REVIEW ARTICLE

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Real-world effectiveness of ustekinumab for patients with ulcerative colitis: a systematic review and meta-analysis

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ABSTRACT

Ustekinumab has recently been approved for the treatment of ulcerative colitis (UC) based on data from clinical trials. However, the effectiveness of ustekinumab in patients with UC in a real-world setting remains unclear. Hence, in this meta-analysis, we aimed to evaluate the effectiveness of ustekinumab in a real-world setting and to investigate the predictors of its effectiveness. A comprehensive literature search was performed to examine the effectiveness of ustekinumab in UC patients admitted between January 2019 and December 2021. Data on clinical remission, response, and corticosteroid-free clinical remission rates were extracted, pooled, and analyzed. Meta-regression analysis was performed to investigate the source of heterogeneity and the impact of moderators on the outcomes of interest. A total of 14 eligible studies were identified. The pooled clinical remission rate was 55.0% at week 8, 36.1% at week 16, 46.6% at month 6, and 38.6% at month 12. The meta-regression analysis showed that prior use of anti-tumor necrosis factor (TNF) agents and vedolizumab and the publication style were significant moderators. Additionally, out of 258 patients, there were 28 adverse events (AEs) (10.9%). The effectiveness of ustekinumab in real-world patients with UC was consistent with the results clinical trials. Moreover, previous treatment with anti-TNF agents and vedolizumab might have affected the effectiveness of ustekinumab.

Keywords: ustekinumab, ulcerative colitis, systematic review, meta-analysis

Abbreviations:
UST: ustekinumab
UC: ulcerative colitis
RCTs: randomized controlled trials
TNF: tumor necrosis factor
VDZ: vedolizumab
AEs: adverse events

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INTRODUCTION

Ustekinumab (UST) is a monoclonal antibody that acts on the p40 subunit of interleukin-12 and interleukin-23. UST has recently been approved for the treatment of moderate to severe ulcerative colitis (UC) based on the efficacy and safety data derived from the UNIFI clinical trials.[1] Although clinical trials showed the efficacy and safety of UST and supported the approval of the use of UST, their results cannot yet be applied to daily clinical practice due to the limitations of the clinical trials' inclusion and exclusion criteria.[2] Since many patients seen in daily clinical practice do not meet the inclusion criteria for randomized controlled trials (RCTs) due to their age, presence of comorbidity, or intake of concomitant therapies, patients enrolled in RCTs are not representative of patients with ulcerative colitis.[3] Therefore, real-world evidence is important to complement the results of clinical trials and to guide physicians regarding treatment decisions. Several guidelines on the management of UC recommend the use of different drug classes, such as anti-tumor necrosis factor (TNF) agents, vedolizumab (VDZ), tofacitinib (TOF), or UST, for the induction of remission as a treatment option, especially for patients with moderately to severely active UC with inadequate response or intolerance to conventional therapy.[4,5] However, UST has not yet been established as a drug for UC. Real-world evidence investigating the predictors of the effectiveness of UST may be integral in clarifying the clinical value of UST in the management of patients with UC. Furthermore, real-world evidence can clarify the safety profile that is not fully revealed in RCTs. Although some studies reported real-world evidence for UC,[6-8] the number of patients included in each study was too small to make any definite conclusions and to investigate the predictors of effectiveness. Therefore, in this systematic review and meta-analysis, we aimed (a) to assess the effectiveness of UST using large real-world data and (b) to investigate the predictors of effectiveness.

MATERIALS AND METHODS

Protocol and registration

The protocol for this study was registered on PROSPERO (CRD42022300184) and was conducted in accordance with the preferred reporting items for systematic review and meta-analysis statements.[9]

Eligibility criteria

The types of studies included prospective and retrospective observational cohort studies, including conference abstracts. The study participants were adult patients (18 years or older) who underwent UST for UC. Patients who received UST only for maintenance therapy of UC or for treatment of diseases other than UC and patients with a previous colectomy were excluded. Studies reporting the effectiveness or safety outcomes of interest were eligible. Controlled clinical trials, such as RCTs, review articles, case reports, letters to the editor, and studies not published in English or Japanese were excluded from the review.

Information sources and search strategy

A comprehensive literature search was conducted including articles published between January 2019 and December 2021 using PubMed and the Web of Science. To ensure literature saturation, the reference lists of included studies were manually scanned. Conference proceedings for the Digestive Disease Week, United European Gastroenterology Week, European Crohn's and Colitis Organization, and Japan Digestive Disease Week were also searched. Literature search

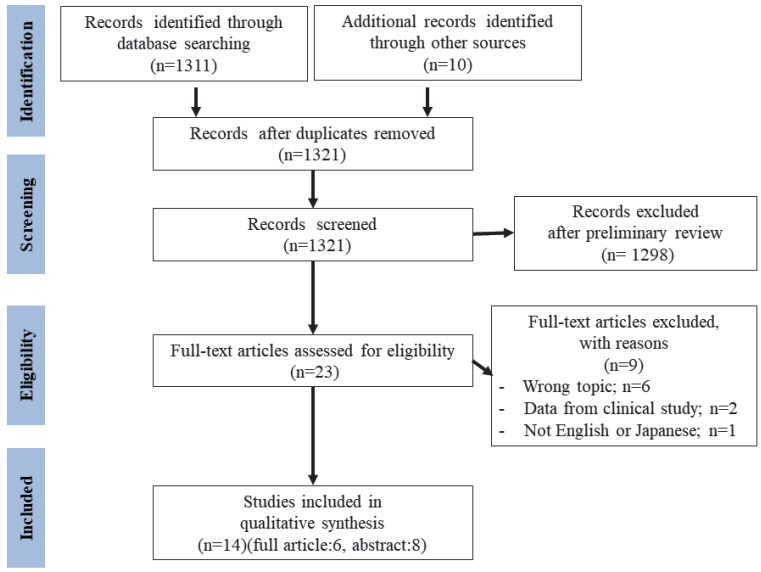

Fig. 1 Flow chart of the systematic review

strategies were developed using the following medical subject headings and text words related to UST in patients with UC: *ulcerative colitis, colitis, inflammatory bowel disease, ustekinumab, Stelara, interleukin-12, or interleukin-23.* The details of the search strategy are included in the appendices. The titles and abstracts of the results were initially scanned to exclude irrelevant studies. Subsequently, the full texts of the selected articles were screened to determine whether they were eligible. Two authors (GU and MN) independently decided which studies to include. Disagreements were resolved by consensus. Figure 1 shows the flow diagram of the study selection.

Data extraction

Two reviewers (GU and MN) independently extracted the data using a predesigned form. Data on the study characteristics included the primary author, year of publication, geographic location, and study design. Data on the patient and disease characteristics included age, sex, disease duration, location of disease, and severity. Data on medication history, percentage of patients with concomitant steroid or immunomodulator, or exposure to biologics or TOF were also included. Lastly, data on the outcome assessment, which included the induction and maintenance regimen of UST, total number of patients who received UST therapy, proportion achieving the outcome of interest, and time point when the outcomes were assessed, were also analyzed.

Outcomes assessed

The primary outcome measure was the clinical remission rate after treatment with the UST, which was defined as the proportion of patients with clinical remission at predefined time points. Secondary outcome measures included the clinical response rate, corticosteroid-free remission rate, discontinuation rate of UST, and adverse events (AEs). The definitions of clinical remission and response determined by the authors of each study were used to calculate the outcomes. When studies reported remission and response rates at various time points, we classified the assessment time points as follows: week 8 (4–8 weeks), week 16 (12–20 weeks), month 6 (24–32 weeks),

and month 12 (44–56 weeks) after the administration of the initial dose of UST. The severity of disease in each study included in this review was classified into three subgroups: mild, moderate, and severe. The classification was based on the mean or median of disease activity indices, such as the Mayo score,[10] simple clinical colitis activity index,[11] or clinical activity index.[12] The thresholds used to categorize the severity were listed in Supplementary Table 1. When multiple indices were reported in a previous study, a score with a higher severity was used to classify the disease severity.

