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REVIEW

An updated systematic review and meta-analysis about the safety and efficacy of infliximab biosimilar, CT-P13, for patients with inflammatory bowel disease

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Abstract

Objective We aimed to evaluate the efficacy and safety of infliximab biosimilar, CT-P13, for patients with inflammatory bowel disease.

Methods We searched PubMed, Scopus, Ovid, and Web of Science for relevant clinical trials discussing CT-P31 administration for IBD patients either naïve to biological therapy or switched from IFX therapy. Data of the rates of clinical response, clinical remission, and adverse events were extracted and pooled in a random effect model meta-analysis using CMA version 2.

Results Thirty-two studies with a total of 3464 IBD patients treated with CT-P13 were identified. The pooled rates of clinical response among Crohn's disease (CD) and ulcerative colitis (UC) at 8–14 weeks were 0.81 (95% CI = 0.72 to 0.87) and 0.68 (95% CI = 0.63 to 0.72), respectively, and at 48–63 weeks were 0.69 (95% CI = 0.48 to 0.85) and 0.54 (95% CI = 0.45 to 0.63) respectively. After switching from IFX to CT-P13, the pooled rates of sustained clinical response among CD and UC at 30–32 weeks were 0.84 (95% CI = 0.57 to 0.96) and 0.96 (95% CI = 0.58 to 0.99), respectively, and at 48–63 weeks were 0.51 (95% CI = 0.22 to 0.79) and 0.83 (95% CI = 0.19 to 0.99) respectively. Moreover, adverse events were reported (CD = 0.10, 95% CI 0.04 to 0.22; UC = 0.18, 95% CI 0.05 to 0.15).

Conclusion CT-P13 is effective and well tolerated in short and long-term periods. Switching to CT-P13 is recommended for the management of IBD.

Keywords CT-P13 · Infliximab · IFX · Inflammatory bowel diseases · Meta-analysis · Systematic review

Introduction

Inflammatory bowel disease (IBD) is a chronic inflammatory disorder of the gastrointestinal tract including ulcerative colitis (UC) and Cohn's disease (CD) [1]. Physicians used biological treatment for the management of gastroenterological and rheumatologic immune-mediated inflammatory disorders such as IBD [2]. Infliximab (IFX), a monoclonal antibody inhibiting tumor necrosis factor α (TNF-α), was the first drug approved by the FDA [3]. IFX therapy is effective in patients with moderate to severe luminal and fistulizing CD, moderate-to-severe UC, and several extra-intestinal IBD complications in children and adults [4]. Biosimilars are highly similar to their originator biological drug or reference medicinal product (RMP). However, biosimilars are not the same as generic versions of small-molecule drugs. Biosimilars have relatively simple chemical structures and can thus be created to be similar to their originator drug while biological drugs are large,

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structurally complex proteins produced in living systems. Therefore, it is not possible for biosimilars to be identical to their RMP. Regulatory authorities require comprehensive and extensive comparability programs to approve biosimilars. This comparability assessment includes information on product quality, as well as non-clinical and clinical data. Biosimilars represent an opportunity to reduce health care costs while offering a similar level of efficacy and safety to that of their RMPs [5].

Biosimilars showed significant results in rheumatoid arthritis [6]. Cohen et al. compared the biosimilar with adalimumab in patients with rheumatoid arthritis; biosimilar had the same effect of adalimumab [7, 8]. Regarding ankylosing spondylitis, biosimilar seems to be an excellent alternative to other biochemical drugs [9], and biosimilars were useful in multiple sclerosis; however, it is still debatable [10].

However, biological treatment is expensive and not available to patients in low-income countries; biosimilars are not costly compared with IFX. Currently, the rising incidence of IBD combined with the increasing use of biological agents has resulted in a growing economic burden, especially in developing countries. Thus, biosimilar would be an excellent choice for IBD patients.

In 2017, a systematic review was published in the Journal of Alimentary Pharmacology and Therapeutics; they included 11 observational studies comprising 829 patients [11]. Recent randomized clinical trials documented that switching from IFX originator to CT-P13 had the same efficacy in maintaining clinical response and remission rates; thus, in our systematic review and meta-analysis, we aimed to provide an updated overview of the literature regarding the effectiveness and safety of CT-P13 in IBD patients with the inclusion of additional studies to assist with evidence-based clinical decision-making.

Methods

We reported this systematic review and meta-analysis based on the preferred reporting items for systematic review and meta-analysis (PRISMA) statement and performed all steps according to the Cochrane handbook [12, 13]. The review was registered in the PROSPERO 2018 (registration number: CRD42017065922).

Literature search strategy

We performed a comprehensive search of four electronic databases: PubMed, Scopus, Ovid, and Web of Science with the following search terms: "biosimilar", "anti-TNF-a", "Infliximab", "Adalimumab", "Etanercept", "Golimumab", "Certolizumab Pegol", "Inflammatory bowel disease", "Crohn's disease", and "Ulcerative colitis" through January 2019.

Study eligibility

Studies satisfying the following criteria were included in our review:

1. Population: studies whose population were adults' patients diagnosed with IBD and received CT-P13 either naïve to biological therapy or switched from IFX therapy.
2. Study design: we selected studies that were described as randomized controlled trials (RCTs), prospective studies, and retrospective studies.
3. Outcome: studies reporting at least one of the following outcomes: the clinical response rate, the clinical remission rate, or adverse events.

We excluded animal experiments and non-English studies.

Study selection and data extraction

We screened the titles and abstracts of retrieved records, followed by full-texts screening for eligibility. Any disagreements were resolved by discussion, and if all authors stated that a study did not meet the inclusion criteria, the study was excluded. We selected RCTs, prospective studies, and retrospective studies evaluating the efficacy and safety of CT-P13 in patients with IBD.

