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Meta-analysis of the Efficacy and Safety of Ustekinumab in the Treatment of Pediatric Inflammatory Bowel Disease

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Abstract

Objective: This study aimed to systematically evaluate the efficacy and safety of ustekinumab (UST) in the treatment of pediatric inflammatory bowel disease (PIBD) and to provide evidence-based support for its clinical application.

Methods: The PubMed and Web of Science databases were searched to identify relevant studies investigating UST for the treatment of PIBD. Two researchers independently performed literature screening, data extraction, and quality assessment. Meta-analysis was conducted using STATA software.

Results: A total of 21 studies involving 839 pediatric patients with IBD were included. The pooled results showed that the 52-week clinical remission rate of UST in pediatric patients with IBD was 61% (95% CI: 50%–71%), the steroid-free clinical remission rate was 53% (95% CI: 44%–63%), and the 52-week clinical response rate was 55% (95% CI: 36%–74%). The 24-week clinical remission and clinical response rates were 45% (95% CI: 36%–54%) and 58% (95% CI: 47%–69%), respectively. The pooled endoscopic remission rate was 38% (95% CI: 20%–56%). The incidence of serious adverse events was 1% (95% CI: 0%–2%). Sensitivity analyses indicated that the results were robust, and Egger's test did not detect significant publication bias ($P = 0.168$).

Conclusion: UST demonstrates favorable clinical efficacy and safety in pediatric patients with IBD, enabling more than half of patients to achieve long-term clinical remission and steroid-free clinical remission. For pediatric patients who have experienced treatment failure with or intolerance to previous biologic therapies, UST may represent an effective alternative therapeutic option.

Keywords: ustekinumab; pediatric inflammatory bowel disease; Crohn's disease; ulcerative colitis; meta-analysis

Inflammatory bowel disease (IBD) refers to a group of chronic, relapsing inflammatory disorders of the gastrointestinal tract, primarily including Crohn's disease (CD) and ulcerative colitis (UC). In recent years, pediatric inflammatory bowel disease (PIBD) has emerged as a major concern in pediatric gastroenterology^[1, 2]. Previous studies have shown that approximately 25% of patients with IBD are diagnosed before the age of 20, indicating that children and adolescents constitute a substantial proportion of the affected population^[3]. Compared with adult-onset IBD, PIBD is often

characterized by more extensive disease involvement and may have long-term adverse effects on growth and development, nutritional status, and quality of life [4]. With the increasing use of biologic therapies, treatment strategies for PIBD have evolved considerably. Anti-tumor necrosis factor (TNF) agents have become a cornerstone in the management of moderate-to-severe PIBD. However, a considerable proportion of patients experience primary non-response, secondary loss of response, or intolerance to these agents, highlighting the need for novel therapeutic strategies and biologics with distinct mechanisms of action [5].

Ustekinumab (UST) is a human monoclonal antibody that targets the shared p40 subunit of interleukin (IL)-12 and IL-23, thereby inhibiting IL-12- and IL-23-mediated inflammatory signaling pathways [6, 7]. In adult patients with IBD, large phase III randomized controlled trials have demonstrated that UST is effective in inducing and maintaining clinical remission in moderate-to-severe CD [7] and improving clinical outcomes in moderate-to-severe UC [8]. In recent years, UST has increasingly been used in pediatric patients with IBD, particularly in those who have failed or are intolerant to anti-TNF therapy. Several real-world studies have evaluated the efficacy and safety of UST in PIBD [9, 10]. However, the available evidence originates predominantly from observational studies with relatively small sample sizes, heterogeneous follow-up durations, and inconsistent definitions of clinical outcomes, resulting in some variability in the reported findings. Additionally, treatment efficacy and safety also vary among individual studies. Although the growing number of real-world studies, including multicenter cohort studies and long-term follow-up investigations, has substantially expanded the evidence base [11-14], quantitative synthesis of the available evidence regarding the efficacy and safety of UST in PIBD remains limited. Therefore, this study conducted a systematic review and meta-analysis of the latest real-world evidence to comprehensively evaluate the efficacy and safety of UST in the treatment of PIBD, with the aim of providing evidence-based support for clinical decision-making and future research.

1. Objectives and Methods

1.1 Inclusion and Exclusion Criteria

The inclusion criteria were as follows: (1) studies involving pediatric patients (<21 years of age) with IBD, including CD, UC, and IBD-unclassified (IBD-U); (2) patients who received UST as induction and/or maintenance therapy; (3) studies reporting at least one efficacy or safety

outcome; (4) randomized controlled trials, clinical trials, prospective studies, retrospective studies, or observational cohort studies; and (5) full-text articles published in English.

The exclusion criteria were as follows: (1) studies including only adult patients; (2) reviews, meta-analyses, case reports, conference abstracts, editorials, commentaries, guidelines, or animal studies; (3) studies from which efficacy or safety data could not be extracted; (4) duplicate publications or studies with overlapping patient populations, in which case the study with the larger sample size or longer follow-up period was retained; and (5) studies in which the efficacy or safety of UST could not be clearly evaluated.

1.2 Literature Search

Two researchers independently conducted a systematic search of the PubMed and Web of Science databases from database inception to May 1, 2026. The search strategy combined Medical Subject Headings (MeSH) and free-text terms. The main search terms included "ustekinumab," "Stelara," "pediatric," "paediatric," "child," "adolescent," "Crohn's disease," "ulcerative colitis," "inflammatory bowel disease," and "IBD," which were combined using the Boolean operators "AND" and "OR." No restrictions were placed on study design, and only articles published in English were included. In addition, the reference lists of the included studies were manually screened to identify any additional eligible studies.

1.3 Outcome Measures

The primary outcome was the clinical remission rate at 52 weeks following UST treatment. Secondary efficacy outcomes included the 24-week clinical remission rate, 24-week clinical response rate, 52-week clinical response rate, steroid-free clinical remission rate, and endoscopic remission rate. Safety outcomes included the incidence of any adverse events, serious adverse events, and treatment discontinuation during follow-up. Definitions of clinical remission, clinical response, steroid-free clinical remission, and endoscopic remission were based on those used in the original studies. Detailed definitions are provided in **Supplementary Table 1**.

1.4 Quality Assessment

Two researchers independently assessed the methodological quality of the included studies. As

most included studies were retrospective or prospective observational studies, methodological quality was evaluated using the Methodological Index for Non-Randomized Studies (MINORS). The MINORS instrument comprises eight items assessing whether the study objective was clearly stated, patient inclusion was consecutive, data collection was prospective, outcome measures were appropriate, outcome assessment was unbiased, follow-up duration was adequate, loss to follow-up was acceptable, and sample size calculation was performed. Each item was scored from 0 to 2, yielding a total score ranging from 0 to 16. Studies were classified as low quality (0–5), moderate quality (6–10), or high quality (11–16) according to the total score. Randomized controlled trials were considered high-quality evidence and evaluated separately. Any disagreements between the two reviewers were resolved through discussion, and, when necessary, by consultation with a third reviewer until consensus was reached.

