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Safety and Efficacy of Ustekinumab in the Treatment of Crohn Disease: A Systematic Review and Meta-analysis

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Abstract

Background and Aims The present systematic review and meta-analysis was designed to estimate the safety and effectiveness of ustekinumab in the treatment of Crohn disease (CD) in clinical trials and observational studies.

Methods We retrieved all the related publications from the PubMed, Cochrane, EBSCO, Google Scholar and EMBASE databases using a systematic search strategy. We only included clinical trials and observational studies that were published in English.

Results Only 31 studies that met the eligibility criteria out of the 733 identified studies were included. The overall clinical response rate in the cohort studies was of 0.539 (95% confidence interval [95%CI]: 0.419–0.659), and in the clinical trials it was of 0.428 (95%CI: 0.356–0.501). The pooled clinical remission rate was of 0.399 (95%CI: 0.295–0.503) in randomized control trials (RCTs,) and of 0.440 (95%CI: 0.339–0.542) in cohort studies. The rate of adverse effects was of 0.158 (95%CI: 0.109–0.207) in cohort studies and of 0.690 (95%CI: 0.633–0.748) in RCTs.

Conclusion Ustekinumab is effective in the treatment of CD. However, more research is required on the safety profiles because there was considerable variation among the included studies.

Keywords
- Crohn Disease
- inflammatory bowel disease
- interleukin
- cytokine
- biologics

Introduction

Crohn disease (CD) is an incapacitating and incurable inflammatory bowel disease.[1] It is a chronic inflammatory disease characterized by inflammation in any part of the gastrointestinal tract, from the mouth to the anus. The terminal ileum and the right colon are the most commonly affected parts because they have the highest bacterial concentration.[2–4] Although many different factors are associated with CD, its exact etiology remains unclear. However, there is evidence that suggests that an improper immune response of the gastrointestinal tract to various microbial or environmental stimuli in genetically susceptible patients is the cause.[5]

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Patients with CD usually develop ulceration in the superficial layers of the bowel mucosa. It may spread deeper, developing granulomas in all the intestinal layers, resulting in a cobblestone appearance.[3] The diagnosis of CD involves a combination of endoscopic, radiographic, and pathological examinations. The endoscopic score is the gold standard for assessing the severity of CD.[6] Patients commonly present with abdominal pain, weight loss, or diarrhea that may be bloody. However, to a lesser extent, extraintestinal manifestations, such as peripheral arthritis, aphthous stomatitis, and uveitis, may develop.[7–9] Moderate to severe cases require conventional therapy, including corticosteroids, which aims to suppress the inflammatory response. Resistant patients may need additional therapies, such as immunosuppressive drugs (thiopurines and methotrexate), antibiotic treatment, anti-tumor necrosis factor therapy, or even surgery in severe cases.[10]

Almost 50% of CD patients require surgical intervention within 10 years of diagnosis.[11] The ideal current medical approach is a combination of immunosuppressants and anti-tumor necrosis factor.[12] However, one third of the patients do not respond to treatment with anti-tumor necrosis factor (TNF), and another one third exhibit a temporary effect that requires additional therapy.[13] Previous studies have implicated interleukin-12 and interleukin-23 in the pathophysiology of CD. As reported, human monoclonal antibodies neutralizing interleukin 12 and interleukin 23 via the shared p40 subunit induce clinical response and remission in patients with active CD.[14]

Ustekinumab, a fully human immunoglobulin 1 monoclonal antibody, is the latest drug approved for moderate to severe CD. This drug blocks the biological activity of interleukin-12 and interleukin-23 through their shared p40 subunit by inhibiting receptors of these two cytokines on antigen-presenting cells, T cells, and natural killer cells.[15] Ustekinumab can be administered subcutaneously or intravenously.[16] Previous studies have shown that ustekinumab administration has increased the rates of remission and response in patients with moderate to severe CD.[13,17]

However, there are common reported adverse effects of long-term ustekinumab therapy, such as nasopharyngitis, upper respiratory tract infection, and diverticulitis.[18] In the present systematic review, we aimed to investigate the efficacy and safety of ustekinumab in CD patients.