Assessment of risk of bias

The quality of the retrieved RCTs was assessed according to Cochrane handbook of systematic reviews of interventions 5.1.0 (updated March 2011). Risk of bias assessment included the following domains: sequence generation (selection bias), allocation sequence concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias), selective outcome reporting (reporting bias), and other potential sources of bias. The authors' judgments were categorized as "Low risk", "High risk", or "Unclear risk" of bias [14].

For the observational studies, we used the Newcastle-Ottawa Scale [15]. Star rating of 0–9 was allocated to each study based on three parameters (S, selection (0–4); C, comparability (0–2); O, outcome (0–3)). Good quality, 3 or 4 stars (★) in selection domain AND 1 or 2 stars in comparability domain AND 2 or 3 stars in outcome domain; Fair quality, 2 stars in selection domain AND 1 or 2 stars in comparability domain AND 2 or 3 stars in outcome/exposure domain; Poor quality, 0 or 1 star in selection domain OR 0 stars in comparability domain OR 0 or 1 stars in outcome/exposure domain. Studies receiving six or more stars were considered of good quality [16, 17].

Data extraction

We independently extracted the data from each included study using a pre-specified uniform data extraction sheet. Extracted data included the following domains: study ID, population, intervention, comparator, outcomes, study design, and baseline characteristics of the study population, quality assessment domains, and effect estimates of the study outcomes.

Outcome measurement

The primary outcomes were the following: the rates of clinical response, clinical remission, and adverse events among IBD patients treated with CT-P13. The secondary outcome was mucosal healing in naïve UC patients.

Remission rate was defined as the percentage of patients who experienced symptoms reduction and revealed while response rate was defined as the percentage of patients who healed and are free from the disease symptoms in patients diagnosed with IBD and received CT-P13 either naïve to biological therapy or switched from IFX therapy [18].

Statistical analysis

We independently analyzed for CD and UC. Statistical analysis was performed using comprehensive meta-analysis V2 (CMA), and a random-effect model was used. A quantitative measure of heterogeneity across studies was also calculated using the I^2 statistic where studies with I^2 values of less than 25% were considered as having a low level of statistical heterogeneity, 25–75% were considered as having a moderate level of statistical heterogeneity, and > 75% were considered high heterogeneity. Moreover, a p value of less than 0.1 was used as evidence of statistically significant heterogeneity [19]. For dichotomous data, event rate and 95% confidence interval (CI) were calculated.

Results

Literature search results

We initially identified a total of 3100 non-duplicate studies by the electronic literature search. Following title and abstract screening, 49 articles were eligible for full-text screening and were examined in detail. Finally, 32 studies were included in the quantitative synthesis. The flow diagram of the literature search and study selection is shown in Fig. 1.

Characteristics of the included studies' population

A total of 3464 patients were included in our systematic review. The patients were treated with CT-P13. The summary of the baseline characteristics of the observational studies of a biosimilar of IFX and the observational studies switching from IFX to CT-P13 in IBD patients is shown in Tables 1 and 2.

Assessment of study validity

The quality of the two retrieved RCTs was relatively low, and all domains were of a low or unclear risk of bias (Appendix S1b). For the observational studies, we used the Newcastle-Ottawa Scale, and the included studies were of a good quality of methodology. The star rating score is shown in Table 1 and Table 2.

Selection

We observed that all included studies demonstrated the way of selection of the research question, and objective in the study was clearly stated. The study population was specified and defined, and all non-exposed groups were selected from the same source population as the exposed group in all studies except Jensen et al. [4].

Comparability and follow up of participants

Regarding comparability, all included studies were comparable, based on the study design and analysis. Confounding factors are controlled and the subjects selected from the same populations, including the same period and the study controls for the most critical factor. Rates of loss-to-follow-up ranged from 3% to 15%, suggesting a low overall potential for attrition bias and all included studies revealed it.

Exposure measurement and outcomes

The assessment of the outcome and outcome measures (dependent variables) were clearly defined, valid, reliable, and implemented consistently across all study participants except four studies [4, 20, 21, 24]. Moreover, all included studies had a follow-up period long enough for outcome assessment.

Measures of treatment effect

In naïve patients, the respective included studies analyzed the rates of clinical response and clinical remission at short term (8–14 weeks), medium term (24–30 weeks), and long term (48–63 weeks). Moreover, in patients who were switched from IFX, the respective included studies analyzed the sustained clinical response rate at medium term (30–32 weeks) and long term (48–63 weeks) and the sustained clinical remission rate at short term (6–16 weeks), medium term (24–32 weeks), and long term (48–63 weeks). The rates of the adverse effects in naïve and switched patients were analyzed

