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Comparative real-world outcomes between ustekinumab, infliximab, and adalimumab in bio-naïve and bio-experienced Crohn's disease patients: a retrospective multicenter study

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Abstract

Background Numerous studies have compared the efficacy of ustekinumab (UST) and anti-TNF agents [infliximab (IFX) or adalimumab(ADA)] in moderate to severe Crohn's disease (CD) patients. This study aims to compare the efficacy of UST, IFX, and ADA while differentiating between bio-naïve and bio-experienced patients, which is an underexplored aspect, particularly in Asia.

Methods We conducted a retrospective multi-center study from 2012 to 2023, categorizing patients into bio-naïve and bio-experienced groups. We evaluated clinical remission rates after induction therapy and clinical outcomes, including CD-related hospitalization, intestinal resection, and drug discontinuation during maintenance therapy.

Results Among the 214 bio-naïve CD patients, 60 received UST, 108 received IFX, and 46 received ADA. After 1:1 propensity score matching between UST and anti-TNF agents groups, 59 patients were analyzed in each group (45 in the IFX group and 14 in the ADA group). We found no significant differences in clinical remission rates ($P=0.071$), CD-related hospitalization ($P=0.800$), intestinal resection ($P=0.390$), or drug discontinuation ($P=0.052$) between the UST, IFX, and ADA groups in bio-naïve CD patients. In bio-experienced CD patients, with 35 in the UST group and 13 in the anti-TNF agents group, the UST group showed a lower risk of drug discontinuation ($P=0.004$) than the anti-TNF agents group.

Conclusions This study suggests that UST, IFX, and ADA are equally effective in bio-naïve CD patients, while in bio-experienced patients, mostly with previous exposure to anti-TNF agents, UST may offer superior drug durability.

Keywords Moderate to severe Crohn's disease, Bio-naïve and bio-experienced patients, Ustekinumab and anti-tumor necrosis factor agents, Efficacy and prognosis

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Introduction

In patients with moderate to severe Crohn's disease (CD), anti-tumor necrosis factor (TNF) agents, such as infliximab (IFX) and adalimumab (ADA), have been reported to have a high clinical response rate at four weeks, reaching up to 81%. However, the clinical remission rate at approximately one year falls short of 40% [1, 2]. Additionally, the discontinuation of anti-TNF agents due to the loss of response is reported to occur in about 10% per patient-year follow-up [3, 4]. In the case of ustekinumab (UST), a clinical trial reported a clinical response rate of 34% at week 6, with a clinical remission rate of approximately 53% at week 44 [5]. Clinical trials comparing the efficacy of anti-TNF agents and UST in bio-naïve CD patients showed no significant difference in clinical response rates at week 6 (44.9% for IFX and 37.9% for UST) [6]. Similarly, clinical remission rates at week 52 for adalimumab (ADA) and UST were 61% and 65%, respectively, with no significant differences [7]. A recent network meta-analysis comparing anti-TNF agents and UST in bio-naïve and experienced CD patients did not show significant differences in clinical remission after induction and during maintenance [8].

A recent retrospective study comparing the efficacy of IFX and UST in bio-naïve CD patients reported clinical response rates at 3 months of 86% for infliximab and 64% for UST, indicating superior results for IFX. However, the drug persistency showed no significant difference between IFX and UST [9]. Another retrospective study comparing ADA and UST in bio-naïve CD patients revealed that the clinical remission rate and drug persistency at 56 weeks showed no significant differences [10]. For bio-experienced CD patients, clinical remission rates after induction therapy were 60.6% for anti-TNF agents and 58.8% for UST, without significant difference [11].

So far, limited studies in Asia have compared the efficacy and clinical outcomes of UST and anti-TNF agents in both bio-naïve and experienced CD patients [12]. To address this gap, we have planned a multi-center study using propensity score matching to compare the efficacy and clinical outcomes between UST, IFX, and ADA.

Methods

Patients

This retrospective cohort study was conducted at three referral centers and included adult patients aged 18 or older with moderate-to-severe CD who had been receiving UST, IFX, or ADA and could be tracked for a minimum of three months from January 2012 to July 2023. Patients were categorized into two subgroups: bio-naïve and bio-experienced. The bio-experienced group consisted of patients who had previously received anti-TNF agents, UST, or vedolizumab before initiating UST or anti-TNF agents. This study was conducted according to the guidelines of the Declaration of Helsinki. The Institutional Review Board of Inje University Haeundae Paik Hospital approved our protocol (File number. 2023-04-012-003). Patients' informed consent requirement was waived because only de-identified data were collected.