Assessment of risk of bias in included studies

Two study investigators (GU and MN) independently assessed the risk of bias in individual studies using the Newcastle-Ottawa scale for cohort studies. Three perspectives were considered: the selection of the study groups, comparability of the groups, and ascertainment of either the exposure or outcome of interest for case-control or cohort studies.[13] Since studies of interest in this review were uncontrolled cohort studies, the domain 'comparability' and 'selection item 2' were not applicable.

Statistical analyses

The pooled clinical remission, clinical response, and corticosteroid-free clinical remission rates were appropriately calculated using a random-effect model,[14] and a conservative approach was used to account for the between-study variability. Meta-analysis was conducted using a double arcsine transformation with a back-transformation to report the pooled prevalence rates.[15] We assessed the statistical heterogeneity using the Q test and inconsistency (I^2) test. A P value < 0.10 and an I^2 value $> 50\%$ indicated significant heterogeneity.[16] To examine the impact of the moderators on the study effect size and the source of heterogeneity within the included studies, meta-regression analysis was performed. The omnibus (QM) tests of each moderator were undertaken and used as a basis for model simplification.[17] We assessed publication bias by examining the funnel plot symmetry and by conducting the Egger's regression test.[18] All analyses were performed using the R version 4.0.5 (Foundation for Statistical Computing, Vienna, Austria), which was equipped with the "meta" and "metafor" packages.

RESULTS

Study selection

From the 1,311 studies identified using the search strategy, we included 14 studies[7,8,19-30] in the quantitative analysis (Figure 1). Of the included studies, six[7,8,19-22] were full-text articles, and eight[23-30] were conference abstracts. Although the studies by Dalal et al[20,24,25] included patients treated in the same institution, each outcome of interest was different and exclusive. Therefore, the data related to the outcome of interest in this review (dose intensification,[20] cs-free clinical remission,[24] and clinical response[25]) were separately extracted from each. In addition, although studies by Fumery et al[7] and Amiot et al[8] included patients from the same cohort, each of the studies analyzed outcomes of different phases: maintenance phase[7] and induction phase.[8] Therefore, we extracted the data on effectiveness from each study. We extracted the data on optimization, discontinuation, and safety of UST only from the study by Fumery et al.[7] Chiappetta et al[22] reported that there were 68 patients who received the UST therapy. However, since one patient received UST for the treatment of psoriasis, we included the remaining 67 patients in this meta-analysis. The main characteristics of the studies included in this meta-analysis are summarized in Table 1.

Table 1 Characteristics of included studies

Authors, year	Country	Study design	Type of manuscript	Sample size, n	Gender, M, %	Age, years	Disease duration, years	Location of disease (extensive/left sided/ proctitis), n
Fumery M et al,[7] 2021	France	R	Full article	103	60.2	39.3 (29.1–52.3)[b]	7.6 (3.6–12.9)[b]	54/43/6
Chaparro M et al,[19] 2021	Spain	P	Full article	95	44.2	47 (16)[a]	NR	55/37/3
Dalal RS et al,[20] 2021	USA	R	Full article	108	43.5	39 (30–56)[c]	9 (4–16)[c]	NR/NR/28
Amiot A et al,[8] 2020	France	P	Full article	103	60.2	39.3 (29.1–52.3)[c]	7.6 (3.6–12.9)[c]	54/43/6
Ochsenkühn T et al,[21] 2020	Germany	R	Full article	19	57.9	46 (25–81)[b]	5 (2–15)[b]	11/7/0
Chiappetta MF et al,[22] 2021	Italy	R	Full article	68	63.2	42 (16–72)[b]	8 (NR)[b]	41/25/2
Hong S et al,[23] 2020	USA	R	Abstract	19	47.4	43 (NR)[b]	9.6 (NR)[b]	10/8/1
Dalal RS et al,[24] 2021	USA	R	Abstract	81	21.0	41.7 (11.5)[a]	8.6 (NR)[a]	22/13/1
Dalal RS et al,[25] 2021	USA	R	Abstract	108	43.5	39 (30–56)[b]	9 (4–16)[b]	NR/NR/28
Haraikawa M et al,[26] 2021	Japan	R	Abstract	19	57.9	47.4 (NR)[a]	NR	NR/NR/NR
Yamana Y et al,[27] 2021	Japan	R	Abstract	11	27.3	40 (24–71)[b]	NR (2.08–12.7)[b]	3/6/0
Asaeda K et al,[28] 2021	Japan	R	Abstract	20	50.0	42.9 (20–74)[b]	NR	16/NR/NR
Ando K et al,[29] 2021	Japan	R	Abstract	71	NR	NR	NR	NR/NR/NR
Dominik E et al,[30] 2021	Austria	R	Abstract	26	69.2	27 (NR)[b]	NR	NR/NR/NR

(Continued on next page)

M: male
R: retrospective
P: prospective
IM: immunomoderator
CS: corticosteroid
TNF: tumor necrosis factor
VED: vedolizumab
TOF: tofacitinib
NR: not reported
[a] Mean (standard deviation)
[b] Median (range)
[c] Median (Interquartile range)

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Table 1 Characteristics of included studies (continued)

Severity of disease	Baseline CRP	Prior IM, n, (%)	Concomitant CS, n, (%)	Prior anti-TNFα, n (%)	Prior ≥2 anti-TNFα, n, (%)	Prior VED, n, (%)	Prior TOF, n, (%)	Concomitant IM therapy, n, (%)	Assessment time point, week
Moderate	7.1 (NR)[a]	87 (84.5)	50 (48.5)	102 (99.0)	72 (69.9)	88 (85.4)	10 (9.71)	24 (23.3)	12–16, 26, 52
Moderate	NR	NR	53 (55.8)	93 (97.9)	55 (57.9)	78 (82.1)	28 (29.5)	16 (16.8)	16, 24, 52
Mild	3.6 (0.8–12.9)[b]	68 (63.0)	62 (57.4)	99 (91.7)	43 (39.8)	NR	NR	18 (16.7)	12–16
Moderate	7.1 (3.1–15.0)[c]	85 (82.5)	50 (48.5)	102 (99.0)	72 (69.9)	88 (85.4)	10 (9.71)	24 (23.3)	12–16
Moderate	NR	NR	9 (47.4)	8 (42.1)	NR	6 (31.6)	NR	1 (5.26)	52
Moderate	NR	NR	37 (54.4)	65 (95.6)	30 (44.1)	47 (69.1)	NR	15 (22.1)	8, 24, 52
Moderate	0.48 (0.8)[a]	16 (84.2)	NR	19 (100)	5 (26.3)	17 (89.5)	2 (10.5)	16 (84.2)	12, 52
Mild	1.24 (2.53)[a]	28 (34.6)	23 (28.4)	34 (42.0)	17 (21.0)	34 (42.0)	NR	8 (9.88)	12–16, 52
Mild	0.36 (0.08–1.29)[b]	68 (63.0)	62 (57.4)	99 (91.7)	43 (39.8)	72 (66.7)	22 (20.4)	18 (16.7)	12–16
Moderate	NR	NR	NR	6 (31.6)	NR	11 (57.9)	NR	NR	8, 24
NR	NR	NR	NR	6 (54.5)	NR	NR	NR	NR	4
Moderate	NR	NR	4 (20.0)	NR	NR	NR	NR	6 (30.0)	8
NR	NR	NR	25(35.2)	NR	NR	NR	NR	27 (38.0)	8, 16, 32
Moderate	NR	NR	NR	NR	NR	NR	NR	NR	8