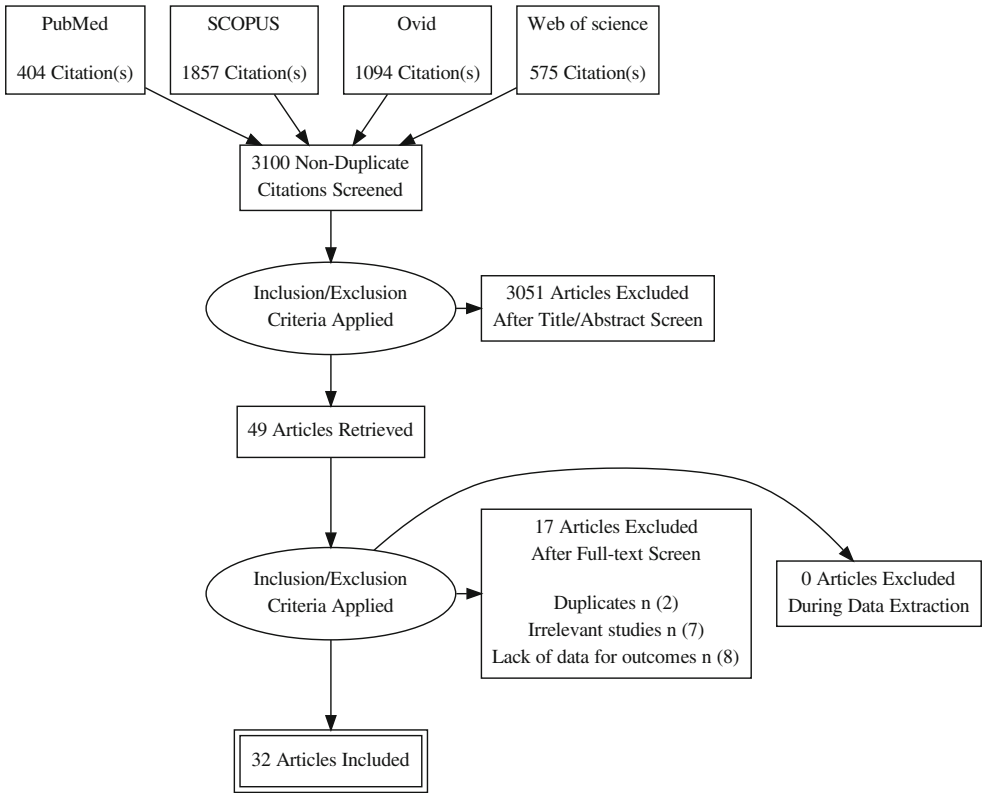


Fig. 1 The flow diagram of articles selection process

separately in the form of infection, infusion reaction, latent TB, and overall adverse events.

Efficacy outcomes among CD patients

The clinical response and clinical remission rates among CD patients

CT-P13 was associated with high clinical response rates at 8–14 weeks (0.81, 95% CI [0.72 to 0.87]), 24–30 weeks (0.78, 95% CI [0.64 to 0.87]), and 48–63 weeks (0.69, 95% CI [0.48 to 0.85]) (Fig. 2a). The pooled effect estimates were heterogeneous at 08–14 weeks and 48–63 weeks (I^2 = 78%, P = 0.0001) and (I^2 = 88.2%, P = 0.0001) respectively.

On the other hand, the pooled rates for clinical remission at 6–16 weeks, 24–30 weeks, and 48–63 weeks were 0.61 (95% CI [0.52–0.68]), 0.57 (95% CI [0.48–0.65]), and 0.55 (95% CI [0.41–0.68]), respectively (Fig. 3a).

The sustained clinical response and remission rates among CD patients switching from IFX to CT-P13

CT-P13 showed high rate of sustained clinical response at 30–32 weeks (0.84, 95% CI [0.57 to 0.96]) and 48–63 weeks (0.51, 95% CI [0.22–0.79]) (Fig. 4a). The pooled effect estimates were heterogeneous at 48–63 weeks (I^2 = 76.4%, P = 0.014).

Furthermore, the pooled rates for sustained clinical remission at the time of switching were (0.78, 95% CI [0.69 to 0.85]). At 6–16 weeks, 24–32 weeks, and 48–52 weeks, the pooled rates were 0.65 (95% CI [0.47 to 0.79]), 0.68 (95% CI [0.52 to 0.81]), and 0.71 (95% CI [0.57 to 0.81]) respectively (Fig. 5a). The pooled effect estimates were heterogeneous at 06–16 weeks, 24–32 weeks, and 48–52 weeks (I^2 = 74.7%, P = 0.008), (I^2 = 80%, P = 0.001), and (I^2 = 84.8%, P = 0.0001).

Efficacy outcomes among UC patients

The clinical response and clinical remission rates among UC patients

The pooled rates for clinical response at 8–14 weeks (0.68, 95% CI [0.63 to 0.72]), 24–30 weeks (0.69, 95% CI [0.63 to 0.75]), and 48–63 weeks (0.54, 95% CI [0.45 to 0.63]); however, the analysis of 48–63 weeks included only two studies (Fig. 2b).

The pooled clinical remission rates at 8–14 weeks, 24–30 weeks, and 48–63 weeks were 0.48 (95% CI [0.43 to 0.56]), 0.49 (95% CI [0.41 to 0.58]), and 0.47 (95% CI [0.36 to 0.59]) respectively; however, the analysis of 48–63 weeks included only two studies (Fig. 3b). Low to moderate heterogeneity was observed at 08–14 weeks, 24–30 weeks, and 48–63 weeks.