Outcomes and assessment

The primary outcome was to compare the efficacy between UST, IFX, and ADA in terms of clinical remission after induction therapy and to assess the occurrence of CD-related hospitalization, intestinal resection, and drug discontinuation during maintenance therapy in both bio-naïve and bio-experienced patient groups. Clinical remission was defined as a Crohn's Disease Activity Index (CDAI) score of less than 150 during the response evaluation after induction therapy. The secondary outcome was identifying factors associated with CD-related hospitalization, intestinal resection, and drug discontinuation.

The index date was when the patient initiated the first, second, or subsequent biological therapy. Separate definitions were applied for bio-naïve patients and bio-experienced patients. The schedule for induction and maintenance therapy, as well as the assessment of response after induction therapy, was as follows: (1) UST: administered intravenously at week 0, with the dose adjusted based on body weight (260 mg for $\leq$55 kg, 390 mg for >55 kg to $\leq$85 kg, or 520 mg for >85 kg), followed by subcutaneous UST 90 mg at week 8, and then maintained every 12 weeks. The response evaluation after induction therapy was performed before the 3rd dose; (2) IFX: administered intravenously at a quantity of 5 mg/kg at weeks 0, 2, and 6, followed by every eight weeks. The response evaluation after induction therapy was performed before the 2nd dose; (3) ADA: administered subcutaneously with an initial dose of 160 mg at week 0, followed by 80 mg at week 2, and then 40 mg every 2 weeks. The response evaluation after induction therapy was performed before the 3rd dose. In South Korea, based on insurance policies, the maintenance therapy for each biological therapy is determined according to the clinical response assessed using the Crohn's Disease Activity Index (CDAI) before and after induction therapy. Therefore, the evaluation of CDAI before and after induction therapy is mandatory and can be obtained from the medical records. Dose intensification for all biologics was possible at the discretion of the physicians. The patients included in the study were followed up until the date of the last biological therapy or the last outpatient visit.

Covariates

We retrospectively gathered data from medical records, including the following variables: gender, age at diagnosis, age at starting biological therapy, disease duration, location, behavior, perianal disease, history of intestinal resection, CDAI before and after biological therapy, concomitant treatments [5-aminosalicylic acid (5-ASA), steroids, immunomodulators], laboratory data [c-reactive protein (CRP), hemoglobin, albumin], and the duration of follow-up.

Statistical analysis

Continuous variables were presented as mean ± standard deviation and compared using a one-way analysis of variance or the Kruskal-Wallis test. Categorical variables were expressed as n (%) and compared using the chi-squared or Fisher's exact test. The comparison between UST, IFX, and ADA involved multiple comparisons, and we applied Bonferroni's method. In this context, we considered *P* values less than 0.0167 statistically significant.

For the comparison between UST and anti-TNF agents, we utilized propensity score matching with a 1:1 ratio using the MatchIt package in the R program [13], employing optimal matching. The matching variables were determined based on differences observed in baseline characteristics between the UST and anti-TNF agents groups. To analyze primary outcomes, including the rate and cumulative survival of clinical remission after induction therapy, CD-related hospitalization, intestinal resection, and drug discontinuation among the three groups (UST, IFX, and ADA), we used the chi-squared or Fisher's exact test, as well as Kaplan-Meier survival curves. To identify the factors associated with each clinical outcome, Cox proportional hazard analysis was employed. In the multivariate analysis, only the factors with a P value < 0.05 in the univariate analysis were included. A P value < 0.05 was considered statistically significant. Statistical analysis was performed using SPSS Statistics 25.0 and R-4.2.2.

Result

Baseline characteristics

In this study, a total of 214 bio-naïve CD patients and 48 bio-experienced CD patients were included. All patients received UST, IFX, and ADA at standard dosages. Among the 214 bio-naïve CD patients, 60 received UST, 108 received IFX, and 46 received ADA (Table 1). The age at diagnosis and the age at the first biological therapy were higher in the UST, with mean ages of 29 years and 35 years, respectively, compared to 26 years and 30 years for IFX and 24 years and 28 years for ADA. There were no significant differences in disease duration, location, behavior, perianal disease, or history of intestinal resection among the groups. The CDAI before starting biological therapy was higher in the UST group, with a mean of 288.6, compared to 276.8 for IFX and 273.2 for ADA. Approximately half of the patients in all three groups were on steroid therapy, and about 85% were concurrently taking immunomodulators. The CRP values were lower in the UST group, with a mean of 1.8 mg/dL, compared to 3.2 mg/dL for IFX and 3.1 mg/dL for ADA. Albumin levels were higher in the UST group, with a mean of 4.1 g/dL, compared to 3.8 g/dL for IFX and 3.7 g/dL for ADA.