1.5 Data Extraction

Data were independently extracted from all eligible studies. Extracted information included study characteristics, baseline patient characteristics, UST treatment regimens, efficacy outcomes, and safety outcomes. Efficacy outcomes included clinical remission, clinical response, steroid-free clinical remission, and endoscopic remission, whereas safety outcomes included adverse events, serious adverse events, and treatment discontinuation.

1.6 Statistical Analysis

Statistical analyses were performed using STATA software (Version 19.5). For dichotomous outcomes, pooled event rates with corresponding 95% confidence intervals (95% CIs) were calculated. A random-effects model was used for all pooled analyses. Between-study heterogeneity was assessed using Cochran's Q test and the I^2 statistic. Sensitivity analyses were conducted by sequentially excluding individual studies to evaluate the robustness of the pooled estimates. Publication bias was assessed using funnel plots and Egger's test. A two-sided P value < 0.05 was considered statistically significant.

2. Results

2.1 Literature Search Results

A total of 394 records were identified through searches of the PubMed and Web of Science databases. After removing duplicates, 358 records remained for title and abstract screening. Based on the predefined inclusion and exclusion criteria, 305 records were excluded, including studies unrelated to the research topic, non-English publications, reviews, conference abstracts, animal studies, and articles for which the full text was unavailable. Full-text assessment of the remaining articles resulted in the exclusion of an additional 32 studies because they did not meet the eligibility criteria or lacked extractable outcome data. Ultimately, 21 studies were included in the systematic review and meta-analysis (**Figure 1**).

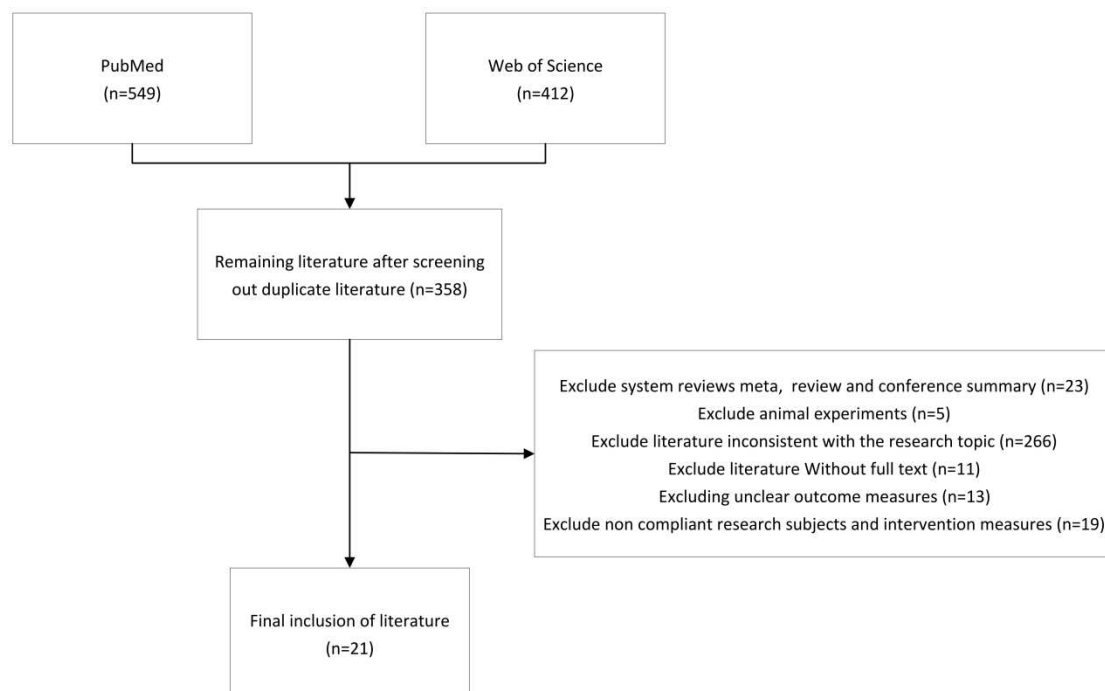


Figure 1. Flowchart of Study Selection.

PRISMA flow diagram showing the systematic search and selection process. A total of 394 records were identified from PubMed and Web of Science databases. After removing duplicates, 358 records underwent title and abstract screening. Of these, 305 were excluded, and 53 full-text articles were assessed for eligibility. Ultimately, 21 studies met the inclusion criteria and were included in the systematic review and meta-analysis.

2.2 Characteristics of the Included Studies

A total of 21 studies^[11-31] involving 839 pediatric patients with IBD were included. The studies were conducted primarily in Europe, North America, and Asia, and most were retrospective

observational studies. The study populations included patients with CD, UC, and IBD-U. Most participants were children or adolescents and had previously received anti-TNF agents or other biologic therapies before initiating UST treatment (**Table 1**).

Table 1. Characteristics of the Included Studies

First Author, Year	Country/Region	Study Design	Disease Type	Sample Size, n	Male Sex	Age	Follow-up Duration	Prior Treatment	Methodological Quality
Chavannes,2019 ^[15]	United States	Multicenter retrospective cohort study	NR	44	NR	<18 years	At least 12 months	Azathioprine, n = 33; infliximab, n = 41; adalimumab, n = 29; certolizumab, n = 1; golimumab, n = 1; vedolizumab, n = 3; thalidomide, n = 2; tacrolimus, n = 5. Twenty patients were exposed to corticosteroids at UST initiation.	Moderate

Dayan,2019 ^[16]	United States	Single-center retrospective cohort study	CD, n = 42; UC/IBD-U, n = 10	52	CD: 21/42; UC/IBD-U: 2/10	<21 years	At least 52 weeks	Biologic-naïve, n = 10; failure of at least one anti-TNF agent, n = 42 (CD, n = 33; UC/IBD-U, n = 9); failure of at least two anti-TNF agents, n = 18 (CD, n = 15; UC/IBD-U, n = 3).	Moderate
Takeuchi, 2021 ^[17]	Japan	Single-center retrospective cohort study	CD or IBD-U with a CD-like phenotype	17	8/17	<20 years	At least 26 weeks	Previously received azathioprine and anti-TNF therapy, n = 16	Moderate
Dhaliwal,2021 ^[12]	Canada	Multicenter prospective cohort study	Refractory UC	25	7/25	2–17 years	52 weeks	All patients had failed anti-TNF therapy, and all had received infliximab; adalimumab, n = 3; failed vedolizumab therapy, n = 12.	High