Table 1 The characteristics of the observational studies of a biosimilar of anti-tumor necrosis factor-a agents (infliximab) in IBD

Diseases	Study, year (reference)	Study design	Name of biosimilar	Numbers of biosimilar Patients (enrolled numbers) (*n*)	Age at study (year)	Dosage and schedule of biosimilar	Concomitant medications	Patient numbers of previous anti-TNF-a agents	Term of study (week)	Newcastle–Ottawascale (NOS)
CD	Jahnsen et al. 2015 [4]	Prospective clinical study	CT-P13	46	39	5 mg/kg on 0, 2, 6, 14 weeks	Steroid 56%, AZA 56%	28% IFX 22%, ADA 9%	14	4 (S: 1, C: 2, 0: 1)
	Jung et al. 2015 [5]	Retrospective clinical study	CT-P13	32	NA	5 mg/kg on 0, 2, 6 weeks then every 8 weeks	5ASA 88%, steroids 14%, AZA61%	0	54	6 (S: 3. C: 2, O: 1)
	Park et al.2015 "luminal CD." [20]	Retrospective clinical study	CT-P13	43	31.8	5 mg/kg 53.5%,5–7 mg/kg 37.2%, 7–10 mg/kg 2.2%, 10 mg/kg 7%	5ASA 6%, steroid 14%, AZA 61%	0	30	3 (S: 2, C: 2, O: 2)
	Park et al. 2015 "fistulizing CD." [20]	Retrospective clinical study	CT-P13	8	27.9	5 mg/kg 87.5%, 5–7 mg/kg 12.5%	AZA 60%	0	30	3 (S: 2, C: 0, O: 2)
	Sieczkowska et al. 2015 [34]	Prospective clinical study	CT-P13	12	15.1	5 mg/kg on weeks 0, 2, 6	NA	0.42	10	6 (S: 2, C: 2, O: 2)
	Gecse et al. 2016 [35]	Prospective clinical study	CT-P13	126	NA	5 mg/kg on 0, 2,6,14 weeks then every 8 weeks	5 ASA 69%, steroid 48%, AZA 62.5%	26% (IFX 22%, ADA 4%)	54	6 (S: 2, C: 2, O: 2)
	Keil et al. 2016 [1]	Prospective clinical study	CT-P13	30	37.9	5 mg/kg on 0, 2, 6, 14 weeks	5 ASA, steroid, AZA	NA	14	6 (S: 2, C: 2, O: 2)
	Hlavaty et al. 2016 [36]	Retrospective clinical study	CT-P13	9	33.9	5 mg/kg on weeks 0, 2, 6	Steroid 33%, AZA 67%	at least 56% (IFX 33%, ADA56%)	30	6 (S: 2, C: 2, O: 2)
	Farkas et al. 2015 [37]	Prospective clinical study	CT-P13	18	26.9	5 mg/kg on 0, 2, 6 weeks then every 8 weeks	5 ASA, steroid	NA	24	6 (S: 2, C: 2, O: 2)
	Sieczkowska-golub et al. 2017 [38]	Prospective clinical study	CT-P13	27	11.79	5 mg/kg on 0, 2, 6, 14 weeks	5-ASA (81%), AZA (69%) MET (6%) steroid (19%)	47% (IFX 25%, ADA 23%)	14	6 (S: 2, C: 2, O: 2)
	Argellesarias et al. 2017 [3]	Prospective clinical study	CT-P13	13	41.2	NA	Steroid 100%	NA	24	6 (S: 2, C: 2, O: 2)
	Kang et al. 2015 [39]	Case series study	CT-P13	8	35.4	5 mg/kg on 0, 2, 6 weeks then every 8 weeks	Steroid 100%	NA	8	6 (S: 2, C: 2, O: 2)
	Kolar et al. 2016 [21]	Retrospective clinical study	CT-P13	90	35.4	NA	Thiopurines/methotrexate (74.3%), corticosteroids (1.4%)	NA	56	6 (S: 2, C: 2, O: 2)
	Gonczi et al. 2017 [40]	Prospective clinical study	CT-P13	209	24	5 mg/kg at 0, 2, 6, every 8 weeks	Steroid 42.6%, AZA 60.3%	IFX (38), ADA (9)	54	6 (S: 2, C: 2, O: 2)
	Hamanaka et al. 2016 [41]	Single cohort study	CT-P13	10	42.85	NA	Steroid and bio-naïve	NA	22	6 (S: 2, C: 2, O: 2)
	Yoon Suk et al. 2016 [42]	Retrospective multicenter study	CT-P13	23	NA	NA	Anti-TNF	23	8	6 (S: 2, C: 2, O: 2)
	Keil et al. 2016 [1]		CT-P13	30	38	5 mg/kg CT-P13	Corticosteroid and antibiotic and	30	14	6 (S: 2, C: 2, O: 2)

Table 1 (continued)

