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The efficacy of CT-P13, a biosimilar of infliximab, in inflammatory bowel diseases: a systematic review and meta-analysis

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Abstract

Background Since 2015, an infliximab biosimilar, CT-P13, has been approved for commercial use in many countries, easing the economic burden borne by society and patients. Many clinical trials investigating CT-P13 for the treatment of IBD have been conducted and reported that it may be a substitute for infliximab. However, the differences between the efficacy of CT-P13 and infliximab-originator require further elucidation.

Methods Data on the rates of clinical response, clinical remission, and mucosal healing of IBD were pooled for random-effects model meta-analysis using Stata MP 17. A total of 30 studies were included.

Results The pooled risk of clinical remission rate of patients with Crohn's disease and ulcerative colitis who were naïve to biologics at 08–14 weeks were 0.66 (95% CI, 0.58–0.75) and 0.48 (95% CI, 0.43–0.54), respectively, and at 100–104 weeks were 0.66 (95% CI, 0.49 to 0.84) and 0.71 (95% CI, 0.62 to 0.79) respectively. The pooled risk of clinical remission rate of patients with Crohn's disease and ulcerative colitis who were transitioned from the original agent at 24–32 weeks were 0.84 (95% CI, 0.77–0.92) and 0.78 (95% CI, 0.63–0.93), respectively, and at 48–54 weeks were 0.72 (95% CI, 0.62 to 0.82) and 0.78 (95% CI, 0.71 to 0.86) respectively. The pooled rates for mucosal healing in ulcerative colitis were 0.56 (95% CI: 0.46 to 0.67) at 08–14 weeks, and 0.64 (95% CI: 0.42 to 0.85) at 48–54 weeks. RCT studies showed no significant change in efficacy after switching, whether Crohn's disease or ulcerative colitis.

Conclusions CT-P13 is effective in short and long-term periods. The application of CT-P13 for the management of IBD was promising.

Keywords CT-P13, Infliximab, Inflammatory bowel disease, Crohn's disease, Ulcerative colitis, Mucosal healing, Meta-analysis

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Introduction

The term inflammatory bowel disease (IBD) refers to a group of idiopathic nonspecific inflammatory intestinal diseases characterized by recurrent abdominal pain, diarrhea, and weight loss. The etiology of IBD is complex, the pathogenesis is not fully understood, and the principal etiology is related to individual genetic factors, intestinal environment, and autoimmunity [1–3]. This disease has a deleterious effect on a large population, especially children, pregnant women, and elderly individuals, because is difficult to control and relapses easily. In recent decades, although the incidence rate has declined in some Western countries according to reports, it has risen in most developed and developing countries, imposing a severe burden on patients and society [4–6]. IBD is difficult to control, owing to the complexity of its pathophysiology. Therefore, the medical community places a high value on its treatment. Currently, the primary objective of treatment for IBD entails the control of inflammation and the prevention of complications [7]. At present, the principal treatment methods include general anti-inflammatory therapy(such as 5-Amino Salicylic Acid), corticosteroids, immunosuppressants, biological agents, and surgical treatment [8]. Currently due to further deepening research on the intestinal microecology of inflammatory bowel diseases, transplants of fecal matter from healthy donors are also being explored [9–11]. Different patients will choose the appropriate treatment based on different changes in their condition.

Biological agents elicit a good response and remission. Infliximab (IFX) was the first biological agent used for treating autoimmune diseases, [12] but its high cost limits its application, necessitating an alternative biosimilar, to reduce the medical economic burden [13]. However, the efficacy of these biosimilar agents requires detailed evaluation. CT-P13 is a low-cost biomimetic of IFX used in treatment of the immune diseases, such as rheumatoid arthritis, ankylosing spondylitis, and IBDs [14, 15]. In recent years, researchers have conducted numerous clinical trials, which revealed that the clinical efficacy of CT-P13 is similar to that of the IFX-originator, and does not cause more serious adverse events. In 2017, a meta-analysis of studies investigating CT-P13 in IBD first statistically proved that CT-P13 is effective and well tolerated in the short and long term, recommending the transition from IFX to CT-P13 [16]. Another meta-analysis conducted after two years reported the same result [17]. However, there were some limitations, such as an insufficient number of included studies and lack of sensitivity analysis, such that the meta-analysis was not considered to offer an adequate representative of the actual condition. Moreover, neither of these two meta-analyses evaluated endoscopic mucosal healing by detail, which has become an important index to evaluate the effect of treatment [16, 17]. The increase in in-depth research in recent years has led to the accrual of new evidence on the efficacy and safety of CT-P13. Many experts and scholars have regarded mucosal healing as the ultimate treatment goal for patients with UC. In our study, we enrolled a higher-quality and larger sample, and also used updated clinical data to evaluate the efficacy and safety of CT-P13 in patients with new-onset and pre-existing disease. Moreover, we analyzed the mucosal healing rate in ulcerative colitis in greater detail.