After performing 1:1 propensity score matching for variables showing differences between the UST and the anti-TNF agents groups, including gender, age at diagnosis, age at first biological therapy, CDAI, CRP, and albumin, 59 patients were selected for each group, with 45 patients in the IFX group and 14 patients in the ADA group (Table 2). Following propensity score matching, no statistically significant differences existed in any of the variables between the UST, IFX, and ADA groups, except for the follow-up duration.

Among the bio-experienced CD patients, there were 35 patients in the UST group and 13 patients in the anti-TNF agents group (Table 3). Since no significant differences were observed in variables between the two groups, propensity score matching was not conducted. The disease duration for bio-experienced CD patients in each group had a relatively long mean period of 7.8 and 7.6 years, respectively. The history of intestinal resection was observed at rates of 25.7% for the UST group and 38.5% for the anti-TNF agents group. The co-administration rate of immunomodulators was 45.7% and 38.5% in the respective groups.

Clinical outcomes of bio-naïve patients after propensity score matching

In bio-naïve CD patients after propensity score matching, the rates of clinical remission after induction therapy in the UST, IFX, and ADA groups were 55 (93.2%) of 59, 39 (86.7%) of 45, and 10 (71.4%) of 14, respectively, showing no statistically significant differences (Table 4). For CD-related hospitalization during the maintenance period, the rates in the UST, IFX, and ADA groups were 8 (13.6%) of 59, 6 (13.3%) of 45, and 1 (7.1%) of 14, respectively. Intestinal resection rates were 1 (1.7%) of 59, 3 (6.7%) of 45, and 1 (7.1%) of 14, respectively, and drug discontinuation rates were 1 (1.7%) of 59, 6 (13.3%) of 45, and 2 of 14 (14.3%), respectively, with no statistically significant differences observed. When comparing cumulative survivals, CD-related hospitalization, intestinal resection, and drug discontinuation showed no significant differences among the three groups (Fig. 1).

Table 1 Baseline characteristics of the bio-naïve Crohn's disease patients

	Ustekinumab (*N* = 60)	Infliximab (*N* = 108)	Adalimumab (*N* = 46)	*P* value
Male/female	44/16 (73.3/26.7)	79/29 (73.1/26.9)	32/14 (69.6/30.4)	0.053[a] 0.022[b] 0.715[c]
Age at diagnosis	29 ± 12	26 ± 12	24 ± 7	0.021[a] 0.961[b] 0.023[c]
Age at first biological therapy	35 ± 12	30 ± 12	28 ± 7	0.002[a] 0.788[b] 0.008[c]
Disease duration, years[†]	5.8 ± 6.3	4.2 ± 4.2	5.1 ± 5.3	0.332[1]
Disease location				0.276[3]
Colon	3 (5.0)	13 (12.0)	4 (8.7)	
Ileum	28 (46.7)	37 (34.3)	14 (30.4)	
Ileocolon	29 (48.3)	58 (53.7)	28 (60.9)	
Disease behavior				0.547[3]
Inflammatory	38 (63.3)	68 (63.0)	26 (56.5)	
Stricturing	15 (25.0)	22 (20.4)	9 (19.6)	
Penetrating	7 (11.7)	18 (16.7)	11 (23.9)	
Perianal disease	22 (36.7)	54 (50.0)	16 (34.8)	0.110[3]
History of intestinal resection	12 (20.0)	24 (22.2)	12 (26.1)	0.756[3]
CDAI before first biological therapy (missing values in six patients)	288.6 ± 47.4 (*N* = 59)	276.8 ± 59.0 (*N* = 105)	273.2 ± 45.5 (*N* = 44)	0.012[a] 0.741[b] 0.062[c]
Concomitant therapies				
Steroid	32 (53.3)	54 (50.0)	22 (47.8)	0.846[3]
Immunomodulators	52 (86.7)	92 (85.2)	39 (84.8)	0.954[3]
5-ASA	42 (70.0)	72 (66.7)	42 (91.3)	0.006[3]
Laboratory data[†]				
Hemoglobin, g/dL	13.0 ± 1.8	13.5 ± 11.4	12.9 ± 1.5	0.268[2]
CRP, mg/dL	1.8 ± 1.7	3.2 ± 3.3	3.1 ± 3.2	0.002[a] 0.876[b] 0.022[c]
Albumin, g/dL	4.1 ± 0.5	3.8 ± 0.6	3.7 ± 0.7	0.001[a] 0.516[b] 0.001[c]
Follow-up duration, years[†]	2.1 ± 0.9	3.7 ± 2.5	4.3 ± 2.9	< 0.001[a] 0.291[b] < 0.001[c]

Values are expressed as n (%) unless otherwise specified

5-ASA 5-aminosalicylic acid, *CDAI* Crohn's Disease Activity Index *CRP* C-reactive protein, *anti-TNF* Anti-tumor necrosis factor