M: male
R: retrospective
P: prospective
IM: immunomoderator
CS: corticosteroid
TNF: tumor necrosis factor
VED: vedolizumab
TOF: tofacitinib
NR: not reported
[a] Mean (standard deviation)
[b] Median (range)
[c] Median (Interquartile range)

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Table 2 Quality assessment with the Newcastle-Ottawa Scale

	Selection				Comparability		Outcome		
Author	Representativeness of the exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at start of study	Comparability of cohorts on the basis of the design or analysis	Assessment of outcome	Was follow-up long enough for outcomes to occur	Adequacy of follow up of cohorts	Total
Fumery M et al[7]	★	NA	★	★	NA	★	★	★	6
Chaparro M et al[19]	★	NA	★	★	NA	★	★	★	6
Dalal RS et al[20,24,25]	★	NA	★	★	NA	★	★		5
Amiot A et al[8]	★	NA	★	★	NA	★	★	★	6
Ochsenkühn T et al[21]	★	NA	★	★	NA	★	★	★	6
Chiappetta MF et al[22]	★	NA	★	★	NA	★	★	★	6
Hong S et al[23]	★	NA	★	★	NA	★	★		5
Haraikawa M et al[26]	★	NA	★	★	NA	★	★	★	6
Yamana Y et al[27]	★	NA	★	★	NA	★	★	★	6
Asaeda K et al[28]	★	NA	★	★	NA	★	★		5
Ando K et al[29]	★	NA	★	★	NA	★	★	★	6
Dominik E et al[30]	★	NA	★	★	NA	★	★		5

NA: not applicable

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Risk of bias

The quality of the included studies was assessed using the Newcastle-Ottawa Scale (Table 2). The mean of the Newcastle-Ottawa scale among the included studies was 5.57 points out of 6. The 'outcome item 3' showed a relatively low score compared to the others. Furthermore, there were some variabilities in the definition of clinical remission and response (Supplementary Table 2, Supplementary Table 3), severity of patients (Table 1), and regimen of UST treatment (Supplementary Table 4), and these differences may be subject to bias. In addition, since there were differences in the prior treatment history and refractory nature of the patients included in each study (Table 1), there might also be a selection bias in the results of the meta-analysis.

Primary outcomes

Clinical remission. The clinical remission rate was assessed in 12 studies.[7,8,19-21,23-29] The pooled clinical remission rates were 55.0% at week 8 (95% CI, 44.8–65.0%), 36.1% at week 16 (95% CI, 28.4–44.1%), 46.6% at month 6 (95% CI, 32.9–60.5%), and 38.6% at month 12 (95% CI 28.5–49.2%) (Figure 2). There was a significant between-study heterogeneity in the analyses of clinical remission at week 16 and month 6 (I^2 = 62%–70%, P = 0.01). Meta-regression analysis

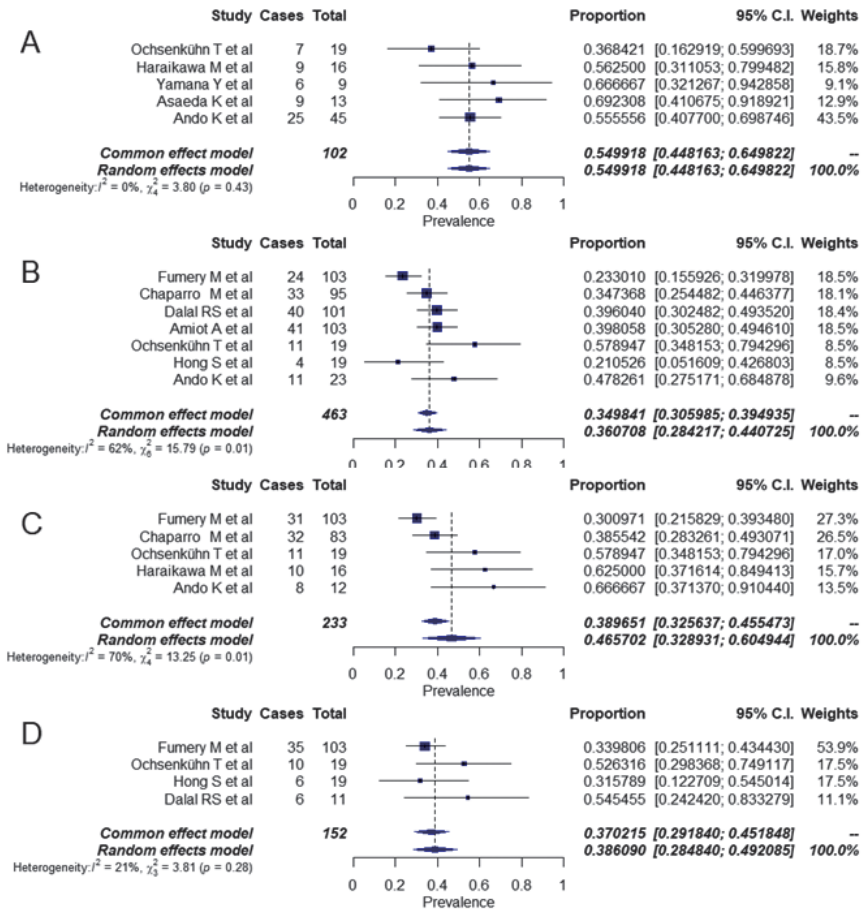

Fig. 2 Forest plot of the clinical remission rate:
(A) at week 8, (B) at week 16, (C) at month 6, and (D) at month 12

was performed to explain the significant between-study heterogeneity in the effectiveness of the UST. The covariates selected in the present meta-regression were the study design; number of centers; prior use of anti-TNF agents, more than two anti-TNF agents, VDZ, or TOF; severity of disease; concomitant use of immunomodulators or steroids; and publication style of studies. The results of the meta-regression analysis showed that prior use of anti-TNF agents and VDZ at week 16 (QM test of moderators: prior anti-TNF agent: QM = 4.1836, P = 0.0408; prior use of VDZ: QM = 4.0142, P = 0.0451), prior use of anti-TNF agents or VDZ, and publication style at month 6 (QM test of moderators: prior anti-TNF agent: QM = 8.2875, P = 0.004; prior use of VDZ: QM = 6.4679, P = 0.011; publication style of studies: QM = 4.6219, P = 0.0316) were significant moderators (Table 3) (Figure 3, 4).

Table 3 All the QM statistics for whether the moderators have a significant effect on clinical remission rate

(A) Clinical remission week 8

Moderator	QM	df	p
Number of center	0.0038	1	0.9506
Prior anti-TNFα	0.0884	1	0.7662
Severity	0.2327	1	0.6295
Concomittant IM	2.8879	1	0.0892
Concomittant steroid	3.1418	1	0.0763
Publish style	2.8879	1	0.0892

(B) Clinical remission week 16

Moderator	QM	df	p
Study design	0.0183	1	0.8923
Number of center	0.0963	1	0.7563
Prior anti-TNFα	4.1836	1	0.0408
Prior more than two anti-TNFα	0.0006	1	0.9804
Prior VDZ	4.0142	1	0.0451
Prior TOF	0.1771	1	0.6739
Severity	0.9828	2	0.6118
Concomittant IM	1.6126	1	0.2041
Concomittant steroid	0.3863	1	0.5343
Publish style	0.0194	1	0.8892