Methods

We conducted this systematic review and meta-analysis following the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) reporting guideline [18].

Retrieval strategy

We conducted a comprehensive search of PubMed, Embase, Cochrane, Web of Science, and Google Scholar. We used the following words and terms for the search: "CT-P13," "infliximab biosimilar," "infliximab," "IBD," "inflammatory bowel disease," "UC," "CD," "ulcerative colitis," and "Crohn disease." The study period extended from the time of database establishment to June 2024. All researchers read each eligible study and related references.

Eligibility criteria

The inclusion criteria for this study were based on PICOS as follows:

1. Patients: adult population diagnosed with IBD, whether active or in remission.
2. Intervention: patients who received CT-P13 alone or transitioned from IFX to CT-P13.
3. Comparison: maintenance of IFX therapy.
4. Outcomes: the results included at least one of the following parameters, viz. clinical response rate, clinical remission rate, mucosal healing rate, or adverse events.
5. Study: the research was a randomized controlled trial (RCT), prospective, or retrospective by design.

We excluded animal experiments and studies published in languages other than English.

Screening relevant studies and quality evaluation

We screened the titles and abstracts of records, and then conducted full-text screening, to determine eligibility. If there were any disagreements, we discussed and resolved them in a group, and the study was excluded if all authors concurred that it failed to meet the inclusion criteria. We chose RCTs, prospective studies, and retrospective

studies that evaluated the efficacy and safety of CT-P13 in patients with IBD.

Risk of bias

The quality of the retrieved RCTs was evaluated using the Cochrane risk bias assessment tool (2019) [19]. The evaluators' judgments were categorized as "low risk," "high risk," or "unclear risk" of bias.

The quality of the observational studies was assessed using the Newcastle-Ottawa Scale (NOS), including selection (selection bias), comparability (selection bias), and outcome (reporting bias and attrition bias). A study is considered to meet the requirements when the NOS score is more than 5 [20].

Endpoint

The primary endpoints in this study were the clinical remission rate and response rate of IBD. Clinical remission in CD was defined as Crohn's Disease Activity Index [CDAI] < 150 points [21]. Clinical remission in UC was defined as a partial Mayo Score [pMayo] of less than 2 points [22, 23]. Clinical response in CD was defined as a decrease in CDAI with more than 70 points [21]. Clinical response in UC was defined as a decrease in the pMayo score with more than 3 points [22, 23]. The Mayo score was used to assess mucosal healing in UC [22, 23].

Statistical analysis

We analyzed Crohn's disease and ulcerative colitis independently. Statistical analysis was performed with a random-effect model using STATA MP 17. The event rate (clinical response rate, clinical remission rate, and mucosal healing rate) and the corresponding 95% confidence intervals (CI) were calculated separately. The heterogeneity across studies was calculated quantitatively using the I^2 statistic, where studies with I^2 values < 25%, 25–75%, and >75% were considered to have low, moderate, and high levels of statistical heterogeneity, respectively. Moreover, P-values < 0.05 were used to indicate statistically significant heterogeneity [17].

Subgroup analysis and sensitivity analysis

To analyze the sources of heterogeneity and the influencing factors on the primary outcome, we performed subgroup analysis and sensitivity analysis. We analyzed patients in groups based on the type of disease they had, whether they were biologics-naïve, and the main observations of the study (clinical response rate and clinical response rate). By referring to a study of Ebada, M.A [17] we then performed subgroup analyses based on the duration of the patient's medication (08–14 weeks, 26–32 weeks, 48–54 weeks, and even 100–104 weeks) to study the short-term (08–14 weeks), medium-term (26–32 weeks), and long-term (48–104 weeks) efficacy. At the same time, the difference in age, gender, concomitant medication, and disease activity of the participants in each study included in this meta-analysis were considered. Thus, to reduce the significant impact of a study on the results, we excluded the literature one by one to test the sensitivity.

