Effectiveness comparison between ustekinumab and infliximab for Crohn's disease complicated with intestinal stenosis: a multicenter real-world study

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Abstract

Background: The efficacy of ustekinumab (UST) and infliximab (IFX) in Crohn's disease (CD) patients with intestinal stenosis remains uncertain.

Objective: This study aims to compare the efficacy of UST and IFX in the treatment of CD patients with intestinal stenosis.

Design: This was a retrospective and multicenter cohort study.

Methods: In this retrospective study, we included CD patients treated with IFX or UST at five centers. We assessed the clinical response rate at weeks 12 and 24, steroid-free clinical remission rate at weeks 24 and 52 for overall patients and those with stenosis, and objective examination (intestinal ultrasound and/or endoscopy) response rate at week 52 for stenosis patients.

Results: A total of 211 CD patients (106 IFX and 105 UST) were included, with 119 (56 IFX and 63 UST) having intestinal stenosis. In the overall patient population, there were no significant differences in clinical response rate and steroid-free clinical remission rate at weeks 12, 24, and 52 between the IFX and UST groups. In patients with stenosis, the steroid-free clinical remission rate at week 52 was significantly lower in the IFX group compared to the UST group (51.79% IFX vs 69.84% UST, $p = 0.044$). The objective examination response rate did not significantly differ between the IFX and UST groups at week 52 (66.67% IFX vs 76.19% UST, $p = 0.690$). In the UST group, steroid-free clinical remission rate was higher in bio-naïve patients than bio-experienced patients at week 24 (75.00% bio-naïve vs 55.38% bio-experienced, $p = 0.043$).

Conclusion: UST may be considered a more advantageous treatment option for those CD patients with intestinal stenosis, as it has better steroid-free clinical remission rates compared to IFX.

Keywords: Crohn's disease, infliximab, stenosis, ustekinumab

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Introduction

Crohn's disease (CD) is a chronic, recurrent inflammatory bowel disease (IBD) characterized by inflammation of the gastrointestinal tract.[1] While the incidence of CD remains stable in the West, it is on the rise in newly industrialized countries.[2,3] Inflammation is the primary manifestation of CD at diagnosis, often leading to complications such as stenosis and fistulas.[4] Studies indicate that complications arise in

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approximately 48%–52% of cases within 5 years of diagnosis and 69%–70% within 10 years, with around half of these cases involving stenosis.[5,6] Moreover, 70%–80% of CD patients require intestinal surgery within 20 years of diagnosis,[7] and some may undergo multiple surgeries due to intestinal stenosis. These complications significantly impact the quality of life and prognosis of CD patients while also increasing their medical burden.[8,9]

Histologically, intestinal stenosis in patients with CD is characterized by a combination of fibrosis and inflammation, involving both fibrotic and inflammatory components.[10] Currently, surgical intervention stands as the primary treatment for CD complicated by intestinal stenosis, given the absence of specific drugs tailored for this condition. However, certain medications have demonstrated efficacy in treating inflammatory intestinal stenosis, depending on their respective mechanisms.[11] Both with and without stenosis, effective biologics for CD patients include anti-tumor necrosis factor-α (anti-TNF-α) such as infliximab (IFX) and anti-interleukin-12/interleukin-23 (anti-IL12/IL23) like ustekinumab (UST).[12]

TNF can stimulate fibroblast proliferation and regulate chemotaxis, resulting in increased fibrogenesis. Animal studies have demonstrated that anti-TNF significantly reduces renal fibrosis.[13] A retrospective clinical study suggests the potential effectiveness of IFX in CD patients with intestinal stenosis.[14] However, caution has been advised against using IFX in CD patients with stenosis, as it may exacerbate symptoms.[15,16] Controversy has arisen in the past regarding the use of IFX in CD patients with stenosis, although current data substantiate its use in this patient population. However, conducting a real-world study on the use of IFX in CD patients with stenosis is still crucial.

ILs play a vital role in mediating various biological reactions in cells and tissues, particularly cell growth, differentiation, and activation during inflammation. Different ILs exert different effects, including an impact on fibrosis.[17] Animal models have indicated that anti-IL12 can alleviate pulmonary fibrosis in mice.[18] Clinical trials have demonstrated that UST can reduce hepatic fibrosis in primary biliary cirrhosis.[19] However, there is a lack of research on the efficacy of UST in CD patients with intestinal stenosis.[8]

Considering the mechanisms of action of anti-TNF and anti-IL12/IL23, both IFX and UST show potential for treating CD patients with intestinal stenosis. However, for CD patients with intestinal stenosis, IFX remains the preferred treatment option owing to the uncertain real-world effectiveness of UST in this specific population. Therefore, this study aims to compare the clinical effectiveness of UST and IFX in CD patients with intestinal stenosis through a multicenter retrospective real-world cohort study.

Materials and methods

Patient population

In this retrospective study, patients diagnosed with CD who underwent treatment with IFX or UST were enrolled from five distinguished IBD centers: Peking Union Medical College Hospital, West China Hospital of Sichuan University, The Second Hospital of Hebei Medical University, The Affiliated Hospital of Qingdao University, and Zhongshan Hospital of Xiamen University. The study spanned from January 2018 to February 2023. The reporting of this study conforms to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement.[20]

Inclusion criteria were as follows: (1) patients diagnosed with active CD according to the current guidelines, with a Crohn's disease activity index (CDAI) score >150.[21,22] (2) Patients who received IFX or UST during the study. (3) Stenosis areas include anastomotic stenosis, small intestinal stenosis, and colonic stenosis, regardless of whether fistulas are present or not. (4) Patients aged ⩾ 16 years.