(C) Clinical remission month 6

Moderator	QM	df	p
Study design	0.3507	1	0.5537
Number of center	3.0936	1	0.0786
Prior anti-TNFα	8.2875	1	0.004
Prior VDZ	6.4679	1	0.011
Severity	1.386	1	0.2391
Concomittant IM	0.0321	1	0.8578
Concomittant steroid	1.3962	1	0.2374
Publish style	4.6219	1	0.0316

(D) Clinical remission month 12

Moderator	QM	df	p
Number of center	1.0845	2	0.5814
Prior anti-TNFα	3.7936	1	0.0514
Prior more than two anti-TNFα	0.3586	1	0.5493
Prior VDZ	3.7217	1	0.0537
Severity	1.1402	1	0.2856
Concomittant IM	1.0255	1	0.3112
Concomittant steroid	0.637	1	0.4248
Publish style	0.005	1	0.9434

QM: test statistic for the omnibus test of moderators
TNF: tumor necrosis factor
df: degrees of freedom
VDZ: vedolizumab
TOF: tofacitinib
IM: immunomodulator

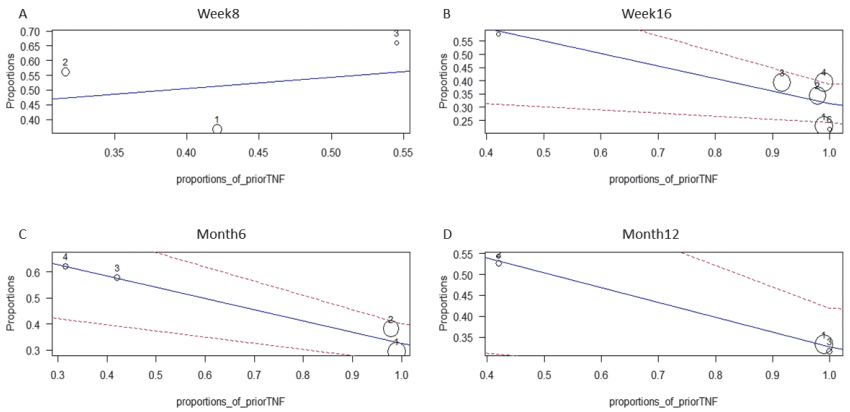

Fig. 3 Meta-regression scatter plot of the clinical remission rate based on the prior use of anti-tumor necrosis factor agents

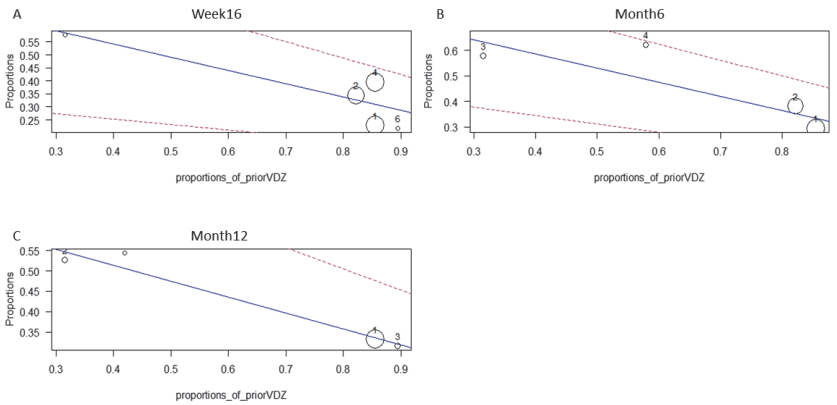

Fig. 4 Meta-regression scatter plot of the clinical remission rate based on the prior use of vedolizumab

Secondary outcomes

Clinical response. The clinical response rate was assessed in 13 studies.[7,8,19-27,29,30] The pooled clinical response rates were 70.2% at week 8 (95% CI, 53.2–85.0%), 56.4% at week 16 (95% CI, 49.7–63.0%), 83.8% at month 6 (95% CI, 74.8–91.3%), and 62.6% at month 12 (95% CI, 16.3–98.1%) (Supplementary Figure 1). There was significant between-study heterogeneity in the analyses of clinical response at week 8 and month 12 (I^2 = 76%–92%, $P < 0.01$). Meta-regression analysis was performed, although the covariates included in the analysis at week 8, month 6, and month 12 were limited because of the lack of studies in which the data were available for the analysis. The meta-regression analysis showed that no covariate was a significant moderator (Table 4).

Table 4 All the QM statistics for whether the moderators have a significant effect on clinical response rate

(A) Clinical response week 8

Moderator	QM	df	p
Number of center	0.0003	1	0.9506
Severity	1.226	1	0.2682

(B) Clinical response week 16

Moderator	QM	df	p
Study design	0.9954	1	0.3184
Number of center	1.6779	2	0.4322
Prior anti-TNFα	0.3354	1	0.5625
Prior more than two anti-TNFα	0.0167	1	0.8971
Prior VDZ	0.0059	1	0.9387
Prior TOF	0.063	1	0.8019
Severity	3.0222	2	0.2207
Concomittant IM	0.0733	1	0.7865
Concomittant steroid	0.2718	1	0.6021
Publish style	0.9954	1	0.3184

(C) Clinical response month 6

Moderator	QM	df	p
Severity	0.0136	1	0.9073
Publish style	0.7295	1	0.3931

QM: test statistic for the omnibus test of moderators
TNF: tumor necrosis factor
df: degrees of freedom
VDZ: vedolizumab
TOF: tofacitinib
IM: immunomodulator

Corticosteroid-free clinical remission. The corticosteroid-free clinical remission rate was assessed in 11 studies.[7,8,19-25,27,29] The pooled corticosteroid-free clinical remission rates were 29.7% at week 16 (95% CI, 18.1–42.7%), 30.1% at month 6 (95% CI, 24.4–36.0%), and 38.8% at month 12 (95% CI, 28.8–49.2%) (Supplementary Figure 2). There was no data on corticosteroid-free clinical remission at week 8. Significant between-study heterogeneity was observed in the analyses of corticosteroid-free clinical remission at week 14 (I^2 = 75%, P = 0.02). The results of the meta-regression analysis showed that no covariate was a significant moderator. Meta-regression analysis at week 8 could not be performed, and covariates included in the analysis at months 6 and 12 were limited due to the lack of data available for the analysis (Table 5).

Table 5 All the QM statistics for whether the moderators have a significant effect on corticosteroid-free clinical remission rate

(A) Corticosteroid-free clinical remission week 16

Moderator	QM	df	p
Study design	0.2123	1	0.6449
Number of center	0.5493	1	0.4586
Prior anti-TNFα	0.5493	1	0.4586
Prior more than two anti-TNFα	0.5493	1	0.4586
Prior VDZ	0.5493	1	0.4586
Severity	0.5493	1	0.4586
Concomittant IM	0.5493	1	0.4586
Concomittant steroid	0.5493	1	0.4586
Publish style	0.5493	1	0.4586

(B) Clinical remission month 6

Moderator	QM	df	p
Study design	0.0001	1	0.9918
Concomittant IM	0.0049	1	0.9441
Concomittant steroid	0.0637	1	0.8008

(C) Clinical remission month 12

Moderator	QM	df	p
Prior anti-TNFα	0.6304	1	0.4272
Prior VDZ	2.6149	1	0.1059
Concomittant IM	0.5228	1	0.4697
Concomittant steroid	0.5238	1	0.4692
Publish style	0.3312	1	0.5649

QM: test statistic for the omnibus test of moderators
TNF: tumor necrosis factor
df: degrees of freedom
VDZ: vedolizumab
TOF: tofacitinib
IM: immunomodulator

Optimization of UST interval in maintenance phase. Four studies[7,19,20,30] reported that there was an interval shortening of the UST (Table 6). The rate of UST interval shortening ranged from 27.2% to 63.1%. Among the three studies,[7,19,20] reporting the outcome after interval shortening, clinical remission, and clinical response was achieved in 5.6%–55% and 30.7%–67.5%, respectively.