[†] Mean ± standard deviation presented for continuous variables

[1] Kruskal-Wallis test, [2]One-way ANOVA, [3]Pearson chi-square, and [4]Fisher's exact test

[a] Ustekinumab vs. Infliximab, [b]Infliximab vs. Adalimumab, and [c]Ustekinumab vs. Adalimumab

Clinical outcomes of bio-experienced patients

Among bio-experienced CD patients, the rates of clinical remission after induction therapy in the UST and anti-TNF agents groups were 27 (77.1%) of 35 and 10 (one missing value, 83.3%) of 12, respectively, showing no statistically significant difference (Table 4). For CD-related hospitalization during the maintenance period, the rates in the UST and anti-TNF agents groups were 12 (34.3%) of 35 and 4 (30.8%) of 13, respectively. Intestinal resection rates were 6 (17.1%) of 35 in the UST group and 2 (15.4%) of 13 in the anti-TNF agents group, with no statistically significant difference. However, drug discontinuation was significantly higher in the anti-TNF agents group, with 7 (53.8%) of 13 compared to 4 (11.4%) of 35 in the UST group. The cumulative survival of CD-related hospitalization and intestinal resection showed no significant difference between the

Table 2 Baseline characteristics of the bio-naïve Crohn's disease patients after propensity score matching

	Ustekinumab (*N* = 59)	Infliximab (*N* = 45)	Adalimumab (*N* = 14)	*P* value
Male/female	44/15 (74.6/25.4)	34/11 (75.6/24.4)	9/5 (64.3/35.7)	0.689[3]
Age at diagnosis	29 ± 12	29 ± 15	24 ± 9	0.262[1]
Age at first biological therapy	35 ± 12	34 ± 14	29 ± 8	0.263[1]
Disease duration, years[†]	5.9 ± 6.3	5.6 ± 5.0	5.3 ± 5.3	0.942[1]
Disease location				0.561[4]
Colon	3 (5.1)	5 (11.1)	2 (14.3)	
Ileum	27 (45.8)	16 (35.6)	5 (35.7)	
Ileocolon	29 (49.2)	24 (53.3)	7 (50.0)	
Disease behavior				0.647[4]
Inflammatory	37 (62.7)	31 (68.9)	7 (50.0)	
Stricturing	15 (25.4)	8 (17.8)	5 (35.7)	
Penetrating	7 (11.9)	6 (13.3)	2 (14.3)	
Perianal disease	22 (37.3)	22 (48.9)	3 (21.4)	0.159[3]
History of intestinal resection	12 (20.3)	8 (17.8)	6 (42.9)	0.128[3]
CDAI before first biological therapy	288.6 ± 47.4	289.9 ± 72.3	296.2 ± 58.2	0.457[1]
Concomitant therapies				
Steroid	31 (52.5)	22 (48.9)	6 (42.9)	0.794[3]
Immunomodulators	52 (88.1)	38 (84.4)	11 (75.6)	0.632[3]
5-ASA	42 (71.2)	30 (66.7)	13 (92.9)	0.159[3]
Laboratory data[†]				
Hemoglobin, g/dL	13.0 ± 1.9	12.9 ± 1.7	13.4 ± 1.7	0.663[2]
CRP, mg/dL	1.8 ± 1.7	2.2 ± 2.1	2.4 ± 3.3	0.721[1]
Albumin, g/dL	4.1 ± 0.5	4.0 ± 0.5	4.1 ± 0.4	0.787[1]
Follow-up duration, years[†]	2.1 ± 0.9	3.6 ± 2.3	3.9 ± 2.2	0.001[a] 0.662[b] 0.002[c]

Values are expressed as n (%) unless otherwise specified

5-ASA 5-aminosalicylic acid, *CDAI* Crohn's Disease Activity Index, *CRP* C-reactive protein, *anti-TNF* Anti-tumor necrosis factor

[†] Mean ± standard deviation presented for continuous variables

[1] Kruskal-Wallis t-test, [2]One-way ANOVA, [3]Pearson chi-square, and [4]Fisher's exact test

[a] Ustekinumab vs. Infliximab, [b]Infliximab vs. Adalimumab, and [c]Ustekinumab vs. Adalimumab

UST and anti-TNF agents groups (Fig. 2). However, the cumulative risk of drug discontinuation was higher in the anti-TNF agents group compared to the UST group.

Associating factors with clinical outcomes

Among the 262 CD patients, seven patients with missing values in CDAI before biological therapy were omitted (Table 5). Risk factors for experiencing CD-related hospitalization were determined for 54 of 255 patients. Bio-experienced CD patients were found to be at a higher risk compared to bio-naïve CD patients [hazard ratio (HR) 2.43; 95% confidence interval (CI) 1.32–4.48]. Female patients were at a higher risk than male patients (HR 1.87, 95% CI 1.02–3.41). Patients taking steroids concurrently were also at a higher risk (HR 2.32, 95% CI 1.30–4.13), while those with lower albumin levels were at a higher risk (HR 0.59, 95% CI 0.35–0.99).