Results

Retrieval results and inclusion of articles and studies

We conducted a comprehensive search of PubMed, Embase, Cochrane, Web of Science, and Google Scholar. A total of 1296 records were retrieved and considered for screening. Eventually, by checking the titles and abstracts of records and conducting full-text screening, 30 eligible studies were included (Three were randomized controlled trials, and the others were prospective and retrospective studies) [24–54]. We show the screening process of studies included in the form of a flowchart (Fig. 1). 14 studies were included in the biotherapy-naïve group. Participants in this group had active disease before the commencement of the study although there were differences in disease severity (eTable.1 in Supplement S1). 14 studies, including those of Argüelles-Arias, were included in the transitioned group. However, the proportion of participants with active disease in the transitioned group was initially not the same (eTable.2 in Supplement S1). In addition, there were 4 high-quality studies were conducted on mucosal healing rates of ulcerative colitis [24–27]. Unfortunately, there was no high-quality research on mucosal healing in Crohn's disease that has been screened out, although 2 studies have mentioned it [25, 35]. A total of 475 patients were included in the meta-analysis of randomized controlled studies, and they all underwent a switching. However, participants in these groups all had clinical remission of the disease, whether it was UC or CD. The main and basic information on the included randomized controlled trial studies is listed in eTable.3 in Supplement S1.

Interestingly, we also found that the definition of the endpoint index differed among various studies (the clinical remission of ulcerative colitis was defined as a partial Mayo score of ≤3 in two studies, and ≤2 in the remaining studies) [35, 41]. And not all the studies have uniform doses of CT-P13. Doses used in most studies were 5 mg/kg at 0, 2, and 6 weeks, and maintenance was 5 mg/kg every 8 weeks, increasing to 10 mg/kg and/or every 4 instead of 8 weeks when necessary. However, in the study of Park, S. H, [44] doses per kilogram of weight were adjusted based on disease activity.

Efficacy of CT-P13

RCTs of patients with Crohn's disease

After pooling the research data, there were 206 patients in the experimental group (switch to CT-P13) and 204 in