Methods

We performed the present systematic review and meta-analysis according to the principles of the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA)[19] statement in the case of clinical trials, and on the principles of the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) statement for observational studies.[20]

Search Strategy and Data Collection

We searched the following online databases for studies published until April 2020: Web of Science, Scopus, Cochrane, and PubMed, without any restrictions regarding time or language of publication. We performed our search using the following keywords: *ustekinumab*, *Crohn's*, and *regional enteritis*, and we combined these words with AND or OR according to the manner suitable for the search. We downloaded the results and exported them into Endnote X8.0.1 (Build 1044) (Clarivate Analytics, Pennsylvania, PA, USA) with automatic removal of any duplicates by the computer. Thereafter, we exported the data into Microsoft Excel (Microsoft Corp., Redmond, WA, USA) and screened the studies manually. First, we screened the title/abstract, and then we screened the full text to include the studies that fulfilled our eligibility criteria and to exclude those that did not fulfill the criteria. Disagreements were resolved by the corresponding author.

Eligibility Criteria and Outcome Measures

We included all the primary studies, including clinical trials, prospective and retrospective cohorts, and case-control studies. The population comprised patients with active CD of any degree. The intervention was ustekinumab given via any route of administration and at any dose in the induction and/or maintenance phases, either in a single-arm study or in comparison to healthy controls. The following outcomes were reported: clinical response, clinical remission, any adverse events, and infusion or injection reactions.

We excluded studies with other criteria. The reported outcomes were measured using C-reactive protein (CRP) levels, the Harvey-Bradshaw Index (HBI), erythrocyte sedimentation rate values, and short inflammatory bowel disease questionnaire scores. We defined the clinical response according to one of the following definitions: 1 - Decrease of Crohn's Disease Activity Index (CDAI) to >100 points; 2 - reduction in the symptoms of the patient, combined with the will to continue Ustekinumab (UST); 3 - Decrease of HBI score to ≥ 3; 4 - Symptom reduction detected by either physician using global assessment; 5 - Decrease in the stool frequency or well-being, as detected with patient-reported clinical improvement. We defined clinical remission using one of the following definitions: 1 - HBI score <5; 2 - CADI score <150 at every time point in the study considering the baseline as the time point, with no change from the baseline score; 3 - Average frequency of stool every day of ≤ 2.8 at every time point in the study, considering baseline as the time point, with no change from the baseline value. The following study-related data were collected: first name of the author, year of publication, country in which the study was conducted, number of patients, route of induction (subcutaneous or intravenous), and the commonest maintenance schedule (every 4 weeks or 8 weeks). The following patient-related variables were recorded: mean age, gender, number of current smokers, duration of the disease (in years), disease location and behavior according to the Montreal classification, perianal disease, f CRP, HBI, and fecal calprotectin at baseline values, concomitant medications (systemic steroids and/or immunosuppressants) at baseline, and number of anti-TNF naïve patients.

Data Extraction and Analyses

We extracted our data and outcomes using Microsoft Excel. Thereafter, we performed our analysis using OpenMeta [Analyst] Software for the single-arm analysis. All the outcomes were dichotomous and were expressed as events and totals, analyzed using the Mantel-Hanszel method. We used the random-effects model for analyzing the heterogeneous data. Outcomes were reported and analyzed at the end of the induction phase and at the end of the maintenance phase (the last reported outcome during the follow-up in the two phases). For crossover studies, we reported the outcomes just before the crossover as the induction phase outcome, and the final follow-up outcome was recorded as the outcome at the end of the maintenance phase. Usually, the induction phase ended after 8 weeks, and the maintenance phase ended at between 24 and 52 weeks, according to the end-point assessed in each study. We expressed the heterogeneity as I2 with a 95% confidence interval (CI).[21]

Risk of Bias Assessment

We assessed each included study for the risk of bias (ROB) according to the Cochrane ROB tool for clinical trials and the Newcastle-Ottawa Scale Quality Assessment Score for observational studies.[22] We assessed each included study and judged them to have low, high, or unclear ROB in case of clinical trials, and by using the scoring system of the National Institute for Health and Care Excellence (NICE) assessment score for observational studies; we considered a total score of ≥ 4 in each study to indicate higher quality. Discrepancies among reviewers about qualitative and quantitative data collection were infrequent and were resolved via discussion until a consensus was reached. The total ROB was also assessed for the studies.