Diseases	Study, year (reference)	Study design	Name of biosimilar	Numbers of biosimilar Patients (enrolled numbers) (*n*)	Age at study (year)	Dosage and schedule of biosimilar	Concomitant medications	Patient numbers of previous anti-TNF-a agents	Term of study (week)	Newcastle–Ottawascale (NOS)
		Retrospective observational study					immunosuppressive therapy			
	Gheorghe et al. 2018 [43]	Non-interventional study	CT-P13	31	41	NA	Corticosteroid and immunosuppressive therapy	31	30	4 (S: 2, C: 0, O: 2)
	Ye et al. 2018 [44]	RCT	CT-P13	220	NA	NA	NA	NA	54	Low risk of bias
UC	Jahnsen et al. 2015 [4]	Prospective clinical study	CT-P13	32	40	5 mg/kg on 0, 2, 6, 14 weeks	Steroid 56%, AZA 56%	0.16	14	4 (S: 1, C: 2, O: 1)
	Jung et al. 2015 [5]	Retrospective clinical study	CT-P13	42	NA	5 mg/kg	5ASA 88%, steroids 52%, AZA55%	0	54	6 (S: 2, C: 2, O: 2)
	Park et al. 2015 [20]	Retrospective clinical study	CT-P13	62	45.2	53.5% (5 mg/kg), 37.2% (5–7 mg/kg), 2.2% (7–10 mg/kg), 7% (10 mg/kg)	5ASA 79%, steroid 55%, AZA 60%	0	30	5 (S: 2, C: 2, O: 1)
	Gecse et al. 2016 [35]	Retrospective clinical study	CT-P13	84	NA	5 mg/kg on 0, 2, 6, 14 weeks then every 8 weeks	5 ASA 81%, steroid 64%, AZA 57%	17% (IFX 11%, ADA 6%)	0.54	6 (S: 2, C: 2, O: 2)
	Keil et al. 2016 [1]	Prospective clinical study	CT-P13	22		5 mg/kg on 0, 2,6,14 weeks	5 ASA 77%, steroid 27%, AZA 56%	0	14	6 (S: 2, C: 2, O: 2)
	Hlavaty et al. 2016 [36]	Retrospective clinical study	CT-P13	4	40.3	5 mg/kg on 0, 2, 6 weeks	Steroid 100%, AZA 25%	25% (ADA 25%)	30	6 (S: 2, C: 2, O: 2)
	Farkas et al. 2015 [45]	Prospective clinical study	CT-P13	21	31.1	5 mg/kg on 0, 2, 6 weeks	5 ASA, steroid	NA	24	6 (S: 2, C: 2, O: 2)
	Argellesarias et al. 2017 [3]	Prospective clinical study	CT-P13	9	43.6	NA	Steroid 100%	NA	24	6 (S: 2, C: 2, O: 2)
	Kang et al. 2015 [39]	Case series study	CT-P13	9	35.4	5 mg/kg on 0, 2, 6 weeks	NA	NA	8	6 (S: 2, C: 2, O: 2)
	Kolar et al. 2016 (12)	Retrospective clinical study	CT-P13	29	35.4	NA	Thiopurines/methotrexate (74.3%), Corticosteroids (1.4%)	NA	56	6 (S: 2, C: 2, O: 2)
	Gonczi et al. 2017 [40]	Prospective clinical study	CT-P13	144	28	5 mg/kg on 0, 2, 6, 14 weeks then every 8 weeks	Steroid 64.6%, AZA 51.4%	IFX 18, ADA 9	54	6 (S: 2, C: 2, O: 2)
	Hamanaka et al. 2016 [41]	Single cohort study	CT-P13	6	42.85	NA	Steroid and bio-naïve	NA	22	6 (S: 2, C: 2, O: 2)
	Yoon Suk et al. 2016 [42]	Retrospective multicenter study	CT-P13	41	NA	NA	Anti-TNF	41	8	6 (S: 2, C: 2, O: 2)
	Keil et al. 2016 [1]		CT-P13	22	38	5 mg/kg CT-P13	Corticosteroid, antibiotic, and	22	14	6 (S: 2, C: 2, O: 2)

Table 1 (continued)

Diseases	Study, year (reference)	Study design	Name of biosimilar	Numbers of biosimilar Patients (enrolled numbers) (*n*)	Age at study (year)	Dosage and schedule of biosimilar	Concomitant medications	Patient numbers of previous anti-TNF-a agents	Term of study (week)	Newcastle–Ottawascale (NOS)
		Retrospective observational study					Immunosuppressive therapy			
	Bálint et al. 2018 [46]	Multicenter observational cohort	CT-P13	61	35	5 mg/kg	Steroid and azathioprine therapy	61	54	6 (S: 2, C: 2, O: 2)
	Gheorghe et al. 2018 [43]	Non-interventional study	CT-P13	36	41	N.A.	Corticosteroid and immunosuppressive therapy	36	30	6 (S: 2, C: 2, O: 2)

Categorical variables are summarized as frequencies (*n*)

IBD Inflammatory bowel disease, *CD* Crohn's disease, *UC* ulcerative colitis, *5ASA* 5-Aminosalicylic acid, *AZA* azathioprine, *IFX* infliximab, *ADA* adalimumab, *IM* immunomodulators, *N.A.* not available

NOS, total score (selection, S (0–4); comparability, C (0–2); outcome, O (0–3)

The sustained clinical response and remission rates among UC patients switching from IFX to CT-P13

CT-P13 was linked with high clinical response rates at 30–32 weeks (0.96, 95% CI [0.58 to 0.99]) and 48–63 weeks (0.83, 95% CI [0.19 to 0.99]). However, the analysis of 30–32 weeks and 48–63 weeks included only one study (Fig. 4b).

The pooled rates for clinical remission at the time of switching were (0.77, 95% CI [0.71to 0.83]). At 8–16 weeks, 24–32 weeks, and 48–63 weeks, the pooled rates were 0.62 (95% CI [0.47 to 0.75]), 0.84 (95% CI [0.72 to 0.92]), and 0.77 (95% CI [0.69 to 0.84]) respectively. However, the analysis of 24–32 weeks included only two studies (Fig. 5b).

Safety outcomes among CD patients

Regarding naïve CD patients, the pooled rates of infection, infusion reaction, latent TB, and over all adverse events were 0.08 (95% CI [0.03 to 0.23]), 0.11 (95% CI [0.05 to 0.23]), 0.02 (95% CI [0.01 to 0.07]), and 0.1 (95% CI [0.04 to 0.22]) respectively (Fig. 6a). While for switched CD patients, the pooled rates were 0.08 (95% CI [0.04 to 0.18]), 0.04 (95% CI [0.02 to 0.09]), 0.03 (95% CI [0.01 to 0.12]), and 0.14 (95% CI [0.09 to 0.23]) respectively (Fig. 7a).