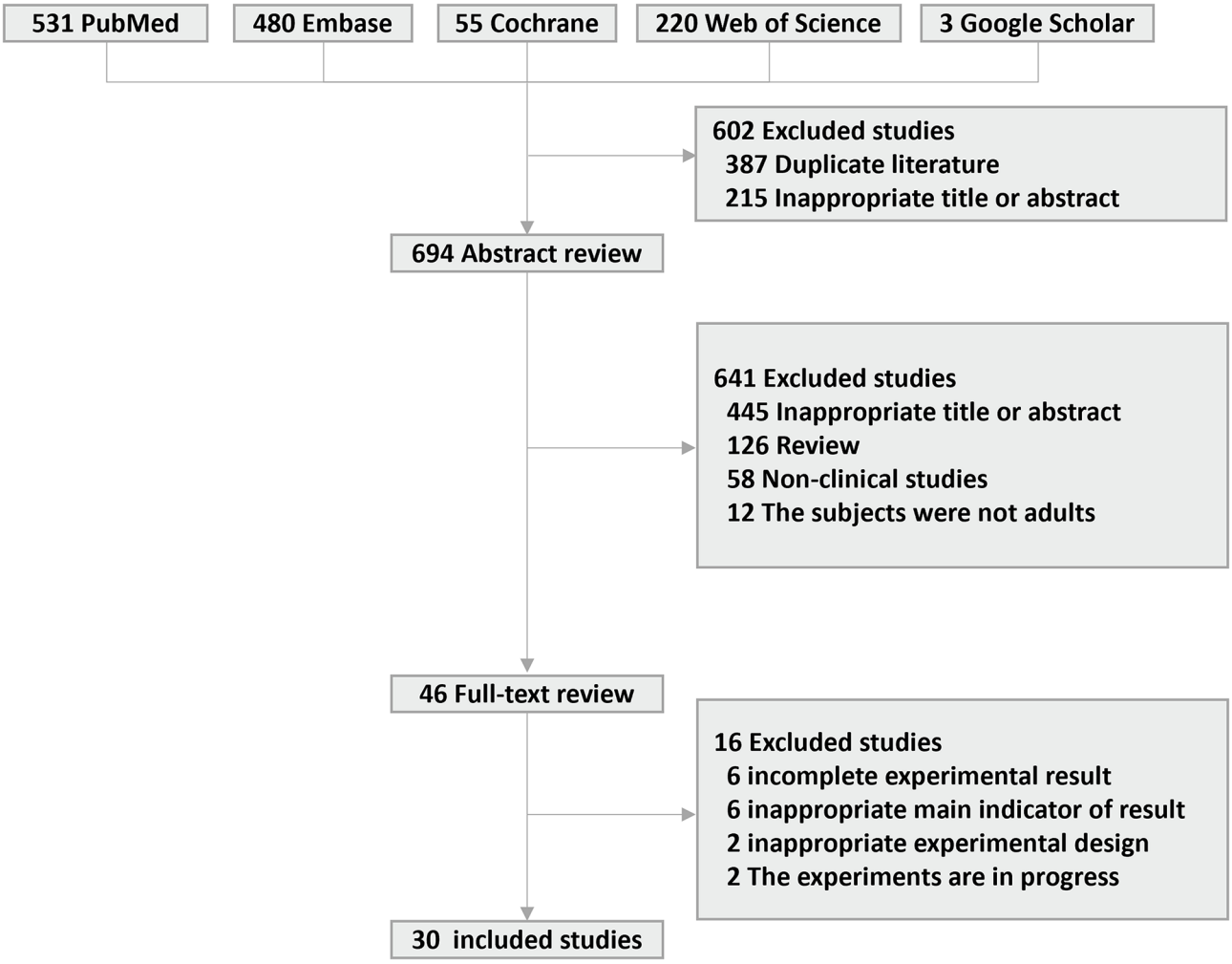

Fig. 1 Flow Chart of Studies Screening. A total of 1296 records were retrieved and considered for screening. Eventually, by checking the titles and abstracts of records and conducting full-text screening, 30 eligible studies were included

the control group (maintenance of IFX therapy). Disease progression occurred in 50 of 206 and 42 of 204 patients in the experimental and control groups, respectively. RCT studies showed no significant change in efficacy after switching. The odds ratio (OR) of the merged result was 1.17 (95% CI: 0.74–1.85). The pooled effect estimates showed a low level of heterogeneity (I^2=1%, P=0.36) (eFigure.1 in Supplement S1).

RCTs of patients with ulcerative colitis

Only 53 patients were included in the CT-P13 group and 52 in the control group (IFX originator therapy). The total OR was 1.48 (95% CI: 0.39–5.61). The pooled effect estimates showed a low level of heterogeneity (I^2=0%, P=0.34) (eFigure 2 in Supplement S1). However, in Volker's study, the sample size was extremely small (only 6 patients each in the experimental and control groups), which could have affected the results of pooling.

Retrospective and prospective studies in biologic-naïve patients with Crohn's disease

CT-P13 was related to high clinical response rates at 08–14 weeks [0.85%, 95% CI (0.79 to 0.91)], 26–32 weeks [0.79, 95% CI (0.68 to 0.90)], 48–54 weeks [0.79%, 95% CI (0.66 to 0.92)], and 100–104 weeks [0.79%, 95% CI (0.65 to0.92)]. Finally, the total pooled rate of clinical response rates on patients with CD was 0.81%, 95% CI (0.76 to 0.85), and heterogeneity remained high (I^2=87.4%, P<0.001). (Fig. 2A). On the other hand, the pooled rates for clinical remission in patients with CD were 0.66 [95% CI (0.58–0.74), 0.63 [95% CI (0.48–0.79), 0.63 [95% CI (0.49–0.78)], and 0.66 [95% CI (0.49–0.84) at 8–14 weeks, 26–32 weeks,48–54 weeks, and 100–104 weeks, respectively. The pooled effect estimates were heterogeneous at 08–14 weeks (I^2=84.5%, P<0.001), 26–32 weeks (I^2=89.7%, P<0.001), 48–54 weeks (I^2=91.9%, P<0.001), and 100–104 weeks (I^2=85.7%, P=0.008). The total pooled rate of clinical remission rates on patients