Discontinuation rates. Five studies[7,19,21,22,30] reported the discontinuation of UST (Table 6). Discontinuation rates ranged from 11.5% to 43.7%. The most common reason for discontinuation was the lack of the effectiveness of UST, as reported in 28.4% of patients (88 out of 310 patients). Treatment discontinuation due to AEs occurred in 1.29% (4 out of 310 patients) of patients.

Table 6 Optimization and discontinuation of ustekinumab

Author	N	Follow up time, week (mean or median)	Shortening of UST interval, n, (%)	Patients with discontinuation, n, (%)	Reason of discontinuation
Fumery M et al[7]	103	48[a]	65 (63.1)	45 (43.7)	Lack of effectiveness (n = 41) Pregnancy (n = 1) Adverse event (n = 1) Personal decision after two episodes of mild skin rash (n=1)
Chaparro M et al[19]	95	82[b]	18 (27.2)	34 (36.0)	Primary non-response (n=21) (22%) Loss of response in (n=12) (13%) Adverse event in (n=1) (1%)
Dalal RS et al[20,24,25]	108	NR	46 (42.6)	NR	NR
Ochsenkühn T et al[21]	19	NR	NR	5 (26.3)	Refractory disease (n=4) (80%) Side effect (n=1) (20%)
Chiappetta MF et al[22]	67	NR	0 (0)	9 (13.4)	Primary failure (n=1, 11.1%) Secondary failure (n=7, 77.8%) AEs (n=1, 11.1%)
Hong S et al[23]	19	NR	NR	NR	NR
Haraikawa M et al[26]	19	NR	NR	NR	NR
Yamana Y et al[27]	11	NR	NR	NR	NR
Asaeda K et al[28]	20	NR	NR	NR	NR
Ando K et al[29]	71	NR	NR	NR	NR
Dominik E et al[30]	26	NR	14 (53.8)	3 (11.5)	Lack of improvement (n=2) (66.7%) Colorectal cancer (n=1) (33.3%)

(Continued on next page)

[a] median
[b] mean
NR: not reported

Table 6 Optimization and discontinuation of ustekinumab (continued)

Interval of UST in maintenance regimen before shortening	Interval of UST in maintenance regimen after shortening	Reason of interval shortening	Outcome after interval shortening
Every 8 weeks	Every 4 weeks	NR	Clinical response (n=20) (30.7%) Clinical remission (n=17) (26.1%)
Three patients (10%) started the maintenance phase with every-12-week schedule, 24 patients (80%) with every-8-week, and 3 (10%) with intensified schedule (every 6 weeks or every 4 weeks)	Every 4 or 6 weeks	Primary failure (n=10) (55%) Partial response (n=3) (17%) Loss of response (n=5) (28%)	1 (5.6%) patient who escalated the dose due to loss of response reached remission.
Every 8 weeks	Every 4 or 6 weeks	No initial response (n=22) (47.8%) Loss of response (n=20) (43.5%)	Remission (n=22) (55.0%) Response (n=27) (67.5%) Drug discontinuation or colectomy (n=12) (13%) within 16 weeks after intensification
Every 8 weeks	NR	NR	NR
Every 8 weeks	NR	NR	NR
NR	NR	NR	NR
NR	NR	NR	NR
NR	NR	NR	NR
NR	NR	NR	NR
NR	NR	NR	NR
Every 8 weeks	Every 4 or 6 weeks	NR	NR

[a] median
[b] mean
NR: not reported

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Safety. Safety outcomes were reported in five studies.[7,19-22] In total, 28 AEs were reported in 258 patients (10.9%). The specific characteristics of an AE are summarized in Table 7. The infection rate was 4.26% (11 out of 243). The most common non-infectious AEs, except inflammatory bowel disease exacerbation, was arthralgia (n = 5, 1.94%), followed by skin rash (n = 4, 1.55%).

Table 7 Adverse events of ustekinumab treatment for patients with ulcerative colitis

	No. of studies, n	Total patients, n	Patients with AE, n, (%)	Source
Any AEs	5	258	28 (10.9)	Fumery M et al,[7] Chaparro M et al,[19] Dalal RS et al,[20] Ochsenkühn T et al,[21] Chiappetta MF et al[22]
Infection	4		11 (4.3)	
Pneumonia	1		1 (0.4)	Fumery M et al[7] (n=1)
Dental abscess	1		2 (0.8)	Fumery M et al[7] (n=2)
Clostridium difficile infection	2		2 (0.8)	Fumery M et al[7] (n=1), Dalal RS et al[20] (n=1)
Urinary tract infection	1		1 (0.4)	Chaparro M et al[19] (n=1)
Rhinopharyngitis	1		1 (0.4)	Fumery M et al[7] (n=1)
Lateral pharyngitis	1		1 (0.4)	Ochsenkühn T et al[21] (n=1)
Otitis media	1		1 (0.4)	Ochsenkühn T et al[21] (n=1)
Covid 19	1		1 (0.4)	Chaparro M et al[19] (n=1)
Malignancies	1		1 (0.4)	
Breast cancer	1		1 (0.4)	Ochsenkühn T et al[21] (n=1)
Others	5		17 (6.6)	
Skin rash	2		4 (1.6)	Fumery M et al[7] (n=3), Chaparro M et al[19] (n=1)
Arthralgia	1		5 (1.9)	Fumery M et al[7] (n=5)
IBD exacerbation	2		10 (3.9)	Fumery M et al [7] (n=6), Dalal RS et al [20] (n=4)
Symptomatic urolithiasis	1		1 (0.4)	Fumery M et al[7] (n=1)
Gastroenteritis	1		2 (0.8)	Fumery M et al[7] (n=2)
Myocardial infarction	1		1 (0.4)	Fumery M et al[7] (n=1)
Fatigue	1		1 (0.4)	Fumery V et al[7] (n=1)
Rectal adenoma	1		1 (0.4)	Ochsenkühn T et al[21] (n=1)
Hearing loss	1		1 (0.4)	Ochsenkühn T et al[21] (n=1)
Atrial fibrillation	1		1 (0.4)	Ochsenkühn T et al[21] (n=1)
Pituitary adenoma	1		1 (0.4)	Chiappetta MF et al[22] (n=1)
Retinal detachment	1		1 (0.4)	Ochsenkühn T et al[21] (n=1)

AE: adverse events
IBD: inflammatory bowel disease

Publication bias evaluation

We found statistically significant evidence of publication bias using the Egger's test in the analysis of clinical remission at month 6 and corticosteroid-free clinical remission at month 6 (Figure 5, Supplementary Figures 3 and 4). Although statistical evidence of publication bias was not found in the Egger's regression test in other analyses, the number of studies included was too small to adequately assess publication bias.[18]