Kim, 2021 ^[18]	United States	Single-center retrospective cohort study	Refractory CD	38	24/38	<21 years	Median 62.1 weeks	All patients had previously received anti-TNF therapy; n = 25 had received one anti-TNF agent and n = 13 had received two or three anti-TNF agents. In addition, n = 29 had previously received immunomodulators, including n = 17 who had received one immunomodulator and n = 12 who had received two or three immunomodulators, although not concomitantly. Prior vedolizumab and corticosteroid	High
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								use were reported in n = 5 and n = 7 patients, respectively.	
Do, 2020 ^[19]	United States	Single- center retrospective study	CD	10	NR	Median age at diagnosis : 9.5 years; median age at UST initiation : 14.5 years	NR	All patients had failed anti-TNF therapy.	Moderate

Cohen, 2021 ^[20]	Canada	Single-center retrospective case series	Refractory CD	11	8/11	12–17 years	NR	All patients had received at least one anti-TNF agent: infliximab, n = 7; adalimumab, n = 1; both infliximab and adalimumab, n = 3.	Moderate
Rosh, 2021 ^[11]	Multiple countries	Multicenter, randomized, prospective, double-blind clinical trial	CD	44	40.90%	Median 13 years; IQR 12–16	16 weeks	Previous biologic exposure, 91%; previous infliximab, 75%; previous adalimumab, 57%; anti-TNF failure or intolerance, 89%.	High
Yerushalmy-Feler, 2022 ^[13]	Multiple countries	Multicenter retrospective cohort study	CD according to Porto criteria	69	33/69	≤18 years	NR	Immunomodulators, n = 59; biologic therapy, n = 68. Most patients had received more than one biologic agent.	High

Alhadab, 2024 ^[21]	Saudi Arabia	Single-center retrospective cohort study	CD after anti-TNF failure, n = 8; UC, n = 5	13	NR	≤16 years	NR	All patients had failed one or more anti-TNF agents, including infliximab and/or adalimumab.	Moderate
Cohen, 2024 ^[22]	Israel	Multicenter retrospective cohort study	UC, n = 39; IBD-U, n = 19	58	24/58	≤18 years	At least 52 weeks	Previous immunomodulator use, n = 50. All patients had received biologic therapy; failure of one biologic agent, n = 20; failure of two biologic agents, n = 28; failure of three biologic agents, n = 10.	High

Li, 2024 ^[23]	China	Retrospective cohort study	CD	16	11/16	<18 years	At least 24 weeks	Infliximab, n = 11; adalimumab, n = 2; vedolizumab, n = 1. Biologic-naïve, n = 5; one biologic agent, n = 8; two biologic agents, n = 3.	High
Pujol-Muncunill, 2024 ^[14]	Ten European countries and Israel	Multicenter retrospective observational study	CD according to Porto criteria	101	52/101	2–18 years	NR	Anti-TNF therapy before UST, n = 100; vedolizumab before UST, n = 22.	High
Mitchel, 2025 ^[24]	United States	Retrospective cohort study	CD	101	48/101	Median 16.4 years; IQR 13.8–18.1	Median 16.6 months; IQR 8.71–31.2	At least one anti-TNF agent, 86/101; two to three anti-TNF agents, 34/101; vedolizumab, 28/101; JAK inhibitors, 1/101; biologic-naïve, 14/101.	High

Yamamoto, 2025 ^[25]	Japan	Retrospective cohort study	Pediatric-onset CD	43	18/43	Median 9.7 years; IQR 6.7–13.0	Median 136 weeks; IQR 102–172	All patients had failed anti-TNF therapy; previous infliximab, n = 30; previous adalimumab, n = 22; previous golimumab, n = 3. Thirty-one patients had received one biologic agent, and 12 had received two biologic agents.	High
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Hsu, 2025 ^[26]	United States	Retrospective study	CD, n = 35; UC, n = 21; IBD-U, n = 6	60	37/60	Median 12 years; IQR 8.5–14.0	Median 16 months; IQR 9–23	Biologic-naïve, 3/60; one prior biologic agent, 39/60; two prior biologic agents, 13/60; three prior biologic agents, 5/60. Previous infliximab, n = 52; adalimumab, n = 13; vedolizumab, n = 13; tofacitinib, n = 2.	High
Iwama, 2024 ^[27]	Japan	Case series	CD, n = 4; UC, n = 2; IBD-U, n = 2	8	5/8	1–7 years; median 4.5 years	Up to 104 weeks	Corticosteroids, 7/8; immunomodulators, 7/8; one prior biologic agent, 6/8; two prior biologic agents, 2/8.	Moderate

Greef, 2026 ^[28]	Multiple countries	Multicenter phase III clinical trial	Pediatric CD	48	27/48	Median 15 years; IQR 14.0–16.0	52 weeks	Biologic-naïve, 27/48; biologic failure, 19/48; immunomodulator failure or intolerance, 23/48; nutritional therapy, 31/48 (parenteral nutrition, 20/48; partial parenteral nutrition, 17/48)	High
Rehman, 2024 ^[29]	United States	Retrospective study	UC, n = 7; IBD-U, n = 3	10	6/10	Median 13 years; IQR 11.5–16.5	56 weeks	Anti-TNF therapy, 10/10; vedolizumab, 2/10; systemic corticosteroids, 10/10; mesalamine, 8/10; methotrexate, 4/10; 6-mercaptopurine, NR; IBD dietary therapy, 4/10.	Moderate

Nambu,2026 ^[30]	Japan	Multicenter retrospective cohort study	VEO-IBD	38	NR	VEO-IBD; <6 years	At least 12 months	NR	High
Rebus, 2024 ^[31]	France	Multicenter retrospective cohort study	PIBD; CD: 28, UC: 5	33	NR	Overall median 10.7 years; IQR 9.2–12.6	52 weeks	All patients had received anti-TNF therapy.	High

2.3 Quality Assessment

The methodological quality of the observational studies was assessed using the MINORS instrument. MINORS scores ranged from 7 to 12, indicating moderate to high methodological quality overall. Most studies clearly stated their objectives, used appropriate outcome measures, and had adequate follow-up durations. However, the majority employed retrospective study designs, and none reported sample size calculations. Two prospective clinical trials were evaluated separately because of their different study designs and were considered high-quality evidence (Table 1).

2.4 Meta-analysis Results

Twelve studies involving 591 pediatric patients with IBD reported the 52-week clinical remission rate. The pooled analysis using a random-effects model demonstrated a 52-week clinical remission rate of 61% (95% CI: 50%–71%; $I^2 = 84.5\%$) (Figure 2).