For intestinal resection, which occurred in 18 of 255 patients, multivariate analysis identified bio-experienced CD patients as the only significant risk factor (HR 6.30, 95% CI 2.09–18.99).

Regarding drug discontinuation, which occurred in 49 of 255 patients, it was found to be more likely in patients receiving IFX (HR 2.67, 95% CI 1.00-7.12) or ADA (HR 3.75, 95% CI 1.37–10.22) compared to UST. Conversely, the concurrent use of immunomodulators (HR 0.54, 95% CI 0.29–0.98) and higher albumin levels (HR 0.50, 95% CI 0.33–0.77) were identified as protective factors.

Discussion

This study conducted a comparative analysis of the effectiveness of UST, IFX, and ADA, stratifying patients into bio-naïve and bio-experienced groups based on real-world data. In bio-naïve CD patients, following

Table 3 Baseline characteristics of the bio-experienced Crohn's disease patients

	Ustekinumab (*N* = 35)	**Anti-TNF agents (*N* = 13)**	***P* value**
Male	22/13 (62.9/37.1)	9/4 (69.2/30.8)	0.747[4]
Age at diagnosis	25 ± 9	24 ± 8	0.771[2]
Age at biological therapy	32 ± 9	31 ± 8	0.593[2]
Disease duration, years[†]	7.8 ± 5.4	7.6 ± 4.8	0.781[2]
Disease location			0.633[4]
Colon	1 (2.9)	1 (7.7)	
Ileum	12 (34.2)	5 (38.5)	
Ileocolon	22 (62.9)	7 (53.8)	
Perianal disease	13 (37.1)	5 (38.5)	1.000[4]
Disease behavior			0.191[4]
Inflammatory	20 (57.1)	4 (30.8)	
Stricturing	9 (25.8)	7 (53.8)	
Penetrating	6 (17.1)	2 (15.4)	
History of intestinal resection	9 (25.7)	5 (38.5)	0.480[4]
CDAI before the second or over biological therapy (missing value in one patient)	292.2 ± 52.6	287.7 ± 58.9 (*N* = 12)	0.714[2]
Concomitant therapies			
Steroid	17 (48.6)	4 (30.8)	0.269[3]
Immunomodulators	16 (45.7)	5 (38.5)	0.653[3]
5-ASA	19 (54.3)	6 (46.2)	0.616[3]
Laboratory data[†]			
Hemoglobin, g/dL	12.2 ± 2.0	13.1 ± 2.0	0.162[1]
CRP, mg/dL	3.4 ± 5.3	2.2 ± 2.3	0.562[2]
Albumin, g/dL	3.7 ± 0.6	3.9 ± 0.4	0.376[2]
Follow-up duration, years[†]	2.3 ± 1.2	2.2 ± 1.2	0.546[2]

Values are expressed as n (%) unless otherwise specified

5-ASA 5-aminosalicylic acid, *CDAI* Crohn's Disease Activity Index, *CRP* C-reactive protein, *anti-TNF* Anti-tumor necrosis factor

[†] Mean ± standard deviation presented for continuous variables

[1] Independent t-test, [2]Mann-Whitney, [3]Pearson chi-square, and [4]Fisher's exact test

Table 4 Major clinical outcome rates after induction and maintenance therapy of ustekinumab and anti-tumor necrosis factor agents after propensity score matching only in bio-naïve patients

Bio-naïve patients	Ustekinumab (*N* = 59)	Infliximab (*N* = 45)	Adalimumab (*N* = 14)	*P* value
Clinical remission	55 (93.2)	39 (86.7)	10 (71.4)	0.071[1]
Hospitalization	8 (13.6)	6 (13.3)	1 (7.1)	0.800[1]
Intestinal resection	1 (1.7)	3 (6.7)	1 (7.1)	0.390[1]
Drug discontinuation	1 (1.7)	6 (13.3)	2 (14.3)	0.052[1]
Bio-experienced patients	Ustekinumab (*N* = 35)	Anti-TNF agents (*N* = 13)		*P* value
Clinical remission (missing value in one patient)	27 (77.1)	10 (83.3) (*N* = 12)		1.000[2]
Hospitalization	12 (34.3)	4 (30.8)		1.000[2]
Intestinal resection	6 (17.1)	2 (15.4)		1.000[2]
Drug discontinuation	4 (11.4)	7 (53.8)		0.004[2]

Values are expressed as n (%)