Exclusion criteria were as follows: (1) Prior exposure to IFX in the IFX group. (2) Prior exposure to UST in the UST group. (3) Patients with insufficient clinical data for evaluating the effectiveness at 12 ± 2, 24 ± 4, and 52 ± 8 weeks.

Intestinal stenosis definition was as follows: (1) The intestinal ultrasound (IUS)/CT examination reveals a bowel wall thickness (BWT) exceeding 3 mm. (2) The IUS/CT revealed that pre-stricture dilation refers to a luminal diameter larger than 3 cm. (3) The IUS/CT examination indicates a reduction in the lumen diameter of at least 50% at the site where stenosis occurs.[23] (4)

Endoscopic stenosis was defined as intestinal stenosis of at least 1 score (SES-CD).

Data collection

Data retrieval was performed in each center by two physicians. The Electronic Medical Record System of each center was used to collect the data. In cases where key data with incomplete information were found in the Electronic Medical Record System, the patients were contacted by telephone for collection. Data were collected at baseline (week 0), as well as at weeks 12, 24, and 52. If no records were available at these time points, the closest medical records within the specified ranges (weeks 12 ± 2, 24 ± 4, 52 ± 8) were utilized. The following data were collected: age, sex, body mass index (BMI), current smoking and drinking, medication history, prior surgery history, disease duration, Montreal classification, CDAI score, C-reactive protein (CRP) levels, erythrocyte sedimentation rate (ESR), albumin (ALB) levels, IUS, and endoscopy results (if available).

Investigated drugs

UST and IFX were administered following standard dosage protocols outlined in the respective instructions. For IFX, a dose of 5 mg/kg was administered via intravenous infusion at weeks 0, 2, and 6 for induction of remission. Subsequently, the same dosage was maintained every 8 weeks to sustain remission. In the case of UST, the dosage was 260 mg for patients weighing $\leqslant 55$ kg, 390 mg for those weighing 55–85 kg, and 520 mg for those weighing >85 kg. Maintenance treatment involved intravenous infusion of 90 mg UST every 8 or 12 weeks. Patients who did not respond adequately to standard doses of IFX or UST might necessitate optimized treatment, including dose escalation and interval reduction.

Primary and secondary outcomes

The primary outcome assessed in this study was steroid-free (without any steroid use in the preceding 30 days) clinical remission at week 52.[24] Secondary outcomes included response rates at weeks 12 and 24, steroid-free clinical remission rates at week 24, the rate of surgery during the 52 week due to stenosis, and objective examination (IUS or endoscopy) response rates at week 52, and occurrence of any adverse event or severe adverse event.

Clinical efficacy was evaluated using the CDAI score. Steroid-free clinical remission was defined as a CDAI score of <150, with no steroid use within the preceding 30 days. Clinical response was characterized by a decrease in CDAI score from baseline >100.[25–27] IUS response was defined as a reduction in BWT (BWT reduction $\geqslant 2$ mm).[28] Endoscopic response was determined by the endoscopist's reported reduction of stenosis (the lumen diameter of the stricture area has increased compared to the baseline).[29] For patients with multiple stenoses, all narrowings were evaluated for IUS response. For colonoscopy, only the distal stenosis within reach of the standard adult endoscope was evaluated for response.

Subgroup analysis

To eliminate the influence of bio-exposed patients and ensure the reliability of our findings, we conducted a subgroup analysis focusing on bio-naïve patients. In addition, motivated by the notable prevalence of bio-exposed patients within the UST group, we carried out a comparative analysis between bio-naïve and bio-exposed patients specifically within this group.

Statistical analysis

Statistical analysis utilized IBM Statistical Package for the Social Sciences software, Windows version 20.0. Quantitative data with a normal or nearly normal distribution were presented as mean $\pm$ standard deviation (mean $\pm$ SD), while data with skewed distributions were expressed as interquartile range (IQR). To compare quantitative variables between the two groups, the *t*-test or its non-parametric counterparts was employed. Qualitative data were represented as percentages (%), and the chi-square (χ^2) or Fisher's test was applied to compare proportions between the two groups. All statistical tests were two-sided, and a p-value <0.05 was considered statistically significant.

Results

Patients

A total of 236 patients (121 IFX and 115 UST) were included from the five IBD centers. Of