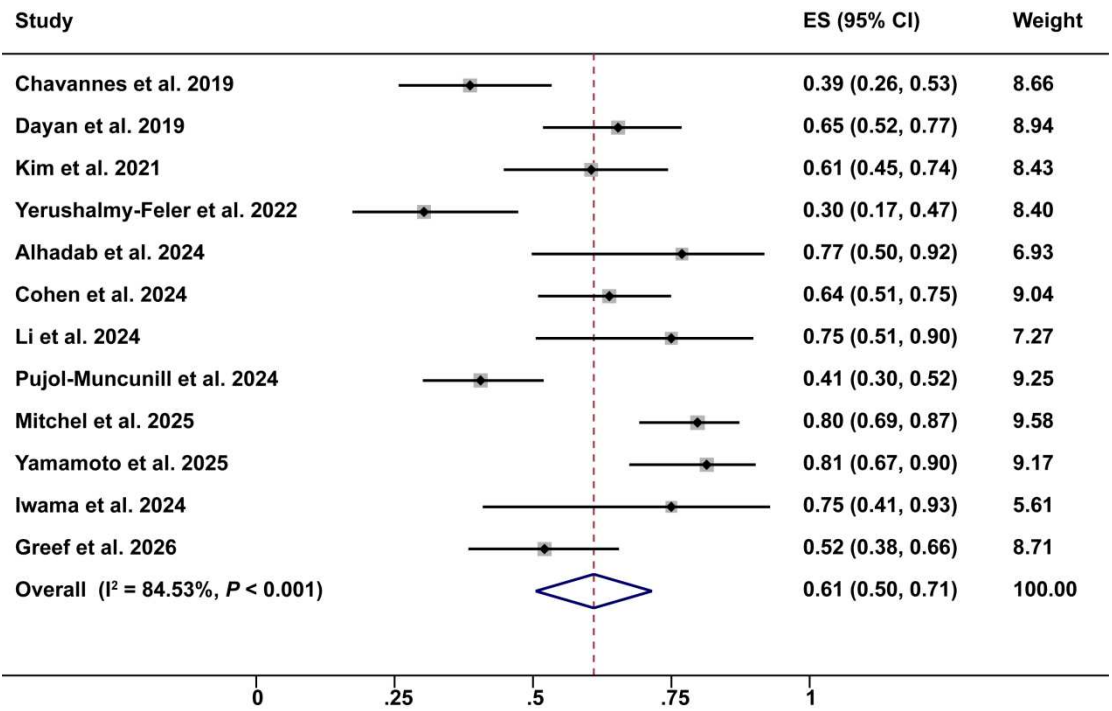


Figure 2. Forest Plot of 52-Week Clinical Remission Rate.

Pooled analysis of 52-week clinical remission rate following ustekinumab treatment in pediatric inflammatory bowel disease. Twelve studies involving 591 pediatric patients were included. The pooled clinical remission rate was 61% (95% CI: 50% – 71%) using a random-effects model. Substantial heterogeneity was observed ($I^2 = 84.5\%$).

Seventeen studies involving 731 patients reported steroid-free clinical remission. The pooled steroid-free clinical remission rate was 53% (95% CI: 44%–63%; $I^2 = 85.4\%$) (**Figure 3**).

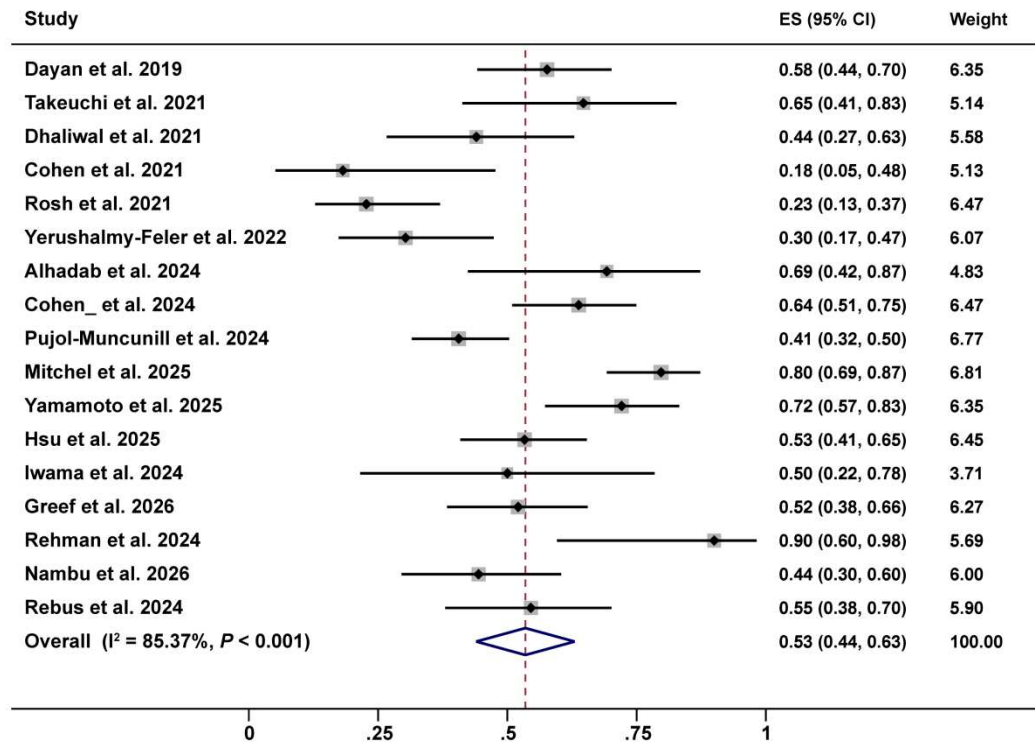


Figure 3. Forest Plot of Steroid-Free Clinical Remission Rate.

Pooled analysis of steroid-free clinical remission rate following ustekinumab treatment in pediatric inflammatory bowel disease. Seventeen studies involving 731 patients were included. The pooled steroid-free clinical remission rate was 53% (95% CI: 44% – 63%) using a random-effects model. Substantial heterogeneity was observed ($I^2 = 85.4\%$).

Four studies involving 140 patients reported the 52-week clinical response rate. The pooled estimate was 55% (95% CI: 36%–74%; $I^2 = 72.6\%$) (**Figure 4**).

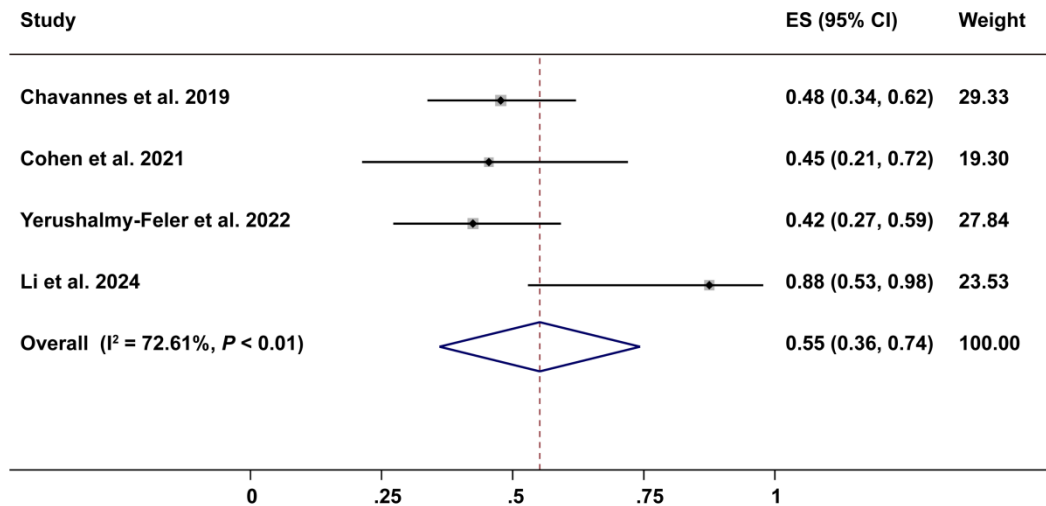


Figure 4. Forest Plot of 52-Week Clinical Response Rate.