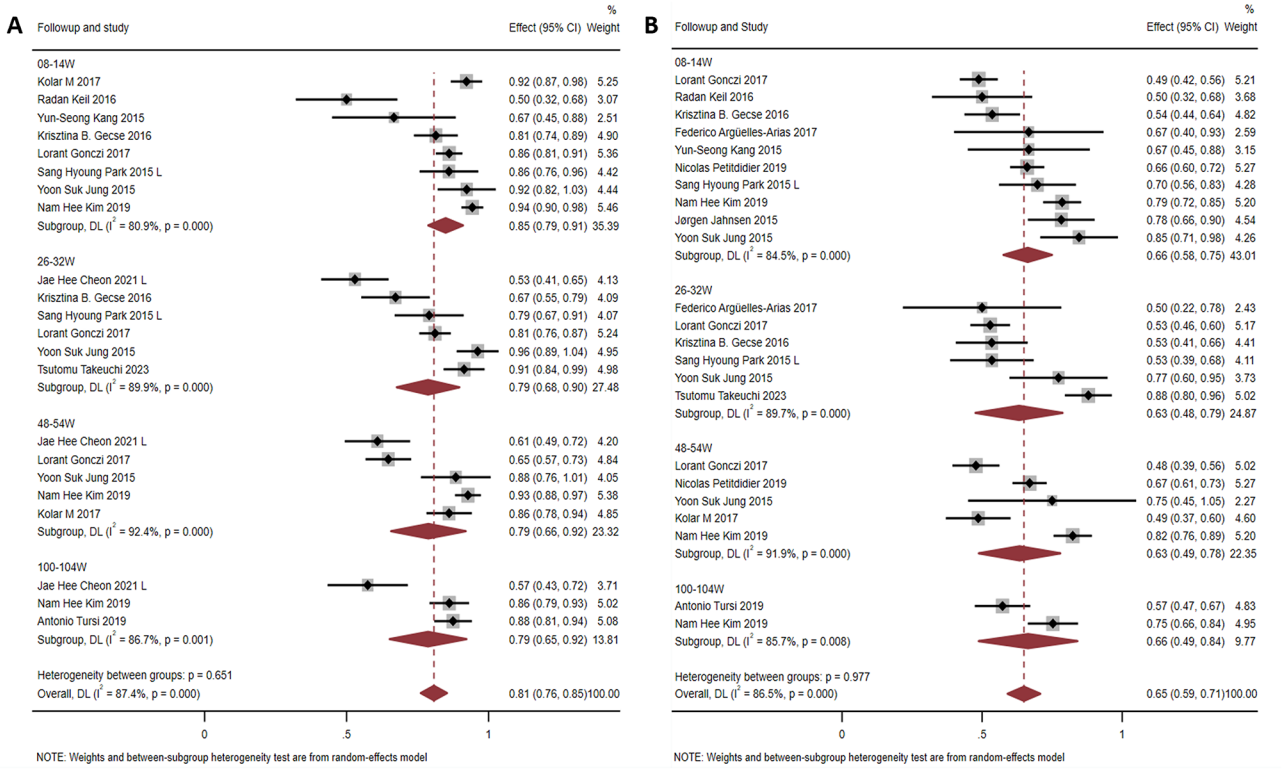

Fig. 2 Forest plot and pooled estimates of biologic-naive patients with Crohn's disease. Subgroup analysis was performed by years of follow-up. (**A**) Forest plot and pooled estimates of clinical response rates on biologic-naive patients with Crohn's disease. (**B**) Forest plot and pooled estimates of clinical remission rates on biologic-naïve patients with Crohn's disease

with CD was 0.65, 95% CI (0.59 to 0.71), and heterogeneity remained high(I^2=86.5%). (Fig. 2B).

Retrospective and prospective studies in biologic-naïve patients with ulcerative colitis

The pooled rates for clinical response at 08–14 weeks, 26–32 weeks, 48–54 weeks, and 100–104 weeks were 0.84 (95% CI: 0.78 to 0.89), 0.80 (95% CIL 0.68 to 0.91), 0.64 (95% CI: 0.48 to 0.80) and 0.73 (95% CI: 0.61 to 0.86), respectively. (Fig. 3A) The pooled clinical remission rates were 0.48 (95% CI: 0.43 to 0.54), 0.53 (95% CI: 0.41 to 0.65), 0.52 (95% CI: 0.44 to 0.60), and 0.71 (95% CI: 0.62 to 0.79) at 08–14 weeks, 26–32 weeks, 48–54 weeks, and 100–104 weeks respectively. Moderate heterogeneity was observed at 08–14 weeks (I^2=50.9%, P=0.038), 26–32 weeks (I^2=77.9%, P<0.001), and 48–54 weeks (I^2=52.6%, P=0.077), and low heterogeneity was observed at 100–104 weeks (I^2=5.4%, P=0.304). The total pooled rate of clinical remission rates on patients with UC was 0.52, 95% CI (0.47 to 0.79), and heterogeneity remained moderate (I^2=69.5%, P<0.001) (Fig. 3B).

Observational studies in transitioned patients with Crohn's disease

After switching to CT-P13, most patients with Crohn's disease maintained clinical remission at 24–32 weeks [0.84, 95% CI (0.77 to 0.92)], and 48–54 weeks [0.72, 95% CI (0.62 to 0.82)]. The pooled effect estimates were heterogeneous at 26–32 weeks (I^2=79.6%, P=0.001), and at 48–54 weeks (I^2=94.4%, P<0.001); a high level of heterogeneity existed between the groups (I^2=92.1%, P<0.001) (eFigure 3. A in Supplement S1).