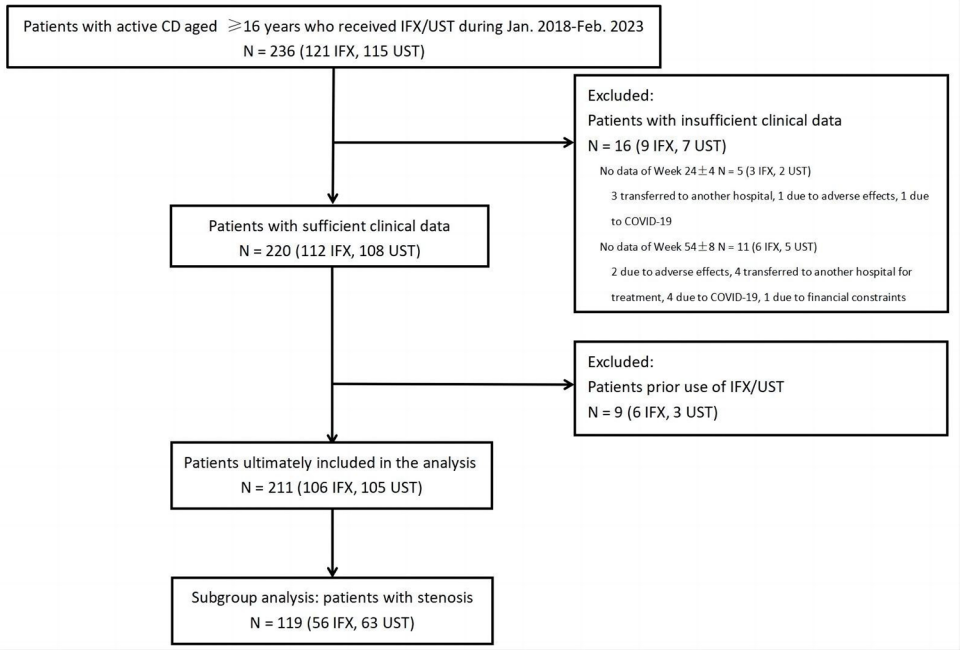

Figure 1. Study overview.
IFX, infliximab; UST, ustekinumab.

these, 6.78% (16/236) of the patients had insufficient clinical data (nine IFX and seven UST). All patients participated in a 12-week follow-up; however, five patients missed the 24-week follow-up for various reasons: three patients were transferred to another hospital, one patient experienced adverse effects, and one patient was affected by COVID-19. Furthermore, 11 patients were unable to attend the 52-week follow-up. The reasons for their absence included adverse effects (two patients), transfer to another hospital (four patients), COVID-19-related issues (four patients), and financial constraints (one patient). As the proportion of patients with insufficient clinical data was less than 10%, they were excluded from the analysis. In addition, six patients in the IFX group had previously used IFX, and three patients in the UST group had previously used UST. These nine (six IFX and three UST) patients were excluded. Ultimately, a total of 211 patients with active CD were included in the analysis (106 IFX and 105 UST), and we performed a subgroup analysis of 119 patients with stenosis (56 IFX and 63 UST) (Figure 1).

Clinical characteristics of all patients

There were no significant differences in sex, age, BMI, disease duration, prior surgery history, current smoking and drinking, Montreal classification, CDAI score, ESR, CRP, or ALB at baseline between the IFX and UST groups ($p > 0.05$). This suggests that the two groups were statistically comparable. The stenosis rate at baseline also showed no significant difference between the two groups, with 52.83% (56/106) in the IFX group and 60.00% (63/105) in the UST group ($p = 0.294$). Regarding previous medication, 6.60% (7/106) of patients in the IFX group and 61.90% (65/105) of patients in the UST group had prior experience with biologics (bio-experienced) ($p < 0.01$). There was no significant difference in the prior use of immunomodulators between the two groups (38.68% IFX vs 35.24% UST, $p = 0.605$). The combined use of steroids at baseline also did not significantly differ between the IFX and UST groups (22.64% IFX vs 14.29% UST, $p = 0.118$). No significant difference was observed in the BWT and bowel wall blood perfusion grading between the two groups (Table 1). During the study period, there was no noteworthy disparity in the rate of treatment optimization (including dose increase and/or interval shortening) between the IFX and UST groups (23.58% IFX vs 17.14% UST, $p = 0.254$).

At baseline, 39 patients were on steroids, with a mean duration of 14.3 weeks (14.5 weeks in the

Table 1. Clinical characteristics of overall patients in the IFX and UST groups.

Characteristic	Total ($n = 211$)	IFX ($n = 106$)	UST ($n = 105$)	p
Age (years), mean ± SD	33.54 ± 14.37	33.69 ± 15.67	33.38 ± 13.00	0.877
Male, *n* (%)	142 (67.3)	74 (69.81)	68 (64.76)	0.434
Disease duration (years), mean ± SD	6.13 ± 5.23	6.30 ± 5.21	5.96 ± 5.27	0.638
Baseline CDAI score, mean ± SD	244.41 ± 77.47	246.40 ± 71.69	242.41 ± 83.20	0.709
BMI (kg/m^2), mean ± SD	19.72 ± 3.42	19.67 ± 3.57	19.76 ± 3.28	0.855
Stenosis, *n* (%)	119 (56.4)	56 (52.83)	63 (60.00)	0.294
Age of diagnosis (years), *n* (%)				0.520
⩽16	32 (15.17)	19 (17.92)	13 (12.38)	
17–40	147 (69.67)	72 (67.92)	75 (71.43)	
>40	32 (15.17)	15 (14.15)	17 (16.19)	
Disease location, *n* (%)				0.751
Ileal (L1)	35 (16.59)	17 (16.04)	18 (17.14)	
Colonic (L2)	38 (18.01)	20 (18.87)	18 (17.14)	
Ileocolonic (L3)	138 (65.40)	69 (65.09)	69 (65.71)	
Upper gastrointestinal (L4)[a]	17 (8.06)	8 (7.55)	9 (8.57)	
Disease behavior, *n* (%)				0.413
Non-penetrating, non-stricturing (B1)	53 (25.12)	30 (28.30)	23 (21.90)	
Stricturing (B2)	89 (42.18)	41 (38.68)	48 (45.71)	
Penetrating (B3)	26 (12.32)	12 (11.32)	14 (13.33)	
Stricturing and penetrating (B2 + B3)	43 (20.38)	23 (21.70)	20 (19.04)	
Perianal lesions, *n* (%)	77 (36.49)	44 (41.51)	33 (31.43)	0.128
Prior surgical history, *n* (%)	83 (39.34)	37 (34.91)	46 (43.81)	0.186
Biologic experienced, *n* (%)	72 (34.12)	7 (6.60)	65 (61.90)	<0.001
Prior immunomodulator, *n* (%)	78 (36.97)	41 (38.68)	37 (35.24)	0.605
Steroids at baseline, *n* (%)	39 (18.48)	24 (22.64)	15 (14.29)	0.118
Current smoker, *n* (%)	34 (16.11)	20 (18.87)	14 (13.33)	0.274
Current drinker, *n* (%)	30 (14.22)	20 (18.87)	10 (9.52)	0.052
Baseline ALB (g/L), mean ± SD	38.45 ± 5.85	38.46 ± 5.76	38.45 ± 5.96	0.991
Baseline ESR (mm/h), mean ± SD	30.99 ± 25.20	27.75 ± 23.81	34.26 ± 26.23	0.060
Baseline CRP (mg/L), mean ± SD	20.93 ± 23.97	19.16 ± 22.02	22.72 ± 25.77	0.282