[1] Pearson chi-square, [2]Fisher's exact test

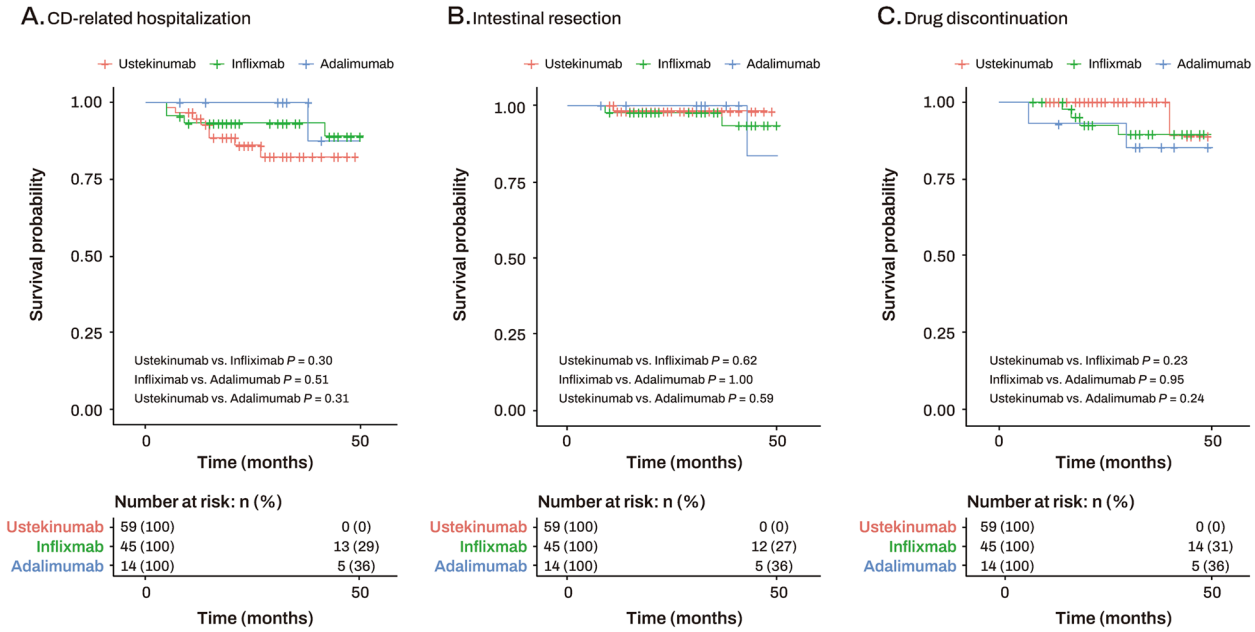

Fig. 1 Clinical outcomes during maintenance therapy in bio-naïve Crohn's disease patients after propensity score matching. **A** CD-related hospitalization, **B** Intestinal resection, **C** Drug discontinuation

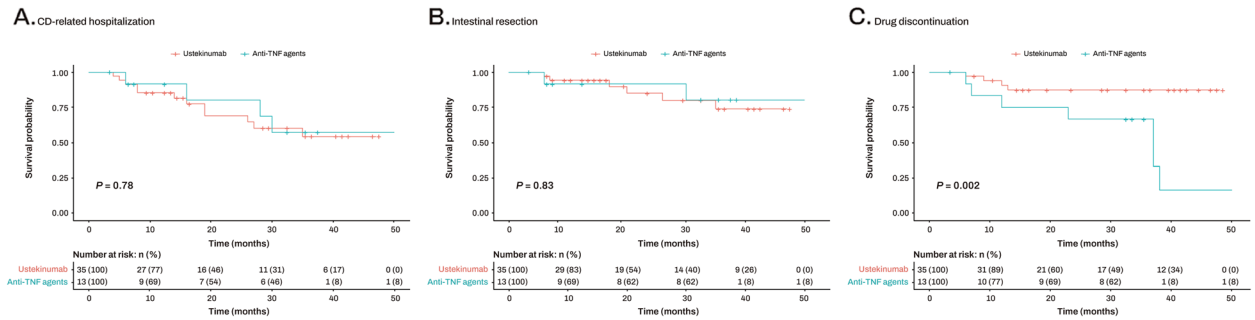

Fig. 2 Clinical outcomes during maintenance therapy in bio-experienced Crohn's disease patients. **A** CD-related hospitalization, **B** Intestinal resection, **C** Drug discontinuation

propensity score matching, UST, IFX, and ADA demonstrated similar outcomes regarding clinical remission after induction therapy and clinical prognosis during maintenance therapy, encompassing CD-related hospitalization, intestinal resection, and drug discontinuation. Among bio-experienced patients, no significant differences were observed between UST and anti-TNF agents concerning clinical remission after induction therapy, CD-related hospitalization, and intestinal resection. However, there was a higher risk of drug discontinuation in the anti-TNF agent group compared to the UST group. When considering all patients, including bio-naïve and bio-experienced CD patients, the risk of drug discontinuation was higher in IFX and ADA compared to UST in multivariate analysis. In summary, in bio-naïve patients, UST, IFX, and ADA demonstrated equivalent efficacy. In bio-experienced patients, UST may offer superior durability compared to anti-TNF agents. Nevertheless, it is essential to note that most bio-experienced patients included in this study had prior exposure to anti-TNF agents, which should be considered when interpreting these results.