Observational studies in transitioned patients with ulcerative colitis

More than two-thirds of patients with ulcerative colitis in each subgroup achieved clinical remission at 24–32 weeks [0.78, 95% CI (0.63 to 0.93)], and 48–54 weeks [0.78, 95% CI (0.71 to 0.86)]. The pooled effect estimates were heterogeneous at 26–32 weeks (I^2=84.5%, P<0.001), and 48–54 weeks (I^2=62.0%, P=0.022), respectively (Fig. 3B in Supplement S1). The total pooled rate of clinical remission rate was 0.79, 95% CI (0.72 to 0.86), and heterogeneity remained high (I^2=75.1%, P<0.001).

Mucosal healing in ulcerative colitis

There is limited data on mucosal healing rates. Only 4 high-quality studies were conducted on mucosal healing rates of ulcerative colitis [24, 25, 28, 53]. The pooled rates for mucosal healing in ulcerative colitis were 0.56 (95% CI: 0.46 to 0.67), 0.79 (95% CI: 0.66 to 0.92), and 0.52 (95% CI: 0.40 to 0.65] at 08–14 weeks, 24–30 weeks,

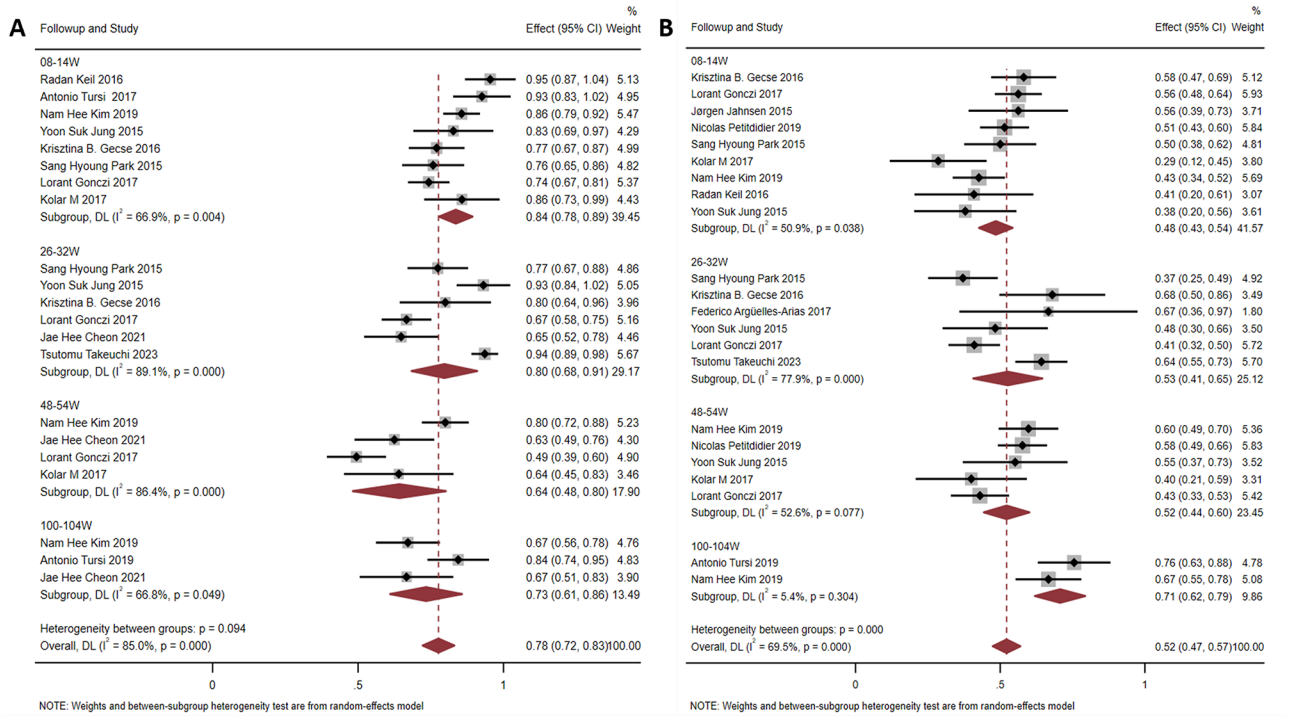

Fig. 3 Forest plot and pooled estimates of biologic-naïve patients with ulcerative colitis. Subgroup analysis was performed by years of follow-up. (**A**) Forest plot and pooled estimates of clinical response rates on biologic-naïve patients with ulcerative colitis. (**B**) Forest plot and pooled estimates of clinical remission rates on biologic-naïve patients with ulcerative colitis

and 48–54 weeks, respectively (Fig. 4). The heterogeneity between studies is low at 08–14 weeks (I^2=00.0%, P=0.827), 24–30 weeks (I^2=00.0%, P=0.556), and 48–54 weeks (I^2=44.7%, P=0.164).