Results of the Literature Search

Our search of the PubMed, Cochrane Library, EBSCO, EMBASE, Google Scholar, and clinicaltrial.gov databases yielded 733 studies. There were 172 duplicates. After removing the duplicates, the remaining 561 studies were subjected to title and abstract screening. We excluded 473 studies, and only 88 studies remained for full-text screening. According to the eligibility criteria, only 31 studies were eligible for the analysis and qualitative synthesis. A PRISMA flow diagram describes the literature search process in ►**Fig. 1**.

The total study population was of 4,487 patients. The majority of the included studies was observational cohort studies with 2,260 patients,[23–49] and 4 of the included studies were RCTs with 2,227 patients.[13,17,50,51] We have presented data on age, gender, location of CD disease, disease phenotype, route of administration, and drug dose.

Quality of the Included Studies

The included RCTs were of moderate to high quality according to the Cochrane tool for the assessment of ROB. Five trials in 4 unique reports stated adequate selective reporting,[13,17,50,51] except the study by Feagan from 2016[50]; we categorized all the studies as having a high ROB due to attrition. Regarding allocation concealment, the ROB was unclear in all studies. All studies reported proper randomization; however, the randomization was unclear in the study reported by Hanauer in 2019[51] was unclear. Participant blinding was performed in all studies except in the study conducted by Hanauer 2019.[51] The researchers who assessed the outcomes in the previous study[51] were not blinded; therefore, the study was considered to have a high ROB; the bias in the other studies was unclear. Some studies have reported other sources of bias.[13,50]

The only single-arm trial was fair in quality according to the National Institutes of Health (NIH) quality assessment tool for before-after (pre-post) studies with no control group.[45]

We assessed the other 26 cohort studies using the NIH quality assessment tool for observational cohort and cross-sectional Studies. The quality of these studies ranged from fair to poor. Only one study showed good quality.[40] Fifteen studies were rated to have fair quality,[23,24,26,27,29,31,34,35,37–39,41,42,44,47] and the remaining 10 trials were of poor quality.[25,28,30,32,33,36,43,46,48,49]

Results

Efficacy and Safety Outcomes

Clinical Response Rate

Twenty-one studies reported the clinical remission rate[13,17,23–26,28,30–35,37,40,42,44,46,48–50]; 3 of these were RCTs,[13,17,50] and the remaining 18 studies were observational cohort studies.[23–26,28,30–35,37,40,42,44,46,48,49] The overall clinical response rate for the cohort studies was of 0.539 (95% CI: 0.419–0.659) with significant heterogeneity ($I^2 = 96.22\%$; $p < 0.001$) that could not be resolved using the leave-one-out tool or subgroup analysis according to country, administration route, or dose. In RCTs, the clinical response rate was of 0.428, (95%CI: 0.356–0.501) with significant heterogeneity ($I^2 = 87.09\%$; $p < 0.001$); however, this was resolved by excluding the study by Sandborn.[17] The clinical response rate became 0.466 (95%CI: 0.439–0.493), and the result became homogenous ($I^2 = 0\%$; $p = 0.702$) (►**Fig. 2**).

Clinical Remission Rate

The clinical remission rate was reported in 23 studies.[13,17,23–28,30–32,34,35,37,38,41,42,44,45,47,48,50,51] It was of 0.399 (95%CI: 0.295–0.503) in the RCTs[13,17,45,50,51] and of 0.440 (95%CI: 0.339–0.542) in the cohort studies.[23–28,30–32,34,35,37,38,41,42,44,47,48] Both results were heterogeneous, ($I^2 = 95.79\%$; $p < 0.001$) for the RCTs and for the cohort studies ($I^2 = 94.04\%$; $p < 0.001$). We could not resolve the heterogeneity by using the leave-one-out tool or the subgroup analysis according to country, administration route, or dose. (►**Fig. 3**)

Adverse Effects

The incidence of adverse effects was reported in 21 studies,[13,17,24,26,28–35,37,38,41,42,44,47–50] at 0.158 (95%CI: 0.109–0.207) for the cohort studies[24,26,28–35,37,38,41,42,44,47–49] and at 0.690 (95%CI: 0.633–0.748) for the RCTs.[13,17,50] Both results were heterogeneous; ($I^2 = 90.08\%$; $p < 0.001$) for the cohort studies and ($I^2 = 82$; $p = 0.004$) for the RCTs. We could not resolve the