Previous clinical trials and meta-analyses that compared the efficacy of UST, IFX, and ADA in moderate to severe CD patients found no significant differences in clinical remission rates in both bio-naïve and bio-experienced groups [7, 8, 11, 14]. Ideally, conducting clinical trials to compare the long-term outcomes of these

Table 5 Risk factors associated with clinical outcomes in Crohn's disease patients

	CD-related hospitalization (*N* = 255, event = 54)				Intestinal resection (*N* = 255, event = 18)				Drug discontinuation (*N* = 255, event = 49)			
	Univariable	Multivariable			Univariable	Multivariable			Univariable	Multivariable		
	P value	HR	95% CI	*P* value	*P* value	HR	95% CI	*P* value	*P* value	HR	95% CI	*P* value
Biologics												
Ustekinumab[a]												
IFX	0.699				0.446				0.042	2.67	1.00-7.12	0.049
ADA	0.066				0.273				0.003	3.75	1.37–10.22	0.009
Naïve[a]/experienced	0.007	2.43	1.32–4.48	0.005	0.005	6.30	2.09–18.99	0.001	0.067			
Male[a]/Female	0.027	1.87	1.02–3.41	0.042	0.418				0.187			
Age at diagnosis	0.755				0.005	1.07	0.96–1.20	0.246	0.716			
Age at first biological therapy	0.957				0.009	0.98	0.87–1.09	0.675	0.950			
Disease duration, years	0.652				0.615				0.541			
Disease location												
Colon[a]												
Ileum	0.971				0.916				0.143			
Ileocolon	0.419				0.459				0.325			
Disease behavior												
Inflammatory[a]												
Structuring	0.213				0.244				0.184			
Penetrating	0.400				0.125				0.157			
Perianal disease No[a]/Yes	0.842				0.039	0.48	0.13–1.78	0.269	0.421			
History of intestinal resection No[a]/Yes	0.473				0.119				0.958			
CDAI before first biological therapy	0.180				0.115				0.155			
Steroid No[a]/Yes	0.004	2.32	1.30–4.13	0.004	0.048	2.49	0.83–7.48	0.103	0.657			
Immunomodulators No[a]/Yes	0.218				0.487				0.035	0.54	0.29–0.98	0.044
5-ASA No[a]/Yes	0.119				0.551				0.629			
Hemoglobin	< 0.001	0.91	0.76–1.10	0.322	0.028	0.81	0.59–1.11	0.186	0.581			
CRP	0.330				0.293				0.233			
Albumin	0.001	0.59	0.35–0.99	0.047	0.062	0.78	0.33–1.88	0.583	< 0.001	0.50	0.33–0.77	0.002

5-ASA 5-aminosalicylic acid, *CDAI* Crohn's Disease Activity Index, *CI* Confidence interval, *CRP* C-reactive protein, *HR* Hazard ratios, *anti-TNF* Anti-tumor necrosis factor

[a] Reference

biologics would offer the highest level of reliability. However, in practice, there are challenges in conducting such trials to assess the long-term effectiveness of these treatments. Consequently, numerous retrospective studies have been undertaken to compare the efficacy of UST, IFX, and ADA. Among these studies, our research is distinctive. It is the first to differentiate between bio-naïve and experienced patients and includes all three biologics (UST, IFX, and ADA) to assess crucial clinical outcomes. Furthermore, the significance of our study is emphasized by the provision of real-world data, particularly in Asia, where such data is limited [12, 15, 16].

Summarizing the results of previous retrospective studies using real-world data, it was observed that in bio-naïve CD patients, anti-TNF agents exhibited higher clinical remission rates after induction therapy than UST [9, 10]. However, in terms of treatment persistence, the findings have been mixed. Some studies found no significant differences in treatment persistence between anti-TNF agents and UST in bio-naïve patients [9, 10, 15], while others reported UST as superior in this regard [12, 17]. In bio-experienced patients, primarily exposed to anti-TNF agents, UST has generally demonstrated better treatment persistence compared to anti-TNF agents [12, 16, 17], as well as vedolizumab [18–20]. Conversely, one study reported lower treatment persistence with UST than anti-TNF agents and vedolizumab in bio-experienced CD patients. However, it should be noted that this study did not conduct matching to account for differing baseline characteristics, which may limit the interpretation of the results due to potential bias [21]. Similarly, after completing propensity score matching, our study found no significant differences in clinical remission after induction therapy and clinical events during the maintenance period in bio-naïve CD patients, aligning with the comparable efficacy indicated in previous studies. However, for bio-experienced CD patients, most of whom had been exposed to anti-TNF agents, UST might be superior in drug persistence, depending on the reasons for discontinuing anti-TNF agents.