Pooled analysis of 52-week clinical response rate following ustekinumab treatment in pediatric inflammatory bowel disease. Four studies involving 140 patients were included. The pooled clinical response rate was 55% (95% CI: 36% – 74%) using a random-effects model. Moderate heterogeneity was observed ($I^2 = 72.6\%$).

Five studies involving 169 patients reported the 24-week clinical remission rate. The pooled clinical remission rate at 24 weeks was 45% (95% CI: 36%–54%; $I^2 = 22.3\%$) (**Figure 5**).

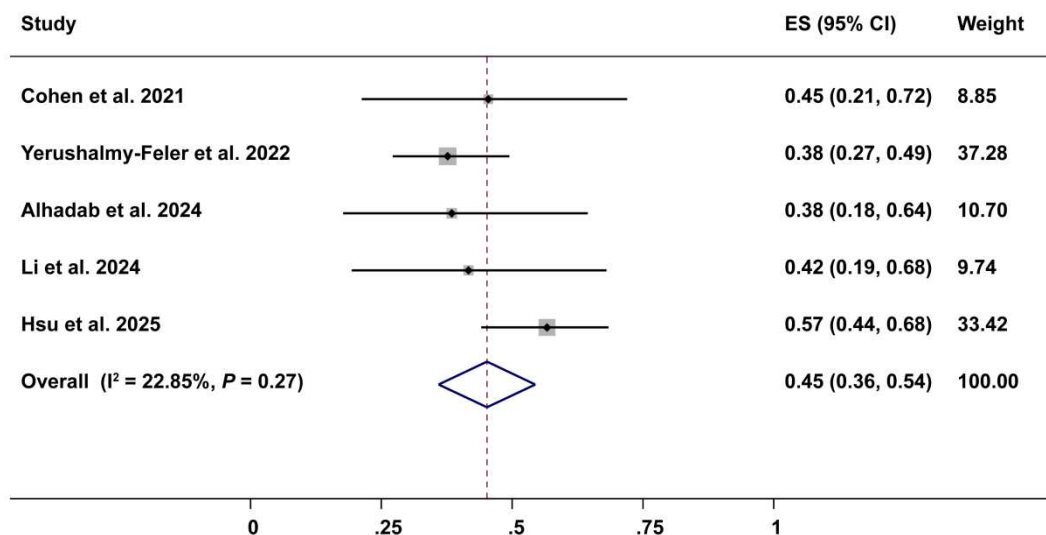


Figure 5. Forest Plot of 24-Week Clinical Remission Rate.

Pooled analysis of 24-week clinical remission rate following ustekinumab treatment in pediatric

inflammatory bowel disease. Five studies involving 169 patients were included. The pooled clinical remission rate at 24 weeks was 45% (95% CI: 36% – 54%) using a random-effects model. Low heterogeneity was observed ($I^2 = 22.3\%$).

Two studies involving 85 patients reported the 24-week clinical response rate. The pooled clinical response rate at 24 weeks was 58% (95% CI: 47%–69%; $I^2 = 0\%$) (**Figure 6**).

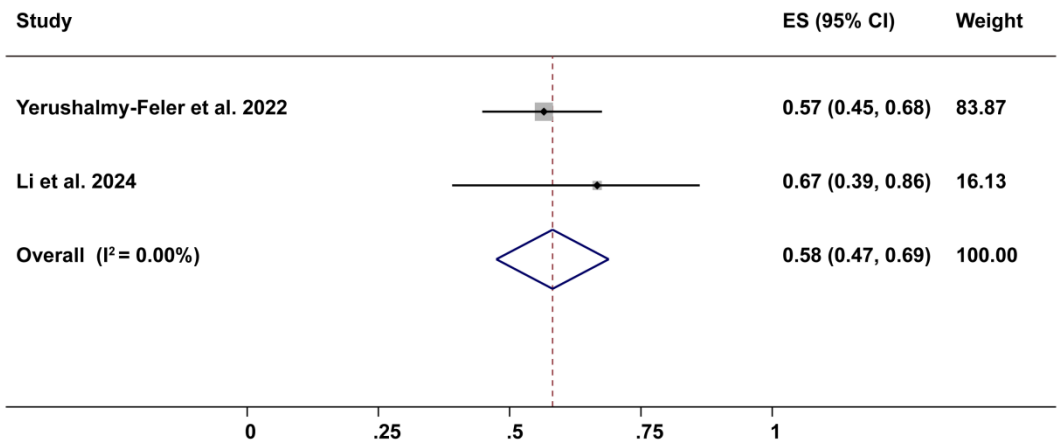


Figure 6. Forest Plot of 24-Week Clinical Response Rate.

Pooled analysis of 24-week clinical response rate following ustekinumab treatment in pediatric inflammatory bowel disease. Two studies involving 85 patients were included. The pooled clinical response rate at 24 weeks was 58% (95% CI: 47% – 69%) using a random-effects model. No significant heterogeneity was observed ($I^2 = 0\%$).

Nine studies involving 248 patients reported endoscopic remission. The pooled endoscopic remission rate was 38% (95% CI: 20%–56%; $I^2 = 86.3\%$) (**Figure 7**).