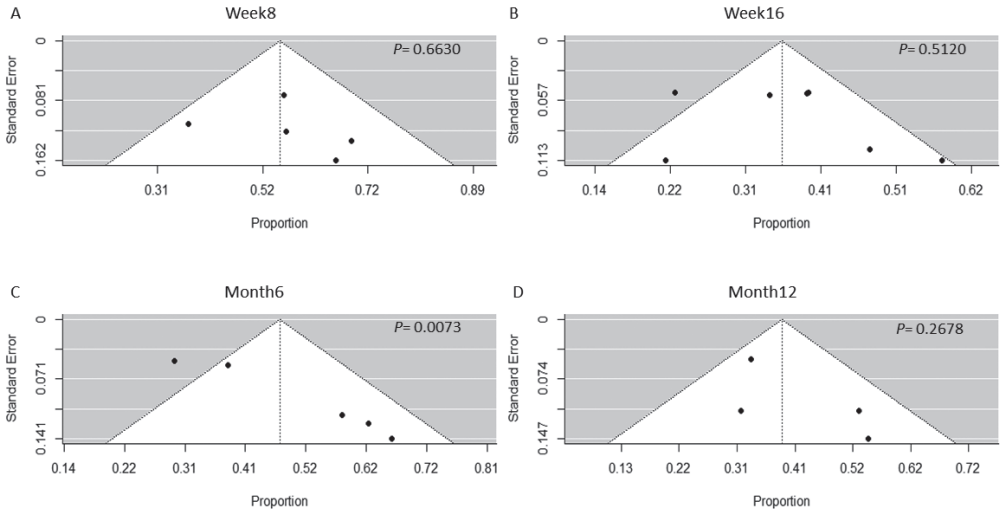

Fig. 5 Funnel plot analysis of the clinical remission rate

DISCUSSION

To the best of our knowledge, this was the most comprehensive systematic review and meta-analysis that evaluated the real-world effectiveness of UST for the treatment of UC. Although a systematic review of real-world effectiveness in inflammatory bowel disease was reported recently,[6] the study included only three studies on UC. In addition, although the effectiveness of UST for patients with UC was demonstrated in the UNIFI clinical trials,[1] the efficacy of RCT was not representative of the real-world population.[3] Therefore, the results of this review can provide valuable information for clinicians to develop treatment strategies for patients with UC in daily clinical practice.

This study showed that the pooled clinical remission and response rate at week 8 were 55% and 70.2%, respectively. In addition, the pooled clinical remission, clinical response, and corticosteroid-free clinical remission rate at week 44 in this meta-analysis were 38.6%, 62.6%, and 38.8%, respectively. On the other hand, the UNIFI trial reported that the clinical remission and response rate of patients who received 6 mg/kg of UST on week 8 were 15.5% and 61.8%, respectively, and the clinical remission, response, and corticosteroid-free clinical remission rate at week 44 were 38.4–43.8%, 68.0–71.0%, and 37.8–42.0%, respectively.[1] The results from this study were consistent with the results of the induction and maintenance therapy reported in the UNIFI trial, despite the fact that patients in real-world settings could have more complex disease characteristics compared with those in the RCT.

Investigating the predictors of response to UST is important for clinicians in the selection of patients who are eligible for UST treatment. Some studies reported that prior use of anti-TNF-α agents was a predictor of the poor efficacy of UST in patients with Crohn's disease.[31,32] In the UNIFI trial, although the effectiveness of UST was also shown in the subgroup of patients who had previous treatment failure with biologics, the same patients seemed to have a lower response to UST than those who took biologics without failure of treatment.[1] However, the impact of previous treatment on the effectiveness of UST in patients with UC has not been well demonstrated. In this study, the results of the meta-regression analysis showed that patients with prior use of anti-TNF-α agents or VDZ had a lower clinical remission rate, although there was no statistically significant correlation at week 8 and month 12. Based on these results, UST might be preferred as an early-line biologic treatment option in patients with UC. However, this result should be interpreted with caution because the effectiveness of anti-TNF-α agents and VDZ in patients with previous UST failure is unknown. Furthermore, since unidentified factors could be responsible for the differential effect sizes across subgroups, the results of the meta-regression analysis could not be interpreted as causal evidence. Therefore, further prospective studies are needed to investigate the predictors of response to biologics and to compare their effectiveness.

Overall, UST was well tolerated. There were no new serious AEs reported in this study, although safety data in real-world practice yielded a lower safety profile lower compared to those in RCTs because of their stricter reporting process of AEs. The reason for discontinuation of UST was lack of effectiveness, whereas the rate of discontinuation due to AEs was low (1.29%) in this study.

Dose escalation or interval shortening of biologics are one of the treatment strategies for the lack of effectiveness of treatments for inflammatory bowel disease.[33] There were four studies,[7,19,20,30] in which the UST interval was shortened in this study. Of these studies that reported the interval shortening of UST, clinical remission was achieved in 5.6%–55.0% of patients with primary or secondary failure of UST. Although predictors of response to dose intensification are not known, interval shortening of UST can be a useful treatment strategy due to the lack of effectiveness of the UST therapy in patients with UC.

This study has several limitations. First, statistically significant between-study heterogeneity was detected, as shown by the I^2 value. Although we performed a meta-regression analysis, the number of studies included in the meta-regression analysis was small. Hence, the statistical power to identify significant factors was limited,[34,35] and heterogeneity was not completely controlled. Furthermore, the definitions of clinical remission and response, time points used to evaluate the efficacy of UST, severity of patients, and dosing regimen of UST varied. Thus, these differences could contribute to heterogeneity, and the reliability of the pooled effect sizes is relatively limited. Second, since some retrospective studies or conference abstracts were included in this study, the results could be biased due to incomplete findings. Third, publication bias, which was shown in the results of the funnel plots and Egger's regression test, could limit the results of this study, although the inclusion of conference abstracts and full papers could minimize the risk of publication bias. Fourth, since data on the endoscopic information were not available in the majority of studies, endoscopic mucosal healing, which was reportedly associated with improved long-term outcomes in patients with UC,[36] could not be assessed in this study. Nevertheless, we believe that the real-world effectiveness of UST in heterogeneous and complex patient populations shown in this review could provide important insights into daily clinical practice.

CONCLUSION

Real-world data supported the effectiveness and safety of UST in patients with UC. The early use of UST prior to other biologic agents, such as anti-TNF-α agents or VDZ, might be one of the treatment strategies for patients with UC to maximize the potential of UST. However, further prospective studies investigating the predictors of the effectiveness and long-term outcomes of UST are required.

CONFLICT OF INTEREST

None declared.

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SUPPLEMENTARY MATERIALS

Supplementary Table 1 Cut-off values used to classify the disease severity

	Mild	Moderate	Severe
Mayo score	3–5	6–10	11–12
Partial Mayo score	2–4	5–6	7–9
Simple clinical colitis activity index	3–5	6–11	12 ≤
Clinical activity index	5–6	7–11	12 ≤

Supplementary Table 2 Definition of clinical remission in each studies

Author	Definition of clinical remission
Fumery M et al[7]	Clinical remission was defined as a partial Mayo Clinic score ≤2 (including stool frequency, rectal bleeding and physician global assessment subscores), with a combined stool frequency and rectal bleeding subscore ≤1.
Chaparro M et al[19]	Partial Mayo Score ≤2
Dalal RS et al[20,24,25]	SCCAI or partial Mayo <3 points
Amiot A et al[8]	Clinical remission was defined as a partial Mayo Clinic score ≤2, with a combined stool frequency and rectal bleeding subscore ≤1.
Ochsenkühn T et al[21]	Remission is defined as a Lichtiger score of three or less.
Chiappetta MF et al[22]	9-point partial Mayo <2 points
Hong S et al[23]	A total score of 2 or less than 1 on the partial Mayo score (range: 0 to 9) and no subscore greater than 1 on any of the Mayo scale component
Haraikawa M et al[26]	CAI ≤4
Yamana Y et al[27]	Partial Mayo ≤2 and each subscore <2
Asaeda K et al[28]	NR
Ando K et al[29]	NR
Dominik E et al[30]	NR

SCCAI: simple clinical colitis activity index
CAI: clinical activity index
NR: not reported