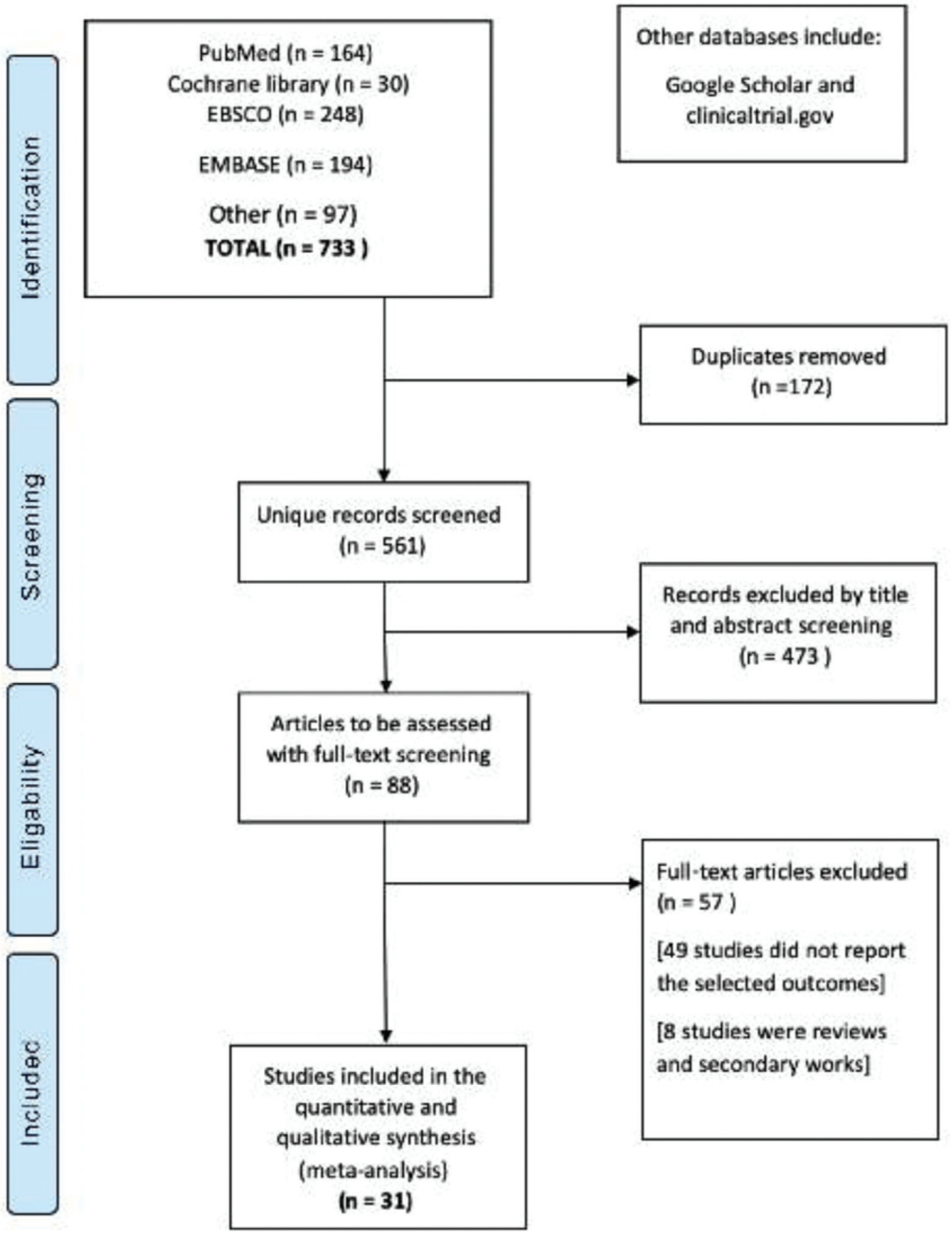

Fig. 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram.

heterogeneity with the leave-one-out tool or subgroup analysis according to country, administration route, or dose. (►**Fig. 4**)