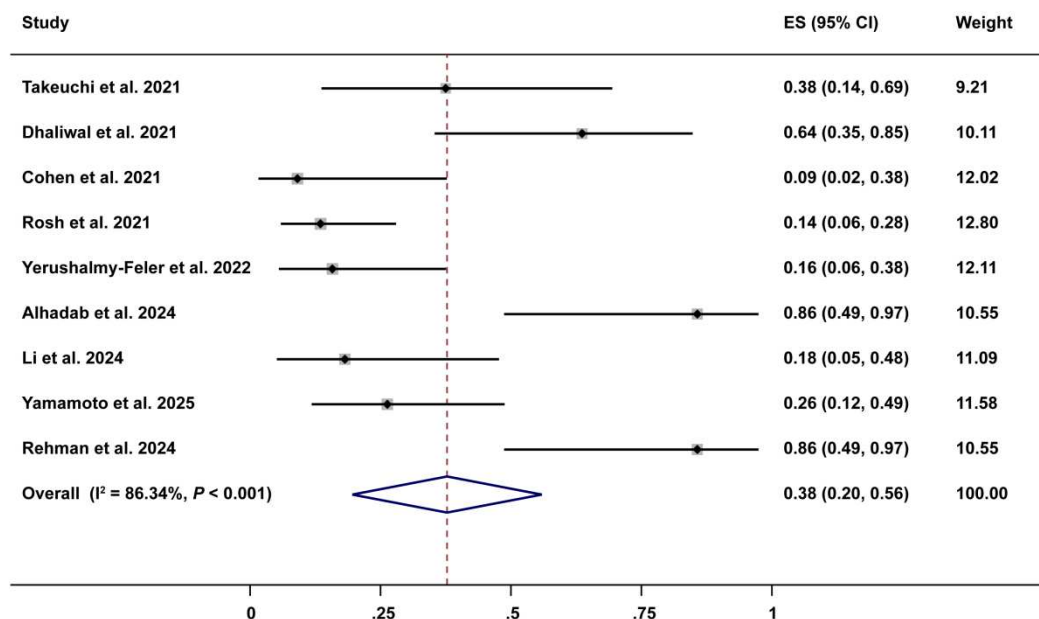


Figure 7. Forest Plot of Endoscopic Remission Rate.

Pooled analysis of endoscopic remission rate following ustekinumab treatment in pediatric inflammatory bowel disease. Nine studies involving 248 patients were included. The pooled endoscopic remission rate was 38% (95% CI: 20% – 56%) using a random-effects model. Substantial heterogeneity was observed ($I^2 = 86.3\%$).

2.5 Safety

Most included studies reported adverse events. Owing to substantial heterogeneity in the definitions and reporting methods of adverse events across studies, these outcomes were summarized descriptively rather than pooled in a meta-analysis (**Table 2**). The reported incidence of adverse events ranged from 0% to 92%. The most frequently reported adverse events included infections, headache, fatigue, infusion reactions, dermatological manifestations, and gastrointestinal symptoms.

Table 2. Outcome Extraction Sheet

Study	N	Remission _16w	Remission _26w	Remission _52w	Response _16w	Response _26w	Response _52w	SteroidFreeRe mission	EndoscopicRe mission	A E	SA E	Discontinuation
Chavannes,2019 ^[15]	44	NR	NR	17	NR	NR	21	NR	NR	8	2	13
Dayan,2019 ^[16]	52	NR	NR	34	NR	NR	NR	30	NR	6	0	13
Takeuchi,2021 ^[17]	17	NR	NR	NR	NR	NR	NR	11	3	1 1	0	1
Dhaliwal,2021 ^[12]	25	NR	NR	NR	NR	NR	NR	11	7	N R	N R	9
Kim,2021 ^[18]	38	NR	NR	23	NR	NR	NR	NR	NR	4	1	8
Do,2020 ^[19]	10	NR	NR	NR	NR	NR	NR	NR	0	0	0	1
Cohen,2021 ^[20]	11	NR	5	NR	NR	NR	5	2	1	0	0	0
Rosh,2021 ^[11]	44	11	NR	NR	23	NR	NR	10	5	3 2	7	4
Yerushalmy-Feler,2022 ^[13]	69	29	26	10	46	39	14	10	3	6	0	13
Alhadab,2024 ^[21]	13	NR	5	10	NR	NR	NR	9	6	3	1	2
Cohen,2024 ^[22]	58	NR		37	NR	NR	NR	37	NR	6	1	24
Li,2024 ^[23]	16	NR	5	12	NR	8	7	NR	2	8	0	0

Pujol-Muncunill,2024 ^[14]	10 1	30	NR	30	54	NR	NR	41	NR	7	0	23
Mitchel,2025 ^[24]	10 1	NR	NR	59	NR	NR	NR	67	NR	3 8	7	4
Yamamoto,2025 ^[25]	43	NR	NR	35	NR	NR	NR	34	5	3 8	7	4
Hsu,2025 ^[26]	60	NR	34	NR	NR	NR	NR	32	NR	6	0	0
Iwama,2024 ^[27]	8	NR	NR	6	NR	NR	NR	7	NR	0	0	0
Greef,2026 ^[28]	48	NR	NR	25	NR	NR	NR	25	NR	4 4	8	5
Rehman,2024 ^[29]	10	NR	NR	NR	NR	NR	NR	9	7	0	0	1
Nambu,2026 ^[30]	38	NR	NR	NR	NR	NR	NR	16	NR	0	0	8
Rebus,2024 ^[31]	33	NR	NR	NR	NR	NR	NR	18	NR	0	0	6

In total, 19 studies were included in the meta-analysis of serious adverse events (SAEs). The pooled incidence of SAEs was 1% (95% CI: 0%–2%; $I^2 = 39.6\%$) (**Figure 8**). Notably, most studies reported no SAEs during follow-up, whereas only a few studies reported an SAE incidence exceeding 10%. Overall, UST demonstrated a favorable safety profile in pediatric patients with IBD.

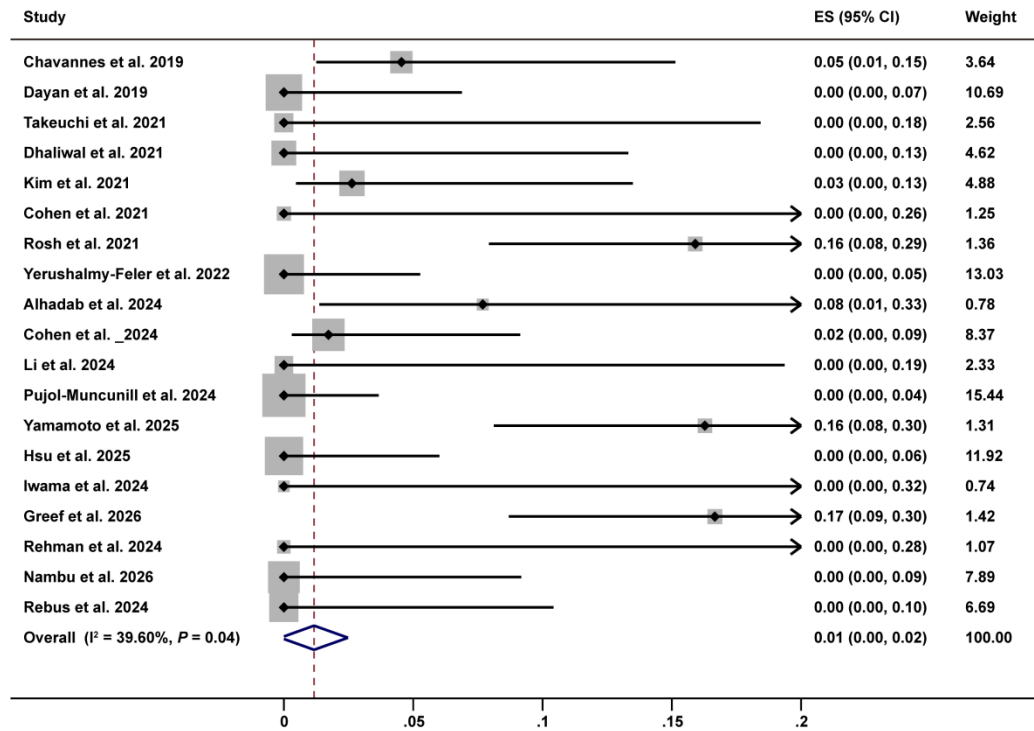


Figure 8. Forest Plot of Serious Adverse Events Incidence.