Supplementary Table 3 Definition of clinical response in each studies

Author	Definition of clinical response
Fumery M et al[7]	NR
Chaparro M et al[19]	NR
Dalal RS et al[20,24,25]	Reduction in SCCAI or Mayo by ≥ 3 points from baseline
Amiot A et al[8]	Defined by a reduction in the partial Mayo Clinic score of at least 3 points and a decrease of at least 30%, with a decrease of at least 1 point on the rectal bleeding subscale or an absolute rectal bleeding score of 0 or 1 from the baseline score
Ochsenkühn T et al[21]	Partial response is defined as a Lichtiger score of 4–10
Chiappetta MF et al[22]	NR
Hong S et al[23]	A decrease in partial Mayo score at 3 months or total Mayo score at 12 months of at least 30% and of at least 3 points from baseline, with an accompanying decrease of at least 1 point on the Mayo rectal bleeding subscore or a rectal bleeding subscore of 0 or 1
Haraikawa M et al[26]	Decrease of CAI ≥3 and CAI ≤10
Yamana Y et al[27]	Decrease of partial Mayo ≥3 and blood subscore 0 or 1
Asaeda K et al[28]	NR
Ando K et al[29]	NR
Dominik E et al[30]	Decrease of Mayo score ≥3

SCCAI: simple clinical colitis activity index
CAI: clinical activity index
NR: not reported

Supplementary Table 4 Outcome measures and treatment regimens in each studies

Author	Primary outcome measure	Secondary outcome measure	Induction regime	Maintenance regime
Fumery M et al[7]	Steroid-free clinical remission at 12 months	Persistence of ustekinumab therapy, dose intensification, Mayo Clinic endoscopic subscore and UCEIS over the study period, colectomy and occurrence of any adverse event or severe adverse event	6 mg/kg iv or 270 mg sc	90 mg dose sc at week 8 after the induction phase
Chaparro M et al[19]	The durability of ustekinumab treatment	The short-term response (at week 16) and the long-term effectiveness (at maximum follow-up), to identify predictive factors of response, to describe the schedules of ustekinumab administration in UC in real-life and the need for dose adjustments, and to assess the safety of ustekinumab in clinical practice	6 mg/kg iv	The maintenance phase started with every-12-week schedule (n=3) (10%), with every-8-weeks (n=24) (80%), with intensified schedule (every-6-weeks or every-4-weeks) (n=3) (10%)
Dalal RS et al[20]	Corticosteroid-free clinical remission	Clinical response at 12–16 weeks and time to intensification	NR	Induction and maintenance dosing every 8 weeks
Amiot A et al[8]	Steroid-free clinical remission at weeks 12–16	Clinical response, persistence of ustekinumab therapy, dose optimisation at weeks 12–16, endoscopic changes between week 0 and weeks 12–16 and occurrence of any adverse event or severe adverse event	6 mg/kg iv (n=93) three scheduled subcutaneous injections of 90 mg between week 0 and week 8 (n=10)	90 mg injected subcutaneously every 8–12 weeks according to the investigator's decision and for up to week 16.
Ochsenkühn T et al[21]	Achievement of clinical remission at one year	NR	6 mg/kg body weight iv	Once every eight weeks subcutaneous injection of 90 mg
Chiappetta MF et al[22]	Achievement of clinical remission at 24 and 52 weeks	Clinical response, reduction of concomitant steroid use, the reduction of the number of patients with elevated CRP at baseline and during follow-up, together with safety. The rate of mucosal healing, and possible causes of withdrawal with persistence in therapy at 52 weeks.	Weight-based 260 mg<55 kg, 390 mg between 55 kg and 85 kg, 520 mg >85 kg) i.v. infusion at week 0	Subcutaneous injection once every eight weeks of 90 mg
Hong S et al[23]	Clinical remission	NR	NR	NR
Dalal RS et al[24]	Steroid-free clinical remission at week 12–16	Steroid-free clinical response at week 12–16, drug survival (time to treatment discontinuation or colectomy due to suboptimal disease control), steroid-free clinical remission at week 52, endoscopic remission, adverse events	NR	NR
Dalal RS et al[25]	Colectomy-free drug survival	Clinical response at week 12–16, steroid-free clinical response, UST dose intensification	NR	NR
Haraikawa M et al[26]	NR	NR	NR	NR
Yamana Y et al[27]	Partial Mayo score at week 4	NR	NR	NR
Asaeda K et al[28]	NR	NR	NR	NR
Ando K et al[29]	NR	NR	NR	NR
Dominik E et al[30]	NR	NR	NR	NR

UCEIS: Ulcerative Colitis Endoscopic Index of Severity
NR: not reported

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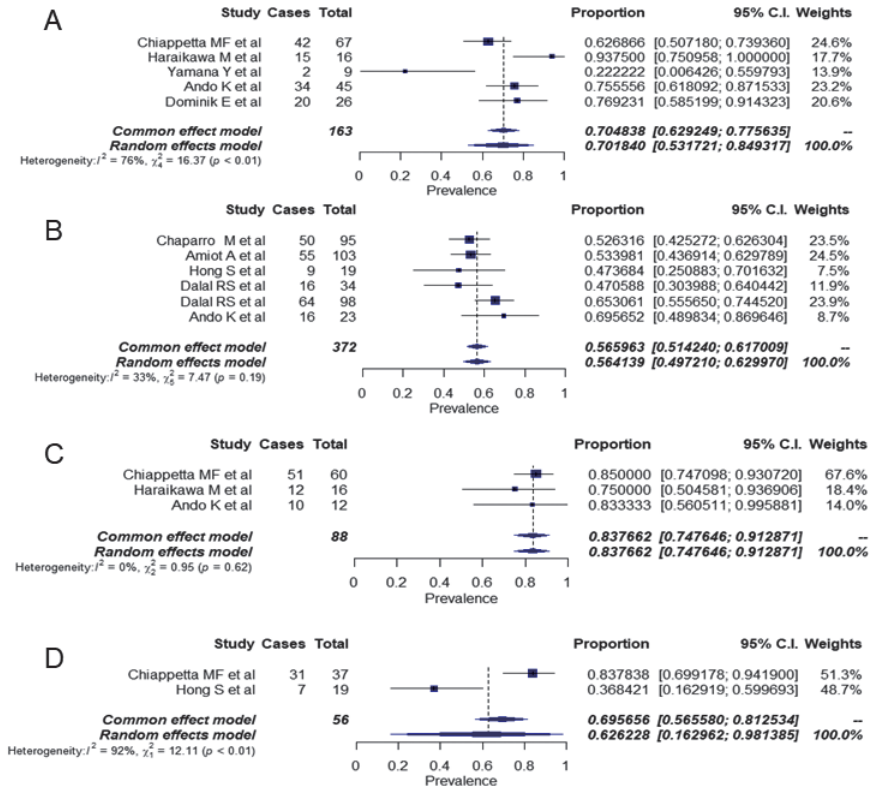
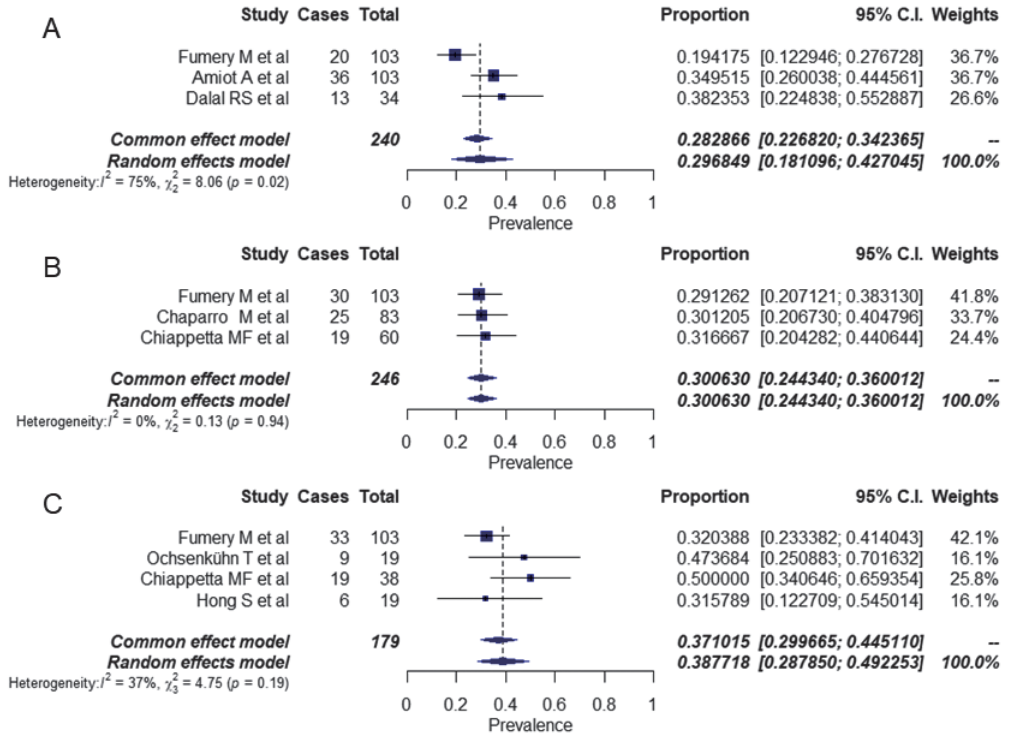
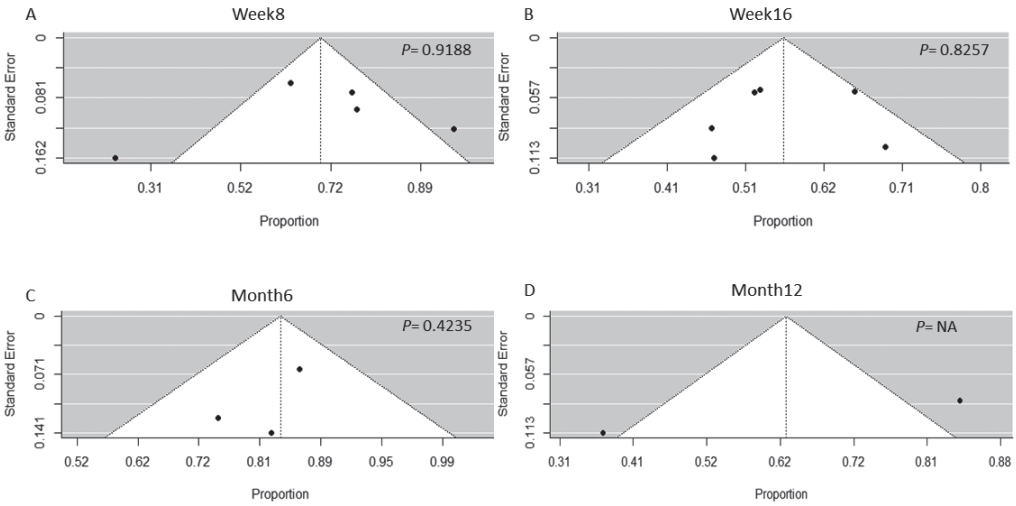