(Continued)

Table 1. (Continued)

Characteristic	Total ($n=211$)	IFX ($n=106$)	UST ($n=105$)	p
	Total ($n=79$)	IFX ($n=41$)	UST ($n=38$)	
Baseline BWT (cm), M (Q_1, Q_3)	0.70 (0.60, 0.80)	0.70 (0.60, 0.80)	0.70 (0.60, 0.90)	0.706
Bowel wall blood perfusion grading, *n* (%)				0.723
None (1)	7 (8.86)	4 (9.76)	3 (7.89)	
Dot (2)	29 (36.71)	13 (31.71)	16 (42.11)	
Dot and strip (3)	9 (11.39)	6 (14.63)	3 (7.89)	
Strip (4)	34 (43.04)	18 (43.90)	16 (42.11)	

[a]Since L4 could coexist with ileal and colonic disease (e.g., L1 + L4, L2 + L4, L3 + L4), all such patients were categorized as both L4 and L1–L3 in this study.
ALB, albumin; BMI: body mass index; BWT: bowel wall thickness (intestinal ultrasound); CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; IFX: infliximab; UST: ustekinumab.

IFX group and 13.9 weeks in the UST group). During treatment, three patients received additional steroids: two from the UST group (one between 8 and 20 weeks and the other between 4 and 48 weeks), both achieving steroid-free clinical remission at weeks 24 and 52, respectively. One patient from the IFX group, who received steroids between 37 and 52 weeks, did not attain clinical remission at weeks 24 or 52. Among those who achieved steroid-free clinical remission at week 52, 23 had used steroids during the study (average steroid use: 15.6 weeks; average duration to achieve steroid-free clinical remission after discontinuing steroids: 34.4 weeks). Similarly, at week 24, 23 patients who had achieved steroid-free clinical remission had used steroids during the study (average steroid use: 15.3 weeks; average duration to achieve steroid-free clinical remission after discontinuing steroids: 8.3 weeks).

Clinical effectiveness after treatment of overall patients

After treatment, there were no significant differences in CDAI scores between IFX and UST group at weeks 12, 24, and 52 ($p>0.05$). There was no significant difference in the response rate at week 12 (46.23% IFX vs 38.10% UST, $p=0.232$) and week 24 (54.72% IFX vs 50.48% UST, $p=0.537$) between the IFX and UST groups. The steroid-free remission rate showed no significant differences between the IFX and UST groups at week 24 (60.38% IFX vs 62.86% UST, $p=0.711$) and week 52 (58.49% IFX vs 67.62% UST, $p=0.170$) (Figure 2). The mean ESR in the IFX group was significantly lower than the UST group at week 12 (13.99 ± 17.28 IFX vs 20.54 ± 23.41 UST, $p=0.022$) and week 24 (14.42 ± 17.66 IFX vs 22.04 ± 23.58 UST, $p=0.009$). There were no significant differences in mean CRP and ALB at weeks 12, 24, and 52 between the IFX and UST groups ($p>0.05$) (Supplemental Table S1).

Clinical characteristics of patients with stenosis

A subgroup analysis of patients with intestinal stenosis was performed. At baseline, the mean BMI of the IFX group (19.02 ± 3.63) was found to be lower than that of the UST group (20.39 ± 3.47), with statistical significance ($p=0.038$). However, despite the statistical significance, the difference in mean BMI was not considered a key variable. In addition, when taking into account other baseline data, no significant differences were observed among the three groups. Therefore, it can be concluded that the three groups are statistically comparable (Supplemental Table S2).