Incidence of Infections

Twenty-one studies reported the incidence of infection outcomes.[13,17,24,25,29–37,39,41–43,47–50] Three of these studies were RCTs with an infection incidence of 0.275 (95%CI: 0.245–0.295),[13,17,50] and the remaining were cohort studies with an infection incidence of 0.076 (95%CI: 0.047–0.105).[24,25,29–37,39,41–43,47–49] The result was significantly homogenous in the analyses of the RCTs; ($I^2 = 0\%$; $p = 0.74$), while it was heterogeneous in the analysis of the cohort studies ($I^2 = 84.45\%$; $p < 0.001$). The heterogeneity could not be solved by using the leave-one-out method or subgroup analyses according to country, dose, or administration route. (►**Fig. 5**)

The Injection or Injection Reaction

Only 10 studies reported the incidence of injection or infusion reaction, at 0.035 (95%CI: 0.027–0.043) for RCTs[13,17,50] and at 0.012 (95%CI: 0.002–0.022) for cohort studies.[25,29,35,37,41,47,49] The result was significantly homogeneous in the analyses of RCTs ($I^2 = 0\%$; $p = 0.389$), while it was heterogeneous in the cohort studies analyses ($I^2 = 48.71\%$; $p = 0.069$). The heterogeneity could not be resolved using the leave-one-out method or subgroup analysis according to country, dose, or administration route. (►**Fig. 6**)

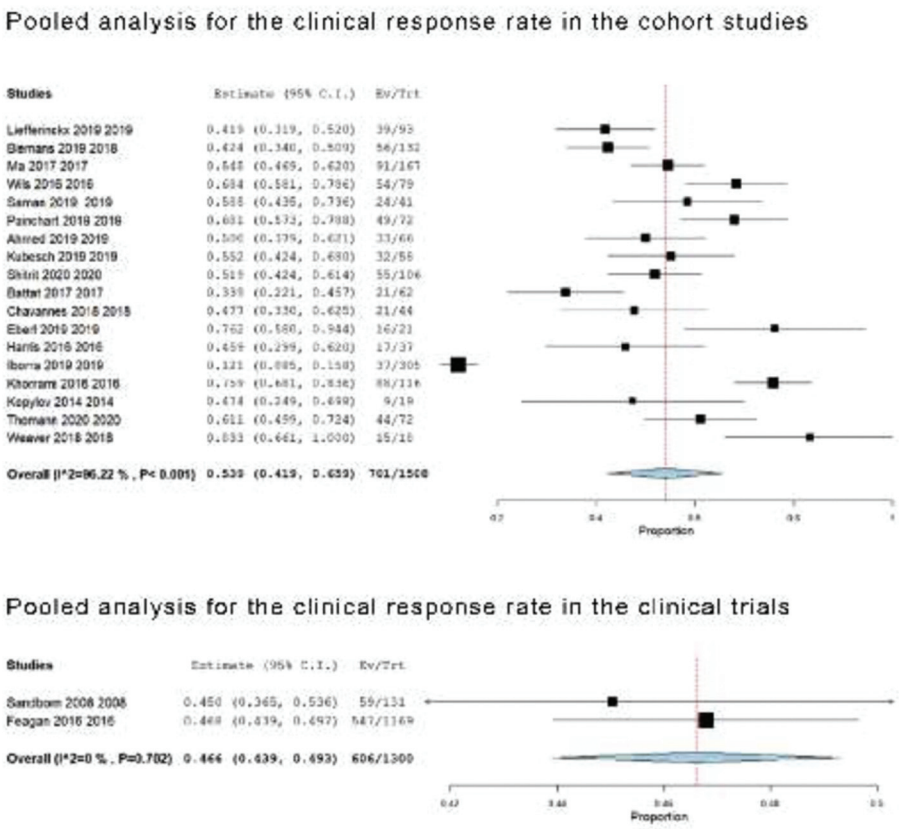

Fig. 2 Pooled analysis of clinical response rate.

Discussion

In the present systematic review and meta-analysis, we pooled data from a total of 27 observational cohort studies [23–49] and 4 RCTs,[13,17,50,51] including a total of 4,487 patients. Our study discusses the safety and efficacy of ustekinumab treatment in patients with moderate to severe CD.

Based on the present results, patients with CD who used ustekinumab had a high clinical response rate (53.9%) and a high clinical remission rate (39.9%) in the observational and RCT subgroups. Moreover, our analysis showed a low prevalence of overall drug-related adverse effects (15.8%), of total incidence of infections (7.6%), and of frequency of drug-induced reactions (3.5%). Our meta-analysis indicated that ustekinumab is well tolerated and is associated with clinical responses and remissions in CD patients.