Safety outcomes among UC patients

In naïve UC patients, the pooled rates of infection, infusion reaction, latent TB, and over all adverse events were 0.03 (95% CI [0.01 to 0. 08]), 0.05 (95% CI [0.03 to 0.09]), 0.02 (95% CI [0.01 to 0.05]), and 0.09 (95% CI [0.05 to 0.15]) respectively (Fig. 6b). On the other hand, the pooled rates among switched UC patients, were 0.06 (95% CI [0.02 to 0.15]), 0.09 (95% CI [0.05 to 0.15]), 0.05 (95% CI [0.01 to 0.19]), and 0.18 (95% CI [0.13 to 0.24]) respectively (Fig. 7b).

Mucosal healing in naïve UC patients

Six studies reported data on mucosal healing among naïve UC patients, the pooled rates at 08–14 weeks, 30 weeks, and 54 weeks were (0.60, 95% CI [0.53 to 0.67]), (0.68, 95% CI [0.45 to 0.85]), and (0.63, 95% CI [0.50 to 0.73]) respectively (Appendix S1a).

Discussion

Infliximab (IFX), a monoclonal antibody inhibiting tumor necrosis factor α (TNF-α), was approved by the FDA, and it is effective in patients with moderate to severe luminal and fistulizing CD, moderate-to-severe UC, and

Table 2 The characteristics of the observational studies switching from infliximab to biosimilar

Diseases	Study, year (reference)	Study design	Name of biosimilar	Dosage and schedule of biosimilar	Concomitant medication	Median term of infliximab before switching (week)	Average term of study after switching to a biosimilar (week)	Disease activity at the period of switching	Numbers of biosimilar patients (enrolled numbers) (*n*)	Age at study (year)	Newcastle–Ottawa scale (NOS)
CD	Kang et al. 2015 [39]	Retrospective clinical study	CT-P13	5 mg/kg every 8 weeks	5ASA 80%, steroids80%, IM 80%	N.A.	59	Remission period	5	27	7 (S: 2, C: 2, O: 3)
	Park et al. 2015 "Luminal CD." [20]	Retrospective clinical study	CT-P13	5 mg/kg 57.5%, 5–7 mg/kg25%, 7–10 mg/kg 5%,10 mg/kg 12.5%	Steroids 30%, AZA 45%	N.A.	30	Being well duringmaintena-nce treatment	40	31	5 (S: 2, C: 2, O: 1)
	Park et al. 2015 "Fistulizing CD." [20]	Retrospective clinical study	CT-P13	5 mg/kg 87.5%,5-– 7 mg/kg 12.5%.	AZA 50%	N.A.	30	Being well duringmaintena-nce treatment	4	33	5 (S: 2, C: 2, O: 1)
	Hlavaty et al. 2016 [36]	Retrospective clinical study	CT-P13	5 mg/kg every 8 weeks(every 4 weeks if any LOR)	AZA 50%	22	44	N.A.	10	36	6 (S: 2, C: 2, O: 2)
	Kolar et al. 2016 (12)	Prospective clinical study	CT-P13	NA	AZA 46%	156	24	69% patients in clinicalremission, 22% with mild tomoderate active disease,5% with active disease	56	N.A.	5 (S: 2, C: 2, O: 1)
	Sieczkowska et al. 2016 [34]	Prospective clinical study	CT-P13	N.A. (30/32 were givenevery 8 weeks till16 weeks)	5ASA 3%, 5ASA+AZA34%, AZA 25%,MTX 3%,5ASA + MTX 25%	10	32	69% clinicalremissio-n), 31% (active disease)	32	N.A.	6 (S: 2, C: 2, O: 2)
	Smits et al. 2016 [22]	Prospective clinical study	CT-P13	N.A. (dosing and intervalremain-ed unchangedunle-ss need of adjustment)	5ASA 4%, steroids7%, thiopurines60%, MTX12%	21	16	Median HBI 3.0	57	36	6 (S: 2, C: 2, O: 2)
	Sieczkowskagolub et al. 2017 [38]	Prospective clinical study	CTP-13	5 mg/kg on 0, 2, 6 weeks	5-ASA (81%) immunomodulator (75%) AZA (69%) MET (6%) steroid (19%)	9	12	NA	9	11.79	6 (S: 2, C: 2, O: 2)
	Argellesarias et al. 2017 [3]	Prospective clinical study	CTP-13	5 mg/kg	All patient received intravenous corticosteroids and antihistamines	67	42	Remission	67	41.2	6 (S: 2, C: 2, O: 2)
	Argüelles-arias et al. 2017 [47]	Prospective clinical study	CTP-13	5 mg/kg	Corticosteroids and antihistamines	67	42	83% were in remission	67	42	6 (S: 2, C: 2, O: 2)

Table 2 (continued)