Sensitivity analysis

Our study considered that the evaluation of drug efficacy may be affected by the patient's age, sex, concomitant use of other medication, disease activity, subjective factors, and follow-up time. Therefore, we conducted the sensitivity analysis of each pooling effect separately. We presented the results of the sensitivity analysis in the Supplement S2. Interestingly, we found after the exclusions, the results did not change significantly and it remained stable.

Discussion

The current study entailed a systematic review and meta-analysis of the clinical efficacy of CT-P13 in patients with IBD. The meta-analysis (which included only a limited number of studies and patients) of the clinical remission rate and response rate of CT-P13, a biosimilar of IFX, revealed that the former is effective irrespective of whether the patients were naïve to biologics or transitioned from IFX-originator to CT-P13. The meta-analysis of the RCTs included in this study showed that the OR approximated 1 and the difference was not statistically significant (P>0.05), which suggests that the effect of CT-P13 is similar to that in IFX in patients with IBD. Similar results were obtained after analysis of the observational studies. The clinical response and clinical remission rates of IBD are extremely high in the first year, but the clinical response rate tends to decline with the passage of time, according to a few observational studies, which can be alleviated by increasing the dose or switching to another tumor necrosis factor (TNF)-α inhibitor (such as adalimumab) in most cases [26, 42]. This may be related to the secondary loss of response (IFX is a human-mouse chimera and the adalimumab is of human origin) [55]. However, some patients required continuous corticosteroid therapy or surgery, which is consistent with the results of two previous meta-analyses. It is possible that future studies could ascertain the relationship between the serum drug-related indices (drug concentration and anti-antibody concentration) and secondary non-response in patients who are dependent on corticosteroid therapy or surgery, although few studies have specifically examined these indicators in all patients [42, 56]. According to the subgroup of follow-up time, compared with the end of the first year, the response rate and remission rate of the follow-up nodes in the second year tended to increase again in our meta-analysis. We speculate that this may be closely related to the attrition bias. Only a few studies were available for inclusion in some