Clinical effectiveness after treatment of patients with stenosis

After treatment, the CDAI scores of the IFX and UST groups decreased at weeks 12, 24, and 52 compared to their baseline. There were

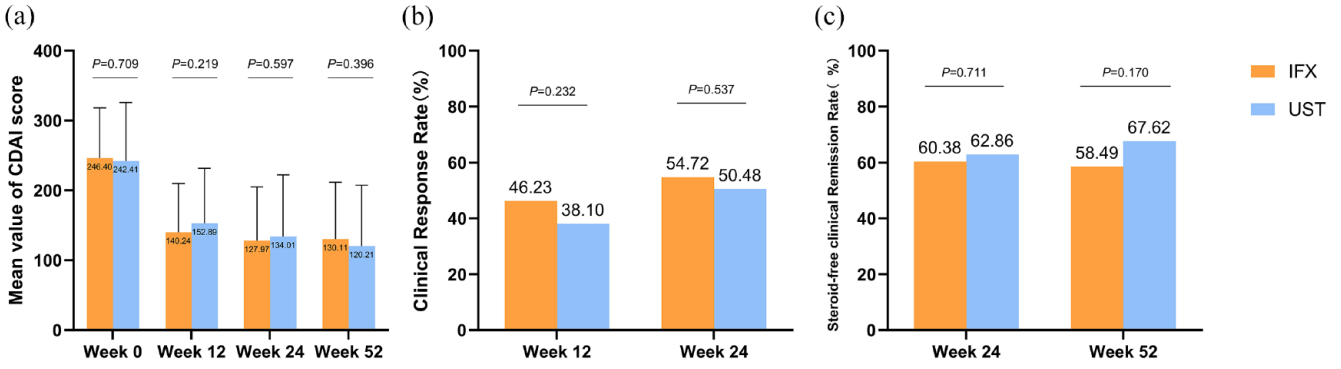

Figure 2. Clinical effectiveness after treatment of overall patients (*N* = 211) between the IFX (*N* = 106) and UST (*N* = 105) groups. (a) Changes in mean CDAI of all patients between the IFX and UST groups. (b) Rate of clinical response at week 12 and week 24 for all patients between the IFX and UST groups. (c) Rate of steroid-free clinical remission at week 24 and week 52 for all patients between the IFX and UST groups.
CDAI, Crohn's disease activity index; IFX, infliximab; UST, ustekinumab.

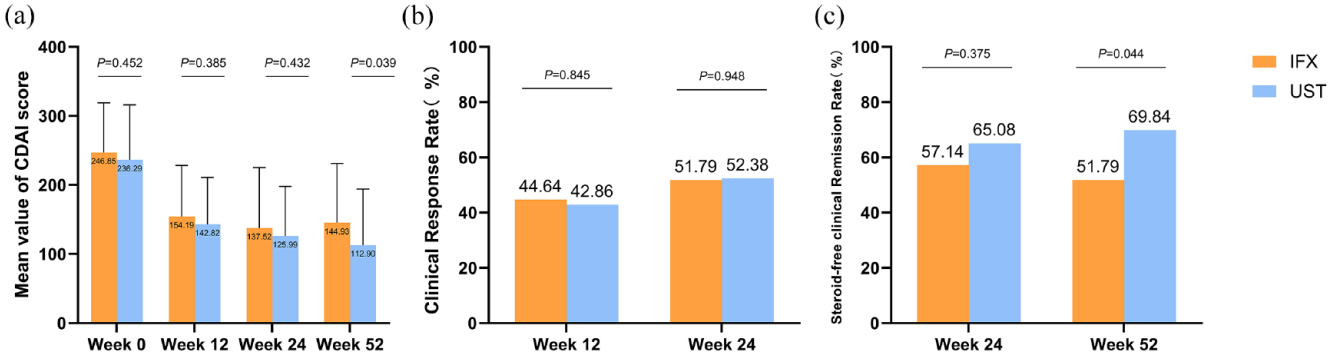

Figure 3. Clinical effectiveness after treatment of patients with stenosis (*N* = 119) between the IFX (*N* = 56) and UST (*N* = 63) groups. (a) Changes in mean CDAI of patients with stenosis between the IFX and UST groups. (b) Rate of clinical response at week 12 and week 24 for patients with stenosis between the IFX and UST groups. (c) Rate of steroid-free clinical remission at week 24 and week 52 for patients with stenosis between the IFX and UST group.
CDAI, Crohn's disease activity index; IFX, infliximab; UST, ustekinumab.

no significant differences in CDAI scores between the IFX and UST groups at weeks 12 and 24 ($p > 0.05$). At week 52, the CDAI score in the IFX group was significantly higher than the UST group (144.93 ± 86.10 IFX vs 112.90 ± 81.14 UST, $p = 0.039$). There were no significant differences in the response rate between the IFX and UST groups at weeks 12 and 24 ($p > 0.05$), and no significant differences in the steroid-free remission between the IFX and UST groups at week 24 (57.14% IFX vs 65.08% UST, $p = 0.375$). However, at week 52, the steroid-free clinical remission rate in the IFX group was significantly lower than the UST group (51.79% IFX vs 69.84% UST, $p = 0.044$) (Figure 3). There was no significant difference in the rate of surgery for stenosis between the IFX and UST groups during the 52-week period (3.57% (2/56) IFX vs 4.76% (3/63) UST, $p > 0.99$) (Figure 4(a)). Furthermore, there were no significant differences in ESR, CRP, and ALB between the IFX and UST groups after treatment ($p > 0.05$) (Supplemental Table S3).