The subgroup analysis, based on the study design, RCT or cohort study, showed consistent and comparable effects in terms of the response and remission rates. However, the subgroup of RCTs had higher rates of total drug-attributed adverse effects, of total incidence of infections, and of drug-induced reactions.

The results obtained from the present systematic review and meta-analysis are clinically significant and can be applied to patients with moderate to severe CD because the studies included in the present report were of moderate to high quality and employed large samples. Moreover, ustekinumab use could be generalized to different populations in which the drug had proven good effect and low incidence of adverse effects.

Ustekinumab was first used for treating patients with moderate to severe CD in an RCT by Sandborn et al. in 2008.[13] This study showed that ustekinumab induced a clinical response in CD patients with a moderate to severe disease score, particularly if they had been taking infliximab drugs. A more recent study by Sandborn et al.[17] showed the beneficial effect of ustekinumab in patients who did not benefit from TNF antagonists. The initial response to ustekinumab showed better response and remission rates during the maintenance phase in this study. A recent meta-analysis of observational studies showed that ustekinumab had an adequate effectiveness level and a good safety profile.[52] In fact, other similar drugs achieved similar response rates.[53]

The RCTs included in our analysis were of moderate to high quality, and the observational cohort studies were of moderate quality. We followed the PRISMA and MOOSE statements strictly while performing and reporting the present meta-analysis. Furthermore, we conducted all steps of the present systematic review according to the Cochrane handbook of systematic reviews for interventions.

The studies included in our meta-analysis had a high dropout rate. However, these studies were analyzed based on the intention-to-treat approach.

The present study has certain limitations. First, we could not compare ustekinumab to other similar treatments or placebo due to a lack of available evidence. Second, we found significant heterogeneity within the included studies for almost all outcomes; this variation could not be resolved

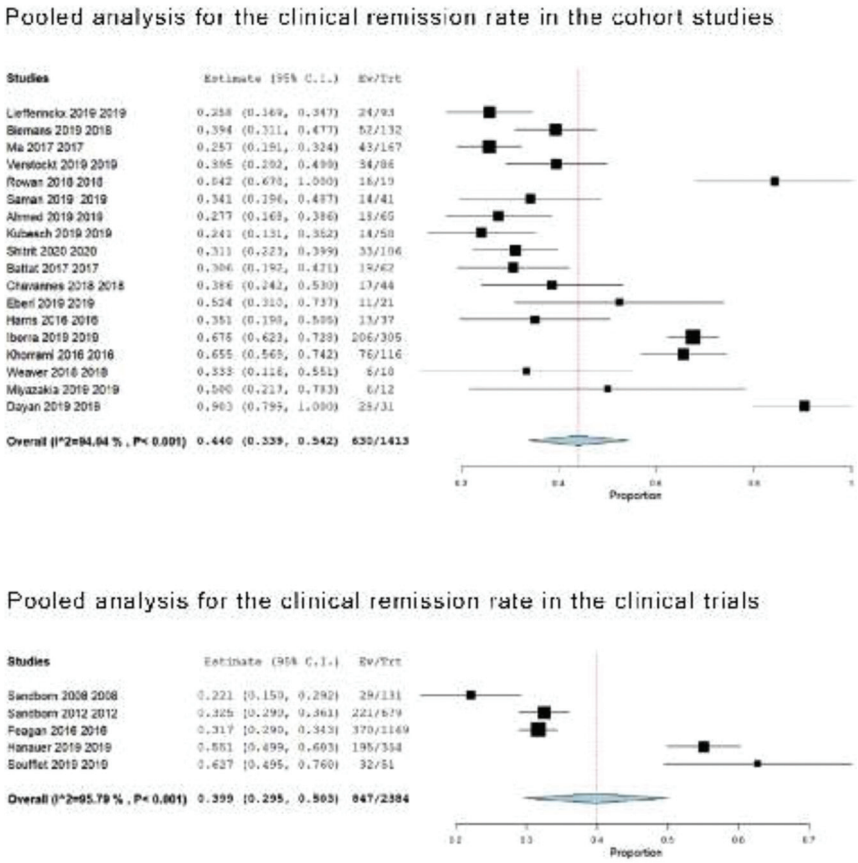

Fig. 3 Pooled analysis of clinical remission rate.

