepatology for researches and committee guidelines, Baghdad, Iraq and Basrah college of medicine ethical committee, verbal and written informed consent had been taken from the patients enrolled in the study and in order to support privacy and confidentiality, I concealed the unique identifying information of people in the data gathering.

Consent to publication: Written informed consent had been taken from participants

Availability of data and material: the datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

COMPETING INTERESTS: Authors have declared that no competing interests exist.

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Authors' contributions: the three authors contributed to the design and implementation of the research, to the analysis of the results and the writing of the manuscript.

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