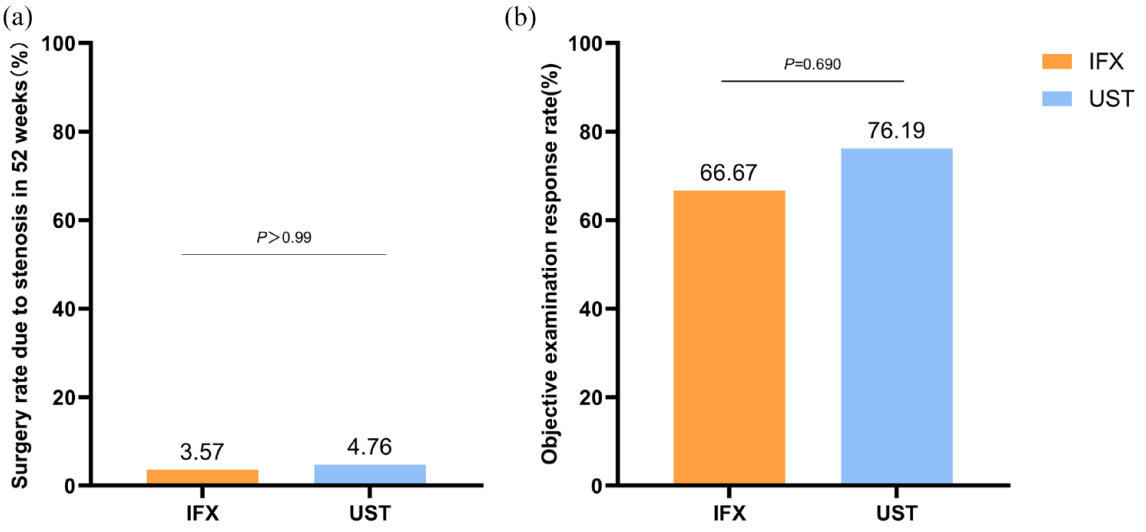

Figure 4. Surgery rate due to stenosis within 52 weeks and objective examination response rate (%) between the IFX and UST groups in CD patients with stenosis. (a) Surgery rate due to stenosis within 52 weeks between the IFX and UST groups in CD patients with stenosis. (b) Objective examination response rate (%) between the IFX ($n = 12$) and UST ($n = 21$) groups in CD patients with stenosis.
CD, Crohn's disease; IFX, infliximab; UST, ustekinumab.

Objective examination (IUS or endoscopy) response rate after treatment of patients with stenosis

Due to the retrospective nature of the study, there were fewer patients with paired ultrasound or endoscopy data at baseline and week 52. Among patients with stenosis, there were 12 (12/56, 21.43%) patients in the IFX group and 21 (21/63, 33.33%) patients in the UST group who had intestinal ultrasonic or endoscopy results at both baseline and week 52. There were no significant differences in achieving an objective examination response rate between the IFX and UST groups at week 52 (66.67% (8/12) IFX vs 76.19% (16/21) UST, $p = 0.690$) (Figure 4(b)).

Comparison between bio-naïve and bio-experienced patients in the UST group

In the UST group, the mean CDAI scores were significantly lower in bio-naïve patients compared to bio-experienced patients at week 12 (134.58 ± 58.65 bio-naïve vs 164.16 ± 87.81 bio-experienced, $p = 0.041$) and week 24 (111.44 ± 65.08 bio-naïve vs 147.90 ± 97.79 bio-experienced, $p = 0.024$). The response rate of bio-naïve patients was significantly higher than bio-experienced patients at week 12 (50.00% bio-naïve vs 30.77% bio-experienced, $p = 0.049$) and week 24 (65.00% bio-naïve vs 41.54% bio-experienced, $p = 0.020$). At week 24, the rate of steroid-free clinical remission was higher in bio-naïve patients compared to bio-experienced patients (75.00% bio-naïve vs 55.38% bio-experienced, $p = 0.043$). However, at week 54, there was no significant difference in the rate of steroid-free clinical remission between bio-naïve patients and bio-experienced patients (70.00% bio-naïve vs 66.15% bio-experienced, $p = 0.683$) (Figure 5).

Subgroup analysis: Clinical effectiveness after treatment of bio-naïve patients

We performed a subgroup analysis to assess the clinical efficacy in 99 patients from the IFX group and 40 patients from the UST group who were not treated with biological agents. Our findings revealed that the 52-week steroid-free clinical remission rate in the UST group was 70.00%, which was higher than that of 52.60% in the IFX group; however, there was no statistically significant difference ($p = 0.251$). Furthermore, the 24-week steroid-free clinical remission rate, as well as the 12-week and 24-week clinical response rates, was all higher in the UST group compared to those in the IFX group; however, these differences did not reach statistical significance in our