Pooled analysis of serious adverse events (SAEs) incidence following ustekinumab treatment in pediatric inflammatory bowel disease. Nineteen studies were included in the meta-analysis. The pooled incidence of SAEs was 1% (95% CI: 0%–2%) using a random-effects model. Low to moderate heterogeneity was observed ($I^2 = 39.6\%$).

2.6 Publication Bias

Publication bias was assessed using a funnel plot and Egger's regression test (**Figure 9**). For the primary outcome of the 52-week clinical remission rate, the funnel plot showed no obvious asymmetry, and Egger's regression test did not detect significant publication bias ($P = 0.168$).

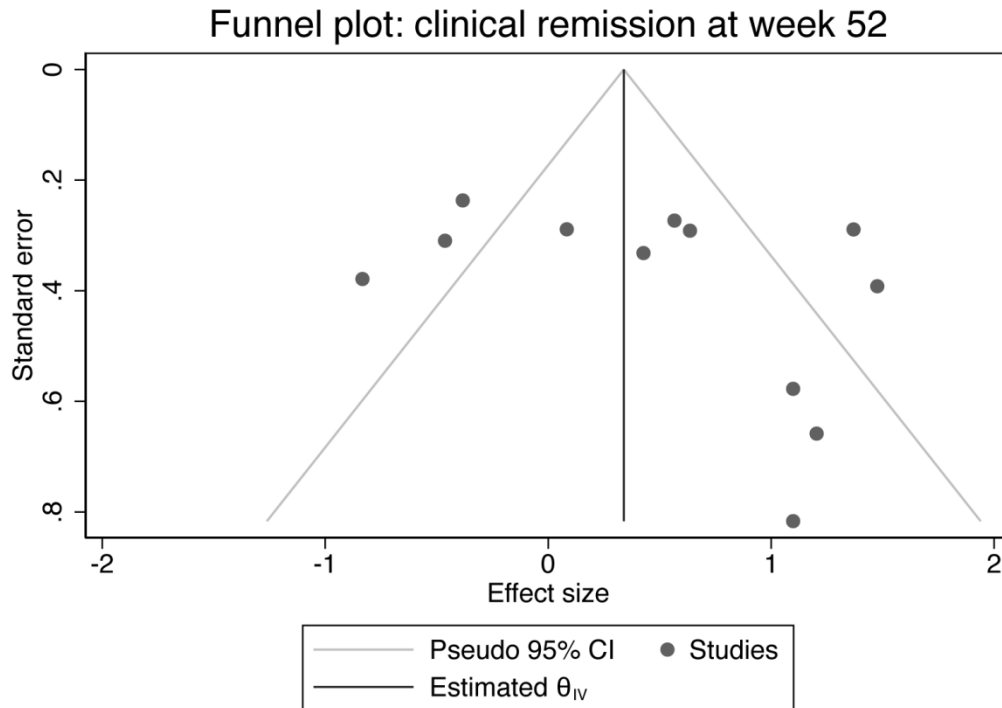


Figure 9. Funnel Plot for Publication Bias Assessment.

Funnel plot assessing publication bias for the primary outcome of 52-week clinical remission rate. The plot showed no obvious asymmetry. Egger's regression test did not detect significant publication bias ($P = 0.168$), suggesting that the pooled estimate was not substantially influenced by publication bias.

2.7 Sensitivity Analysis

Sensitivity analysis was performed using a leave-one-out approach. Sequential exclusion of individual studies yielded pooled remission rates ranging from 0.59 to 0.64, which were consistent with the primary analysis. No single study substantially influenced the overall pooled estimate, indicating that the results were robust.

3. Discussion

In recent years, with the widespread use of biologic therapies in PIBD, treatment goals have evolved from symptom control toward sustained clinical remission, steroid-free remission, and mucosal healing ^[32]. For patients who experience treatment failure or intolerance to anti-TNF agents, biologics with alternative mechanisms of action provide additional therapeutic options. UST is a

human monoclonal antibody that targets the shared p40 subunit of IL-12 and IL-23, thereby inhibiting Th1- and Th17-mediated inflammatory pathways and reducing intestinal inflammation [33]. Numerous previous studies have demonstrated that the IL-12/23 signaling axis plays a central role in the pathogenesis and persistence of chronic intestinal inflammation in IBD by promoting inflammatory cell recruitment, cytokine production, and mucosal injury [34]. Although the efficacy and safety of UST have been well established in adult patients with CD and UC [7, 8], high-quality quantitative evidence regarding its use in pediatric patients remains limited. Therefore, the present study systematically synthesized the available clinical evidence to comprehensively evaluate the efficacy and safety of UST in the treatment of PIBD.

This meta-analysis included 21 studies involving 839 pediatric patients with IBD, covering multicenter prospective studies, prospective clinical trials, and numerous real-world cohort studies. The pooled results demonstrated a 52-week clinical remission rate of 61%, a steroid-free clinical remission rate of 53%, and a 52-week clinical response rate of 55%. At 24 weeks, the pooled clinical remission and clinical response rates were 45% and 58%, respectively, while the pooled endoscopic remission rate was 38%. Notably, most patients included in this analysis had previously received anti-TNF therapy, and many had experienced failure of multiple biologic agents, indicating that the study population represented a highly treatment-experienced and refractory cohort. Despite these challenging clinical characteristics, more than half of the patients achieved clinical remission or steroid-free clinical remission after 52 weeks of UST treatment, highlighting the therapeutic potential of UST as an effective treatment option for refractory PIBD. The findings of this study are generally consistent with those of previous systematic reviews. Fang et al. [9] reported that the available evidence for UST in PIBD was derived primarily from cohort studies and case series, with approximately one-third to one-half of pediatric patients with CD achieving clinical remission during short-term treatment or after one year of follow-up. They also concluded that UST demonstrated an acceptable safety profile. Subsequently, Marques et al. [10] reported a similar conclusion, suggesting that UST showed promising efficacy for both induction and maintenance of remission in PIBD. However, they emphasized that the available evidence was limited by the small number of studies, relatively short follow-up periods, and the lack of standardized dosing regimens, and proposed that more high-quality studies are required to verify these findings. Compared with these previous systematic reviews, the present study incorporates more recently published

multicenter cohort studies and prospective clinical trials and provides quantitative pooled estimates of key efficacy outcomes, thereby offering a more comprehensive and robust assessment of the therapeutic efficacy of UST in PIBD.