Diseases	Study, year (reference)	Study design	Name of biosimilar	Dosage and schedule of biosimilar	Concomitant medication	Median term of infliximab before switching (week)	Average term of study after switching to a biosimilar (week)	Disease activity at the period of switching	Numbers of biosimilar patients (enrolled numbers) (*n*)	Age at study (year)	Newcastle–Ottawa scale (NOS)
	Bergqvist et al. 2018 [48]	Prospective clinical study	CTP-13	5 mg /kg	5-Aminosalicylates, thiopurines, methotrexate, corticosteroids	195	37	Remission	195	37	6 (S: 2, C: 2, O: 2)
	Bhandare et al. 2018 [49]	Retrospective clinical study	CTP-13	NA	Azathioprine/6-mercaptopurine and methotrexate (50%)	52	34.7	Remission	52	34.7	6 (S: 2, C: 2, O: 2)
	Plevris et al. 2018 [50]	Prospective clinical study	CTP-13	5 mg/kg on 6, 12 weeks	NA	110	33	Remission	110	33	6 (S: 2, C: 2, O: 2)
	Veloz et al. 2019 [51]	Prospective clinical study	CTP-13	5 mg/kg	Thiopurines, methotrexate	67	41	Remission	67	41	6 (S: 2, C: 2, O: 2)
	Veloz et al. 2018 [23]	Prospective clinical study	CTP-13	5 mg/kg	thiopurine	116	40.5	Remission	116	40.5	6 (S: 2, C: 2, O: 2)
	Ratnakumaran et al. 2018 [24]	Prospective clinical study	CTP-13	NA		173	42.7	Remission	173	42.7	5 (S: 1, C: 2, O: 2)
	Jahnsen et al. 2015 (1)	Prospective clinical study	CTP-13	5 mg/kg on 6, 12 weeks	Azathioprine/6-mercaptopurine (54.45%), steroids (10.9%), methotrexate (13%)	13	39	Remission	13	39	6 (S: 2, C: 2, O: 2)
	Jarzębicka et al. 2015 [52]	Prospective clinical study	CTP-13	5 mg/kg	5-ASA, 1; AZA, 8; AZA and 5-ASA, 11; MTX,	32	11.1	Remission	32	11.1	6 (S: 2, C: 2, O: 2)
	Jung et al. 2015 (2)	Retrospective clinical study	CTP-13	5 mg/kg	1; MTX and 5-ASA, 8	27	29.5	Remission	27	29.5	6 (S: 2, C: 2, O: 2)
	Buer et al. 2016 [53]	Prospective clinical study	CTP-13	4–6 mg/kg at m week interval	5-Aminosalicylates (90.6%), corticosteroid (12.5%),azathioprine (62.5%)	99	36	Remission	55	35.4	6 (S: 2, C: 2, O: 2)
	Yoon Suk et al. 2018 [42]	Retrospective clinical study	CTP-13	5 mg/kg	Anti-TNF	NA	8	Remission 86%	55	NA	6 (S: 2, C: 2, O: 2)
	Jørgensen et al. 2017 [54]	Randomized, non-inferiority, double-blind, phase 4 trial	CTP-13	5 mg/kg	Anti-TNF	NA	52	Remission	37	47.6	Low risk of bias
	Hernández et al. 2017 [55]	Observational and Retrospective clinical study stud	CTP-13	5 mg/kg	Steroids	NA	NA	Remission 80%	58	46	7 (S: 2, C: 2, O: 3)
	Strik et al. 2017 [56]	Prospective clinical study, open-label, interventional, noninferiority,	CTP-13	5 mg/kg	NA	NA	NA	Remission	44	42	Low risk of bias

Table 2 (continued)

Diseases	Study, year (reference)	Study design	Name of biosimilar	Dosage and schedule of biosimilar	Concomitant medication	Median term of infliximab before switching (week)	Average term of study after switching to a biosimilar (week)	Disease activity at the period of switching	Numbers of biosimilar patients (enrolled numbers) (*n*)	Age at study (year)	Newcastle–Ottawa scale (NOS)
		multicenter, phase IV trial									
UC	Kang et al. 2015 [39]	Retrospective clinical study	CT-P13	5 mg/kg	5ASA 50%, steroids100%	N.A.	36	Remission period	4	38	7 (S: 2, C: 2, O: 3)
	Park et al. 2015 [20]	Retrospective clinical study	CT-P13	5 mg/kg 61.3%, 5–7 mg/-kg35.5% 7–10 mg/kg 2.2%	5ASA 79%, steroids55%, AZA 60%	N.A.	30	Being well duringmaintena-nce treatment	16	43	5 (S: 1, C: 2, O: 2)
	Hlavaty et al. 2016 [36]	Retrospective clinical study	CT-P13	5 mg/kg every 8 weeks(every 4 weeks if any LOR)	AZA 50%	37	44	NA	2	27	6 (S: 2, C: 2, O: 2)
	Kolar et al. 2016 (12)	Prospective clinical study	CT-P13	5 mg/kg	AZA 46%	156	24	69% (clinicalremissio-n), 22% (mild to moderateactive disease),5% (active disease)	18	N.A.	5 (S: 1, C: 2, O: 2)
	Sieczkowska et al. 2016 (4)	Prospective clinical study	CT-P13	5 mg/kg	5ASA 43%, AZA 14%,5ASA+ AZA 43%	5	20	Patients switched afterinduction with infliximab,two patients switchedduring induction.	7	N.A.	6 (S: 2, C: 2, O: 2)
	Smits et al. 2016 [22]	Prospective clinical study	CT-P13	N.A. (dosing and intervalremain-ed unchangedunle-ss need of adjustment)	5ASA 65%, steroids15%, thiopurines 54%	26	16 (+2)	Median SCCAI 1.5	26	41	6 (S: 2, C: 2, O: 2)
	Argellesariaset al. 2017 [3]	Prospective clinical study	CTP-13	NA	All patient received intravenous corticosteroids and antihistamines	31	43.6	Remission	31	43.6	6 (S: 2, C: 2, O: 2)
	Argüelles-arias et al. 2017 [23]	Prospective clinical study	CTP-13	5 mg/kg	Corticosteroids and antihistamines	31	43	Remission			6 (S: 2, C: 2, O: 2)
		Prospective clinical study	CTP-13	5 mg/kg	5-Aminosalicylates, thiopurines, methotrexate, corticosteroids	118	38	Remission	118	38	6 (S: 2, C: 2, O: 2)

Table 2 (continued)