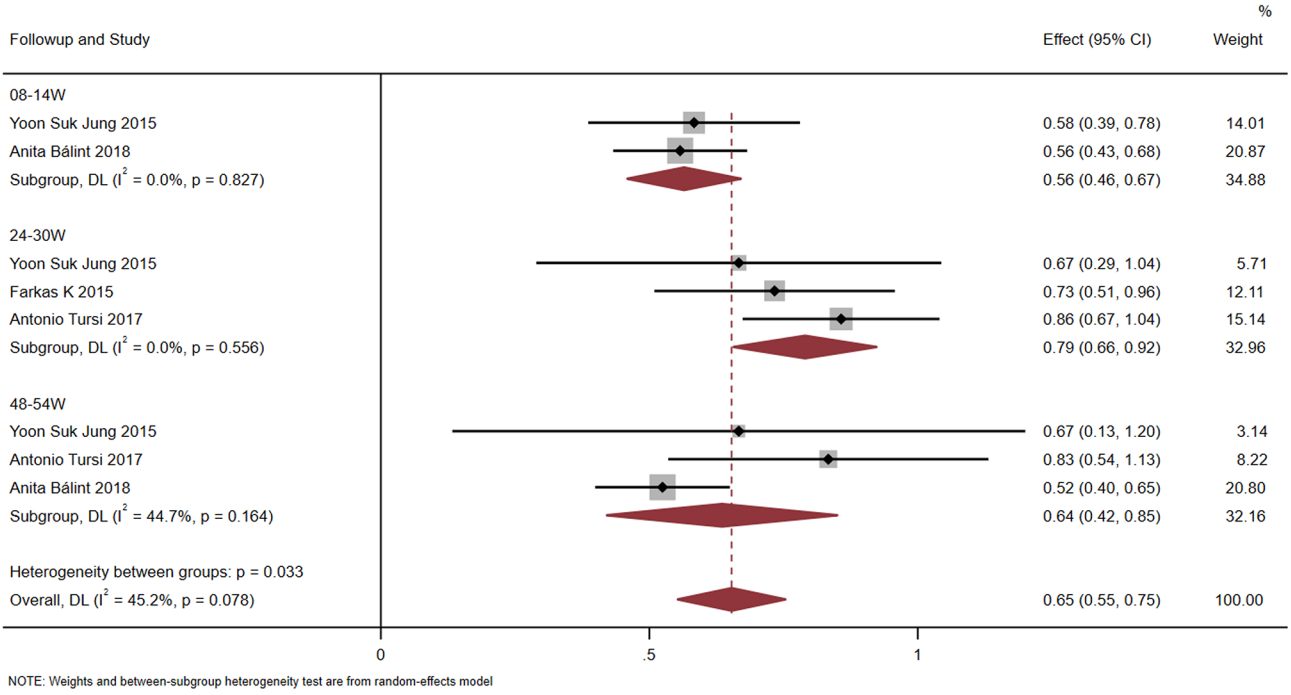

Fig. 4 Forest plot and pooled estimates of mucosal healing rates with ulcerative colitis. Subgroup analysis was performed by years of follow-up

subgroups in the subgroup analysis of our study; thus, the results of this meta-analysis may not accurately represent the general situation. There are similar results in the transitioned group.

The strengths of our review are as follows. We further analyzed the endoscopic mucosal healing rate (based on an endoscopic Mayo score of 1 or 0) in patients treated with CT-P13 for ulcerative colitis and found that it could be maintained at a relatively high level in the short and long term, which was not discussed in previous meta-analysis studies. Moreover, in this study, we attempted to update the research data accrued in recent years; thus, the high volume of studies and papers expanded the accuracy of the outcomes. Furthermore, we conducted a subgroup analysis depending on the span of follow-up, to explore and explain the origins of heterogeneity.

However, our research also has some limitations. First, the subgroups included in each stage of the study were different, and the definition of the endpoint index differed among various studies (the clinical remission of ulcerative colitis was defined as a partial Mayo score of ≤3 in two studies, and ≤2 in the remaining studies), which may be one of the reasons for bias, necessitating another meta-analysis. The evaluation criteria of treatment efficacy are constantly updated owing to the further exploration of IBD and improvement in knowledge in human healthcare. Second, in long-term studies (follow-up period of more than one year), the frequency of discontinuation increased, resulting in a greater risk of bias (attrition bias) in the study. However, we still included these studies in the analysis in order to explore the long-term effect. Moreover, some of the included studies did not have a proper control group, did not provide information on other medication, and unique basic characteristics (such as age, sex, weight, and smoking history), which are responsible for the heterogeneity of populations, and consequently, influence the outcomes. Furthermore, the study was not buttressed by RCT data (only three RCTs met the eligibility criteria), and few studies involved endoscopic evaluation of efficacy. Some differences existed in the baseline characteristics of the patient populations of various studies, including previous exposure to TNF-α antagonist drugs that may have affected the treatment response, which may also be the cause of heterogeneity in each study. During the study, we also observed the lack of meta-analysis of other objective markers of disease activity, such as fecal calprotectin, and C-reactive protein, this is similar to previously published articles. In the future research, we will continue to further study and analyze these objective indicators indicating the development of inflammation of IBD, and obtain more objective data and results for clinical therapy plan.

In addition, a randomized controlled study and some reviews have shown that the effect of subcutaneous injection of CT-P13 is similar to that of intravenous administration, which indicates the possibility of developing a reagent for subcutaneous injection in the future, reducing the length of stay and expense of patients [57–61]. Despite the intravenous injection methods used in all the

studies we included, we look forward to more studies in the future to confirm the safety and efficacy of subcutaneous injection.

In conclusion, this systematic review and meta-analysis showed that CT-P13, a biosimilar of infliximab, was effective in patients with IBD in some European, American, and Asian countries. Although further studies are warranted, our results support the application of CT-P13 in the treatment of IBD. Our research will have a significant effect on the commercial approval of CT-P13 in other regions and countries.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12876-024-03480-9.

Supplementary Material 1

Supplementary Material 2

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Author contributions
XL.Z and XY.H had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. XL.Z, XY.H, and XW.T: Concept and design. XL.Z , XY.H, XW.T, LM.L, L.L, XS.H, and Q.Y: Acquisition, analysis, or interpretation of data. XL.Z , XY.H, XW.T, LM.L, and L.L: Drafting of the manuscript. XL.Z , XY.H, XW.T, LM.L, and L.L, XS.H, and Q.Y: Critical revision of the manuscript for important intellectual content. XY.H, and XW.T: Statistical analysis. XL.Z, and XW.T: Supervision and administration.

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Data availability
The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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