From the perspective of treatment duration, the pooled clinical remission rate increased from 45% at 24 weeks to 61% at 52 weeks. Although the estimates at different time points were obtained from different sets of studies and therefore cannot be directly compared longitudinally, these findings suggest that some pediatric patients may require prolonged treatment to achieve optimal clinical benefit. This observation is consistent with findings from the UNITI/IM-UNITI trial in adult CD and the UNIFI trial in adult UC, both of which demonstrated that UST is effective not only for induction therapy but also for maintaining long-term clinical remission [7, 8, 35]. The present findings suggest that a similar therapeutic pattern may exist in pediatric patients. Consequently, treatment efficacy should not be judged solely on the basis of early clinical response, as continued therapy may lead to further improvements in clinical outcomes.

This study also demonstrated that the pooled steroid-free clinical remission rate with UST was 53%. In pediatric patients with IBD, achieving steroid-free remission is of greater clinical significance than symptom improvement alone. Long-term glucocorticoid exposure is associated with a range of adverse outcomes, including growth retardation, reduced bone mineral density, metabolic disturbances, and an increased risk of infection [9, 36]. Consequently, minimizing or eliminating corticosteroid dependence has become a key therapeutic objective in the management of PIBD. More recently, the STRIDE-II consensus identified steroid-free remission as a major long-term treatment target, emphasizing its importance in disease management [32]. The present findings suggest that UST not only effectively controls disease activity but may also facilitate corticosteroid withdrawal in a substantial proportion of pediatric patients, thereby reducing the risk of long-term steroid-related complications. Given that most patients included in this meta-analysis had previously received multiple biologic therapies, and many had experienced treatment failure, the observed steroid-free remission rate further supports the potential role of UST as a long-term treatment option for refractory PIBD.

The pooled endoscopic remission rate in this study was 38%, which was lower than both the clinical remission and steroid-free clinical remission rates. This finding suggests that improvement in clinical symptoms does not necessarily correspond to complete resolution of mucosal

inflammation in pediatric patients with IBD. As therapeutic targets in IBD have shifted from symptom control toward mucosal healing and the prevention of long-term disease complications, endoscopic outcomes have become increasingly important indicators of treatment efficacy [32]. However, the analysis of endoscopic remission included only nine studies involving 248 patients, and substantial between-study heterogeneity was observed. This heterogeneity may be attributable to differences in the timing of endoscopic assessment, endoscopic scoring systems, disease subtypes, and the fact that repeat endoscopic evaluation was performed only in selected patients in routine clinical practice. Furthermore, repeated endoscopic examinations are often associated with poor acceptance and compliance among pediatric patients, limiting the availability of high-quality evidence. Consequently, the current evidence remains insufficient to fully evaluate the effect of UST on mucosal healing in PIBD. Future studies employing standardized endoscopic assessment criteria and longer follow-up periods are warranted to better define its efficacy in achieving mucosal healing.

With regard to safety, the pooled analysis of 19 studies demonstrated that the incidence of serious adverse events (SAEs) associated with UST was only 1%, with relatively low between-study heterogeneity. These findings indicate that UST has a favorable safety profile and that safety outcomes are generally consistent across studies. The most commonly reported adverse events included infections, headache, infusion reactions, dermatological manifestations, and gastrointestinal symptoms, most of which were mild and did not require treatment discontinuation. Although a small number of studies reported severe infections, hypersensitivity reactions, or other SAEs, most investigators considered these events unlikely to be directly attributable to UST. These findings are consistent with long-term follow-up studies in adult patients, which have similarly reported no new safety signals. Given that pediatric patients are expected to receive treatment for longer durations than adults, further long-term studies are needed to evaluate the potential effects of UST on growth and development, infection risk, and long-term immune safety.

High between-study heterogeneity was observed for several efficacy outcomes in this meta-analysis. The I^2 values for the 52-week clinical remission rate, steroid-free clinical remission rate, and endoscopic remission rate all exceeded 80%. Several factors may have contributed to this heterogeneity. First, the characteristics of the study populations varied considerably across the included studies, encompassing patients with CD, UC, IBD-U, and very early-onset IBD (VEO-IBD). These disease subtypes differ in their clinical presentation, disease course, and potentially

their response to UST treatment. Second, although most studies primarily included patients who had experienced failure of previous anti-TNF therapy, some also enrolled biologic-naïve patients. Previous studies have shown that biologic-naïve patients generally achieve higher remission rates, whereas prior exposure to multiple biologic agents is associated with diminished treatment response. Third, substantial variation existed in treatment protocols across studies, including induction dosing, maintenance dosing intervals, and dose-escalation strategies. In addition, the definitions of clinical remission, timing of endoscopic assessment, and duration of follow-up were not standardized. Collectively, these methodological and clinical differences are likely to have contributed to the observed heterogeneity. Despite the substantial heterogeneity, the sensitivity analyses demonstrated that sequential exclusion of individual studies resulted in only minimal changes in the pooled effect estimates, and Egger's test detected no significant publication bias. These findings indicate that the overall conclusions of this meta-analysis are robust, although the pooled estimates should be interpreted with appropriate caution in light of the heterogeneity among the included studies.

4. Summary

Based on the currently available evidence, this study systematically evaluated and quantitatively synthesized the efficacy and safety of UST in PIBD, providing a more comprehensive evidence base for its clinical use. Nevertheless, several limitations should be acknowledged. Most of the included studies were observational in design, and substantial heterogeneity existed with respect to patient characteristics, prior biologic exposure, disease severity, and UST treatment regimens, all of which may have influenced the pooled estimates. In addition, evidence regarding endoscopic outcomes and long-term follow-up remains limited, and the heterogeneous reporting of adverse events precluded quantitative synthesis of some safety outcomes.

Overall, UST demonstrated favorable clinical efficacy and an acceptable safety profile in pediatric patients with IBD. Importantly, it provided sustained clinical benefit even in a predominantly treatment-experienced population with refractory disease following failure of multiple biologic therapies. Further large-scale, prospective, multicenter studies with standardized outcome definitions and longer follow-up are warranted to better define the long-term efficacy, safety, and optimal treatment strategies for UST in PIBD.

Declaration

Abbreviations: .UST, ustekinumab; PIBD, pediatric inflammatory bowel disease; IBD, inflammatory bowel disease; CD, Crohn's disease; UC, ulcerative colitis; IBD-U, IBD-unclassified; TNF, tumor necrosis factor; IL, interleukin; MeSH, Medical Subject Headings; MINORS, Methodological Index for Non-Randomized Studies; CI, confidence interval; SAE, serious adverse event; VEO-IBD, very early-onset inflammatory bowel disease; Th1, T helper 1; Th17, T helper 17; IQR, interquartile range; NR, not reported.

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