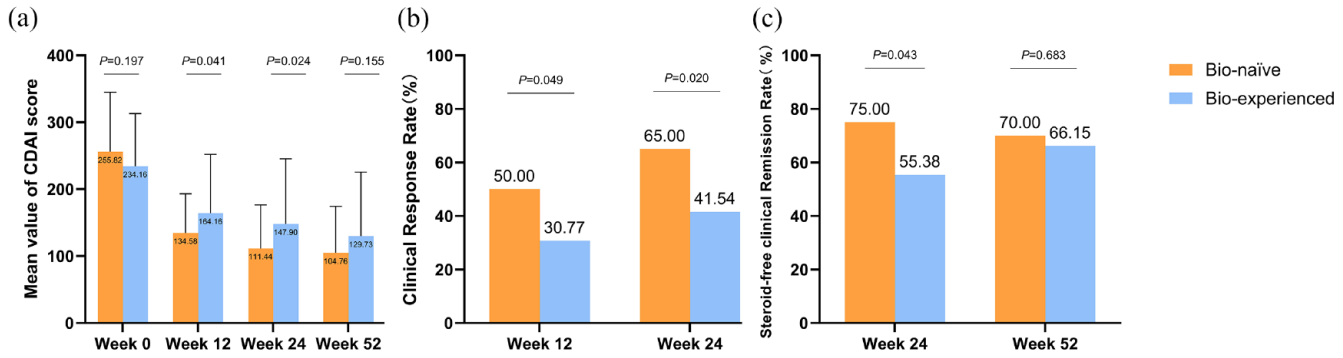

Figure 5. Clinical effectiveness after treatment in the UST group ($N = 105$) between the bio-naïve ($N = 40$) and bio-experienced ($N = 65$). (a) Changes in mean CDAI in the UST group between the bio-naïve and bio-experienced. (b) Rate of clinical response at week 12 and week 24 for the UST group between the bio-naïve and bio-experienced. (c) Rate of steroid-free clinical remission at week 24 and week 52 for the UST group between the bio-naïve and bio-experienced.
CDAI, Crohn's disease activity index; UST, ustekinumab.

subgroup analysis results ($p > 0.05$) (Supplemental Table S4).

Safety

Among the 214 patients with available follow-up data, a notable number exhibited good tolerability to the medication. Crucially, there were no fatalities during the monitoring phase. In the IFX group, nine individuals (8.3%) reported adverse events, specifically including hepatic impairment ($n = 1$), renal impairment ($n = 1$), rash ($n = 4$), reduced neutrophil count ($n = 1$), tachypnea ($n = 1$), and *Mycobacterium tuberculosis* infection ($n = 1$). It is worth noting that two patients from this group stopped treatment due to adverse reactions linked to decreased neutrophil count and tachypnea, respectively. In the UST group, six patients (5.7%) encountered adverse events, namely hepatic impairment ($n = 3$), renal impairment ($n = 1$), *Mycobacterium tuberculosis* infection ($n = 1$), and pyrexia ($n = 1$). One patient from the UST group stopped treatment owing to abnormalities in liver and kidney function (Supplemental Table S5).

Discussion

The effectiveness of IFX and UST in treating patients with CD complicated by intestinal stenosis has not been compared and evaluated in studies to date. The most obvious finding to emerge from this study is the significantly higher steroid-free clinical remission rate for UST (69.84%) compared to IFX (51.79%) in CD patients with intestinal stenosis. Another major finding is that IFX may have a faster response than UST in overall patients (with or without intestinal stenosis), but IFX and UST have similar response rates in patients with stenosis. The research has also shown that UST is superior to IFX in terms of ultrasound and endoscopic responses. Furthermore, the findings from our study suggest that UST and IFX may potentially reduce the need for surgical intervention in CD patients with intestinal stenosis.

Our study found that both UST and IFX were effective in the treatment of CD patients with intestinal stenosis, and UST was more effective than IFX. This discovery holds substantial implications for the selection of biological agents in clinical practice for CD patients with intestinal stenosis. Optimizing the dose has the potential to enhance the efficacy of biological agents. Given that there was no notable disparity in the frequency of dose optimization between the UST and IFX groups, we are confident that the patients who underwent dose optimization will not alter the conclusion. A case report exists on UST for treating CD patients with intestinal stenosis, but it was a combination of UST and vedolizumab (VDZ).[30] Previous post hoc analyses of clinical trials of UST and IFX for CD patients with intestinal strictures have shown that UST and IFX can improve the condition of patients with strictures

and their clinical symptoms.[31,32] Previous studies have suggested that patients may experience complete obstruction after receiving IFX treatment, regardless of whether they had a previous stenosis.[15,16] However, other studies have indicated that anti-TNF (IFX, ADA) is effective for most CD patients with intestinal stenosis.[14,33] More recently, larger sample size studies from STRIDENT or CREOLE have provided strong evidence that anti-TNF (ADA) is effective for CD patients with intestinal stenosis.[34,35] The superiority of UST over IFX in sustaining clinical remission for CD with intestinal stenosis may be attributed to the enhanced capacity of anti-IL-12/23 to regulate inflammation at the stenosis site and inhibit fibrosis formation compared to anti-TNF. IL-12/23 has been proven to mitigate fibrosis in animal experiments and clinical studies focusing on non-intestinal organs.[18,19] Previous investigations have confirmed that administration of a vaccine targeting the IL-12/23 p40 peptide leads to reduced collagen deposition in a mouse model of chronic TNBS-induced colitis.[36] Consequently, IL-12/23 inhibition holds promise for an anti-fibrotic effect in the context of intestinal fibrosis.[11] It is worth mentioning that, contrary to certain prior findings,[15,16,37,38] our study showed that anti-TNF was effective in CD patients with intestinal stenosis and did not cause additional stenosis.[39] Hence, our findings address the question of whether IFX can be utilized in treating CD patients with intestinal stenosis.