In the multivariate analysis, we found that the risk of drug discontinuation was higher for IFX and ADA compared to UST. This observation may be attributed to the retrospective nature of our study, which resulted in variations in follow-up duration between the UST and anti-TNF agent groups. Additionally, factors related to the initial choice of these treatments and the reasons for discontinuing anti-TNF agents likely influenced these results. Therefore, when interpreting the results of this study as a whole, it can be inferred that UST, blocking interleukin (IL)-12 and IL-23, may be a beneficial option for CD patients who do not respond to anti-TNF agents. This interpretation is supported by mechanistic evidence indicating an increase in IL23-positive T cells in CD patients who do not respond to anti-TNF agents [22]. This aligns with the treatment sequence previously suggested for CD patients who have failed anti-TNF agents, as supported by various studies [19, 20, 23, 24]. In our study, the concurrent use of immunomodulators was found to be a factor that reduces the risk of drug discontinuation. Recommendations regarding combination therapy for CD patients vary in recent guidelines, but some commonalities exist. Most guidelines recommend combination therapy during induction in bio-naïve CD patients treated with anti-TNF agents [25, 26] or IFX [27, 28]. For UST, the benefits of combination therapy have not been established [29–32]. When it comes to maintaining remission, the recommendations are somewhat limited. Nonetheless, one guideline suggests combination therapy with anti-TNF agents, particularly IFX [25], which is supported by meta-analysis [33]. It is important to note that combination therapy with anti-TNF agents has been associated with lower immunogenicity [34, 35], suggesting that combination therapy may benefit patients receiving it from a mechanical perspective. Notably, we observed that the proportion of patients receiving combination therapy in bio-experienced CD patients was approximately 40%, while it was around 85% in bio-naïve patients. This rate difference in the use of combination therapy between these two groups highlights the need for further research on the role of combination therapy in maintaining remission for both categories of patients.

This study has several limitations, primarily due to its retrospective nature. Firstly, it cannot eliminate the potential for selection bias. However, we attempted to mitigate this limitation by employing propensity score matching to ensure that variables were as similar as possible at baseline. This approach helps reduce the potential for bias when interpreting results in the bio-naïve group. Secondly, despite data being collected from three different institutions, the number of enrolled patients was similar to that in other studies. Particularly in the case of the bio-experienced CD patients, a comparison had to be made between UST and anti-TNF agents due to the small number. Thirdly, in bio-experienced CD patients, we could not compare clinical outcomes based on the types of prior biologics and reasons for discontinuation due to the lack of this information. Additionally, differences in follow-up duration between the UST and anti-TNF agent groups should be considered when interpreting the results, as these variations could influence the observed outcomes, where UST demonstrated superiority in drug persistency over anti-TNF agents in bio-experienced CD patients. Fourthly, information regarding treatment targets such as fecal calprotectin or endoscopic healing was lacking, preventing comparison on the effectiveness

of different biologics based on these parameters. These limitations should be acknowledged when interpreting the study findings.

In conclusion, in bio-naïve CD patients, there was no observed difference in efficacy between UST, IFX, and ADA after propensity score matching. However, in bio-experienced CD patients, most of whom were exposed to anti-TNF agents, UST may have an advantage regarding drug durability depending on the reason for drug discontinuation. Further refined studies with long-term follow-up are warranted to address this issue.

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Authors' contributions
Author contributionsStudy concept and design: Ji Eun Na. Tae-Oh Kim. Acquisition, analysis, or interpretation of data: Ji Eun Na, Su Bum Park, Soyoung Kim, Seung Bum Lee. Writing and Drafting of the manuscript: Ji Eun Na, Tae-Oh Kim. Critical revision of the manuscript for important intellectual content: Yong Eun Park, Jong Ha Park, Tae-Oh Kim, Jong Hoon Lee, Su Bum Park, Soyoung Kim, Seung Bum Lee. Statistical analysis: Ji Eun Na. All authors approved the final submission.

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Availability of data and materials
Data are available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate
This study was conducted according to the guidelines of the Declaration of Helsinki. The Institutional Review Board of Inje University Haeundae Paik Hospital approved our protocol (File number. 2023-04-012-003). Patients' informed consent requirement was waived because only de-identified data were collected.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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