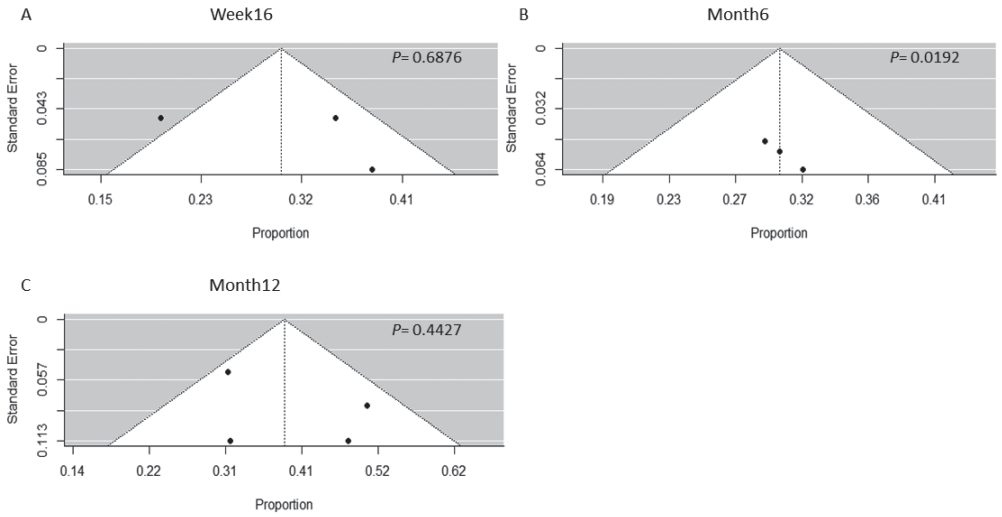
Supplementary Fig. 1 Forest plot of the clinical response rate: (A) at week 8, (B) at week 16, (C) at month 6, and (D) at month 12



Supplementary Fig. 2 Forest plot of the corticosteroid-free clinical remission rate: (A) at week 16, (B) at month 6, and (C) at month 12



Supplementary Fig. 3 Funnel plot analysis of the clinical response rate



Supplementary Fig. 4 Funnel plot analysis of the corticosteroid-free clinical response rate

Search strategy Details of literature search from electronic databases

PubMed

Search terms	Results
1. Colitis, Ulcerative[Mesh]	37353
2. Colitis[Mesh]	57536
3. "colitis, ulcerative"[MeSH Terms] OR ("colitis"[All Fields] AND "ulcerative"[All Fields]) OR "ulcerative colitis"[All Fields] OR ("ulcerative"[All Fields] AND "colitis"[All Fields])	53613
4. "ustekinumab"[MeSH Terms] OR "ustekinumab"[All Fields]	2564
5. "ustekinumab"[MeSH Terms] OR "ustekinumab"[All Fields] OR "stelara"[All Fields]	2568
6. ("interleukin 12"[MeSH Terms] OR "interleukin 12"[All Fields] OR "interleukin 12"[All Fields]) AND "23"[All Fields] AND ("antibodies, monoclonal"[MeSH Terms] OR ("antibodies"[All Fields] AND "monoclonal"[All Fields]) OR "monoclonal antibodies"[All Fields] OR ("monoclonal"[All Fields] AND "antibody"[All Fields]) OR "monoclonal antibody"[All Fields])	405
7. "interleukin 12"[MeSH Terms] OR "interleukin 12"[All Fields] OR "il 12"[All Fields]	30216
8. "interleukin 23"[MeSH Terms] OR "interleukin 23"[All Fields] OR "il 23"[All Fields]	8463
9. 1 or 2 or 3	114882
10. 4 or 5 or 6 or 7 or 8	37003
11. 9 and 10	1880
12. 11 NOT "review"[Publication Type]) NOT ("infant"[MeSH Terms] OR "child"[MeSH Terms] OR "adolescent"[MeSH Terms])) NOT "clinical study"[Publication Type]	1214
13. 12 and ("2019/01/01"[Date - Publication]: "2021/03/31"[Date - Publication])	308

Web of Science

Search terms	Results
1. ulcerative colitis	65247
2. colitis	121615
3. inflammatory bowel disease	102093
4. ustekinumab	817
5. interleukin 12	51186
6. interleukin 23	15663
7. 1 or 2 or 3	172633
8. 4 or 5 or 6	64439
9. 7 and 8	3165
10. 9 Not Review Articles Not Letters NOT Editorial Materials NOT (Korean or French or Spanish or German) NOT (Book Chapters Or Corrections or Retracted Publications)	2520
11. 10 and PY= (2019-01-01-2021-12-31)	1003