Previous studies comparing IFX and UST in the treatment of overall CD patients (with or without intestinal stenosis) suggested that IFX and UST have similar therapeutic efficacy.[40–42] Our results are also consistent with previous studies that showed similar efficacy of IFX and UST in overall CD patients. Our study indicates that there was no statistically significant variance in inflammation markers, including ESR, CRP, and ALB, between the IFX and UST groups by week 52. This similarity can likely be attributed to the comparable effectiveness of IFX and UST as biological agents for the treatment of CD. Consequently, both groups achieved a high remission rate by week 52, with the majority of patients demonstrating normalized inflammation markers such as ESR, CRP, and ALB. However, a trend was observed in our study that IFX had a faster response in overall CD patients, while UST was more effective in maintaining long-term remission in both overall CD patients and those with intestinal stenosis. We believe that this can be attributed to the rapid regulation of inflammation by IFX.[32] In addition, the response rate of IFX was similar to that of UST in CD patients with intestinal stenosis. We speculate that the rapid inflammatory control effect of IFX may be weakened in patients with intestinal stenosis, while UST may exhibit a faster response in these patients. According to our findings, in clinical practice, if the response to UST is insufficient within 24 weeks, an immediate switch to another biological agent may not be necessary. While UST exhibits a slower response, it could potentially lead to a more long-term maintenance remission.

In a meta-analysis examining surgery rates among CD patients with or without intestinal stenosis, the reported rates varied from 8.2% to 66.7% over a duration of 5.5–105.8 months.[8] Concerning surgical rates in patients with intestinal stenosis, findings from a multicenter retrospective study suggest that anti-TNF therapy can reduce the surgery rate within 1 year for those with this complication.[43] This is consistent with our study, which shows a surgical rate of 3.57% within 52 weeks after IFX treatment. Meanwhile, our study shows a surgical rate of 4.76% within 52 weeks after UST treatment. Unfortunately, there remains a lack of data on the surgery rate related to stenosis after UST use. Our findings suggest that IFX and UST, when administered within 52 weeks, may potentially reduce the necessity for surgical intervention in CD patients with stenosis, thus confirming the effectiveness of these two biological agents for this specific group.

Objective examination response rates have rarely been used as an outcome in previous studies, yet they are crucial in studies of stenosis. We utilized the available pre- and post-treatment matched ultrasound or endoscopic results for analysis. Although the achievement of an objective examination response rate was higher for UST (76.19%) compared to IFX (66.67%), there was no statistically significant difference ($p = 0.690$), possibly due to the small sample size. However, the trend still remains that UST is more likely to reduce the degree of stenosis. This also suggests that UST may play a role in controlling inflammation and potentially inhibiting fibrosis at the site of stenosis.

In 2020, UST was approved for treating patients with CD in China.[44] Since the use of UST for CD treatment occurred later than IFX in China, a higher number of patients in the UST group had prior exposure to biological agents in our study. We compared the clinical efficacy between bio-experienced and bio-naïve patients in the UST group, revealing that bio-naïve patients treated with UST had higher effectiveness, which is consistent with previous studies.[45,46] This result will help predict the effectiveness of UST in the treatment of CD patients.

To our knowledge, this is the first real-world study to compare the efficacy of IFX and UST in treating CD patients with intestinal stenosis. However, it is important to acknowledge the limitations and shortcomings of this study. First, this was a retrospective cohort study. Although the primary findings indicate significant differences ($p < 0.05$), we calculated the test power with an α level of 0.05, resulting in a power = 0.72, suggesting that the sample size may be marginally insufficient. Furthermore, there was an inadequate amount of paired data before and after treatment for objective examinations (ultrasounds or endoscopy), and some centers reported no detailed descriptions, including pre-stenotic dilation, stenosis length, and lumen diameter at the site of stenosis. However, our analysis using available objective examination results demonstrates a trend toward differences, affirming the reliability of our other findings. Second, objective examinations (ultrasound, endoscopy) may be affected by differences in assessment between different physicians before and after treatment, which is an unavoidable problem in retrospective studies. We look forward to future prospective studies that use standardized assessments for objective examinations before and after treatment, such as having the same physician perform the examinations before and after treatment whenever possible. Third, we were unable to match patients who had previously used biologic agents between the two groups; however, through subgroup analysis, we observed a consistent trend in the results among patients who had not used biologic agents. In addition, some patients were lost to follow-up in our study inevitably, but the proportion of these patients was small (6.78%), so excluding these patients will not affect the reliability of the results.[47] Finally, although our study demonstrated that steroid-free clinical remission rates at week 52 were significantly lower in the IFX than in UST groups, we note that the number of patients on steroids in each group is low and interpretation requires further future studies.

Conclusion

Our study demonstrates that IFX and UST are effective in treating CD patients with intestinal stenosis. Specifically, UST exhibits superior efficacy compared to IFX in the treatment of CD patients with intestinal stenosis, and it demonstrates enhanced effectiveness in biologic-naïve patients. Looking ahead, further animal experiments are warranted to substantiate the impact of biological agents like UST on intestinal fibrosis. Clinical studies should also investigate the comparison of intestinal fibrosis pre- and post-treatment. In addition, efforts should be directed toward identifying more therapeutic targets for anti-fibrosis drugs based on the mechanisms of fibrosis formation.

Declarations

Ethics approval and consent to participate

Each center secured approval from the Ethics Committee (Ethics Approval Number: I-22PJ1092).

Consent for publication

This was received as part of the ethical approval.

Author contributions

Xidong He: Data curation; Methodology; Resources; Validation; Visualization; Writing – original draft; Writing – review & editing.

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Competing interests

The authors declare that there is no conflict of interest.

Availability of data and materials

The data underlying this article are available in the article and its online supplementary material.

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Supplemental material

Supplemental material for this article is available online.

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