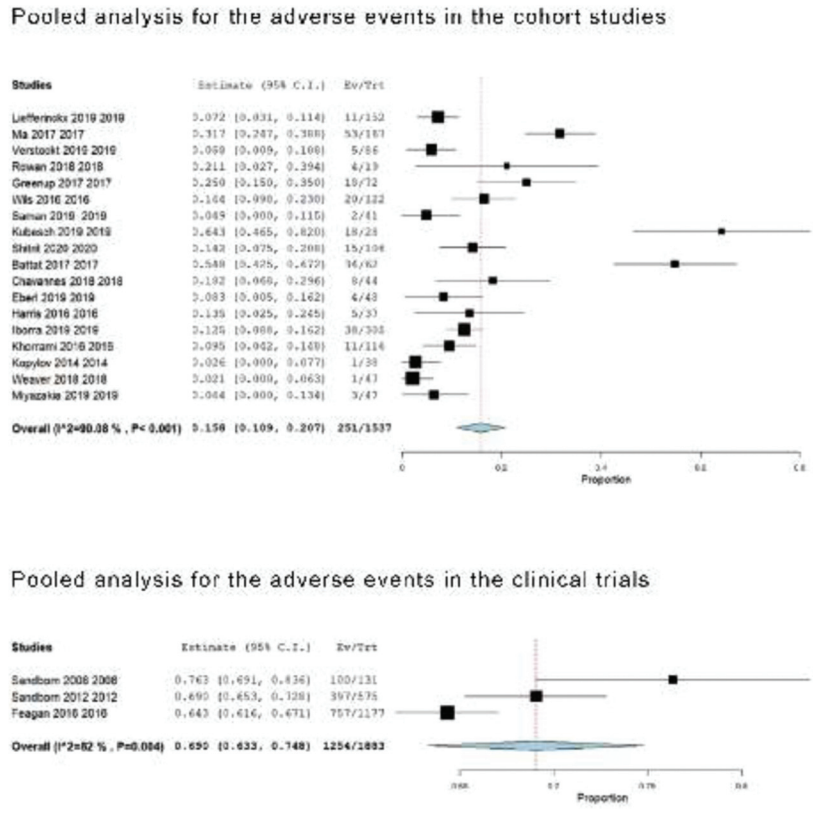

Fig. 4 Pooled analysis of adverse events.

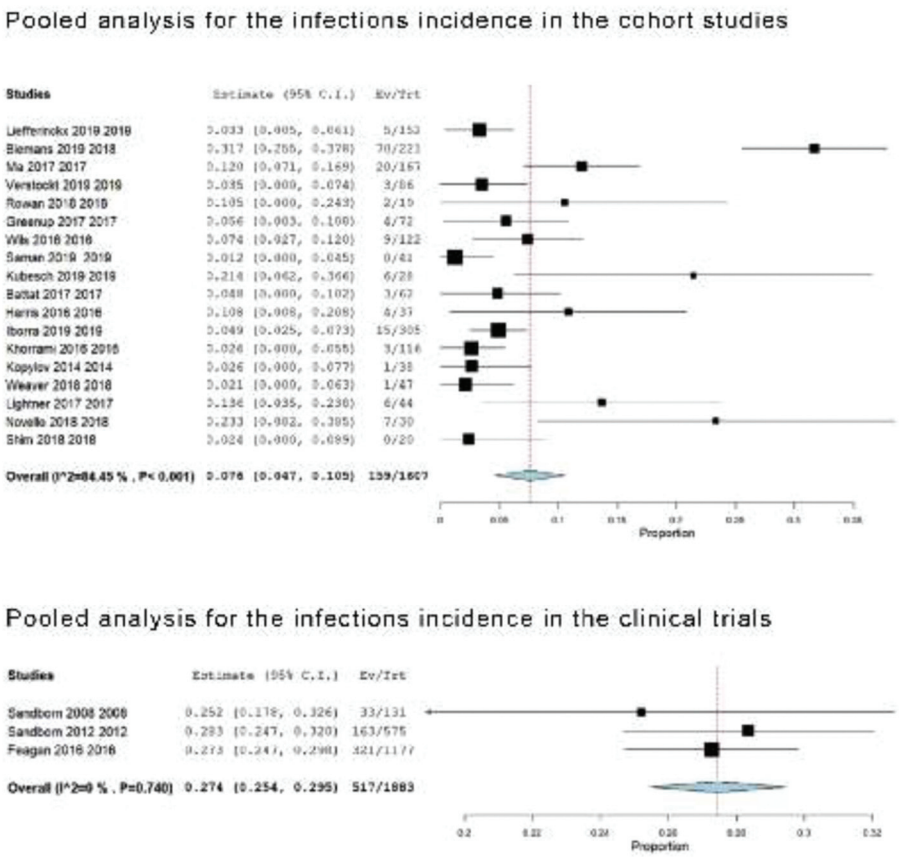

Fig. 5 Pooled analysis of the incidence of infections.

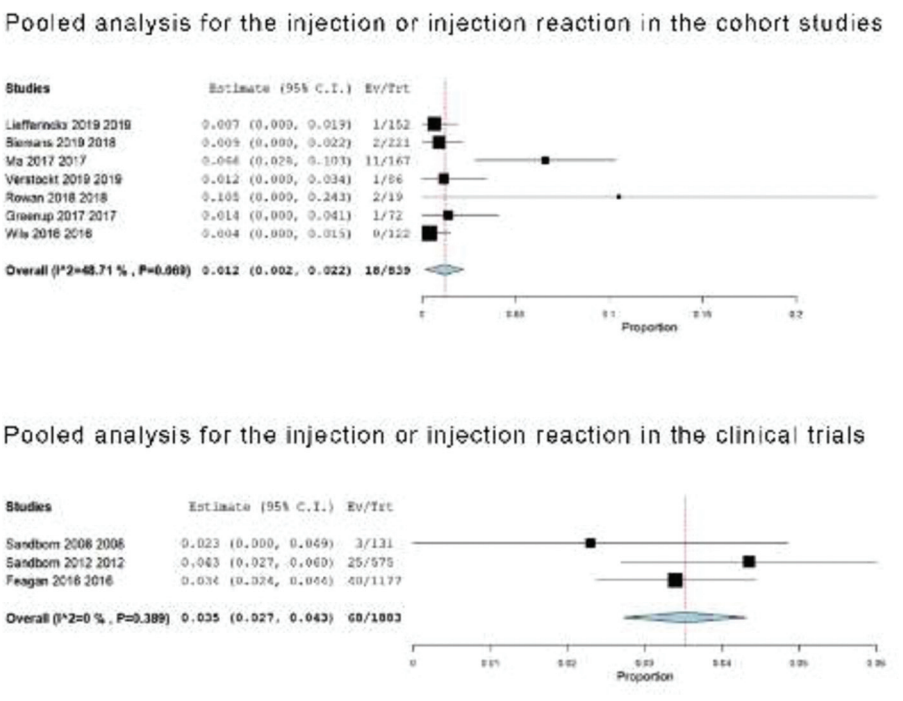

Fig. 6 Pooled analysis of injection reactions.

with the use of the leave-one-out method or subgroup analysis based on the country, dose, or administration route. This heterogeneity might be attributed to the use of the drug in different populations with variable demographic and disease characteristics. Finally, we could not determine the publication bias among the included studies because the open meta-analyst software does not enable this type of analysis.[54]

We have some recommendations for future research on this subject using this drug. These include the implementation of large-sized RCTs with longer follow-up periods. Moreover, future studies should compare ustekinumab to the best available drug used for these cases to use it at a broader level and integrate it into the conventional treatment for CD.

Conclusion

Our analysis showed that, in patients with moderate to severe CD, treatment with ustekinumab was well tolerated and was associated with high response and remission rates. Future large-sized RCTs are needed to obtain a deeper understanding regarding the effect of ustekinumab in patients with CD.

Authorship Statement

All authors participated sufficiently in the work and approved the final version of the manuscript. Khorshid M. A. designed the study and developed the methodology. Khorshid M. A., Cordie A., and Abd-Elsalam S. wrote the manuscript. The three authors screened each study independently following two steps: the first step was abstract screening for eligibility criteria, and the second step was full-text article screening for the eligibility criteria of the present systematic review and meta-analysis. Disagreements were resolved by the corresponding author (Abd-Elsalam S.).

Conflict of Interests

The authors have no conflict of interests to declare.

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