Diseases	Study, year (reference)	Study design	Name of biosimilar	Dosage and schedule of biosimilar	Concomitant medication	Median term of infliximab before switching (week)	Average term of study after switching to a biosimilar (week)	Disease activity at the period of switching	Numbers of biosimilar patients (enrolled numbers) (*n*)	Age at study (year)	Newcastle–Ottawa scale (NOS)
	Bergqvist et al. 2018 [48]										
	Bhandare et al. 2018 [49]	Retrospective clinical study	CTP-13	5 mg/kg	Azathioprine/6-Mercaptopurine and Methotrexate	44	34.7	Remission	31	37	6 (S: 2, C: 2, O: 2)
	Veloz et al. 2019 [51]	Prospective clinical study	CTP-13	NA	Thiopurines, methotrexate	31	37	Remission	51	46	6 (S: 2, C: 2, O: 2)
	Veloz et al. 2018 [23]	Prospective clinical study	CTP-13	5 mg/kg	Thiopurine	51	46	Remission	14	42.7	6 (S: 2, C: 2, O: 2)
	Ratnakumaran et al. 2018 [24]	Prospective clinical study	CTP-13	NA	NA	14	42.7	Remission	4	40	5 (S: 1, C: 2, O: 2)
	Jahnsen et al. 2015 (1)	Prospective clinical study	CTP-13	5 mg/kg on 6, 12 weeks	Azathioprine/6-mercaptopurine (54.45%), steroids (10.9%), methotrexate (13%)	4	40	Remission	7	12.3	6 (S: 2, C: 2, O: 2)
	Jarzębicka et al. 2015 [52]	Prospective clinical study	CTP-13	5 mg/kg	5-ASA, 3; AZA, 1; AZA and 5-ASA	7	12.3	Remission	9	34	6 (S: 2, C: 2, O: 2)
	Jung et al. 2015 (2)	Retrospective clinical study	CTP-13	5 mg/kg	5-Aminosalicylates (90.6%), corticosteroid (12.5%),	9	34	Remission	4	35.4	6 (S: 2, C: 2, O: 2)
	Buer et al. 2016 [53]	Prospective clinical study	CTP-13	NA	Azathioprine (62.5%)	44	35	Remission	2	11.6	6 (S: 2, C: 2, O: 2)
	Yoon Suk et al. 2018 [42]	Retrospective clinical study	CTP-13	5 mg/kg	anti-TNF	NA	8	Remission 67%	51	NA	6 (S: 2, C: 2, O: 2)
	Jørgensen et al. 2017 [54]	Randomized, non-inferiority, double-blind, phase 4 trial	CTP-13	5 mg/kg	anti-TNF	NA	52	Remission	7	47.6	Low risk of bias
	Hernández et al. 2017 [55]	Observational and Retrospective clinical study stud	CTP-13	5 mg/kg	Steroids	NA	NA	Remission 80%	72	46	7 (S: 2, C: 2, O: 3)

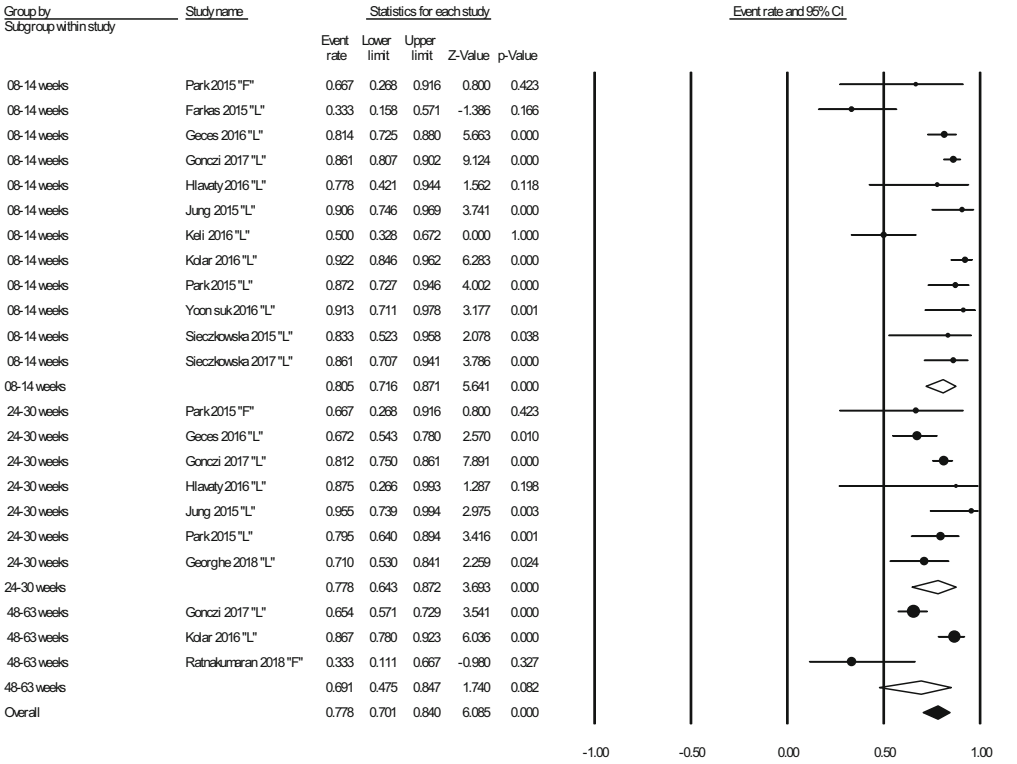
Categorical variables are summarized as frequencies (*n*)

CD Crohn's disease, *UC* ulcerative colitis, *5ASA* 5-Aminosalicylic acid, *AZA* azathioprine, *IFX* infliximab, *ADA* adalimumab, *IM* immunomodulators, *N.A.* not available

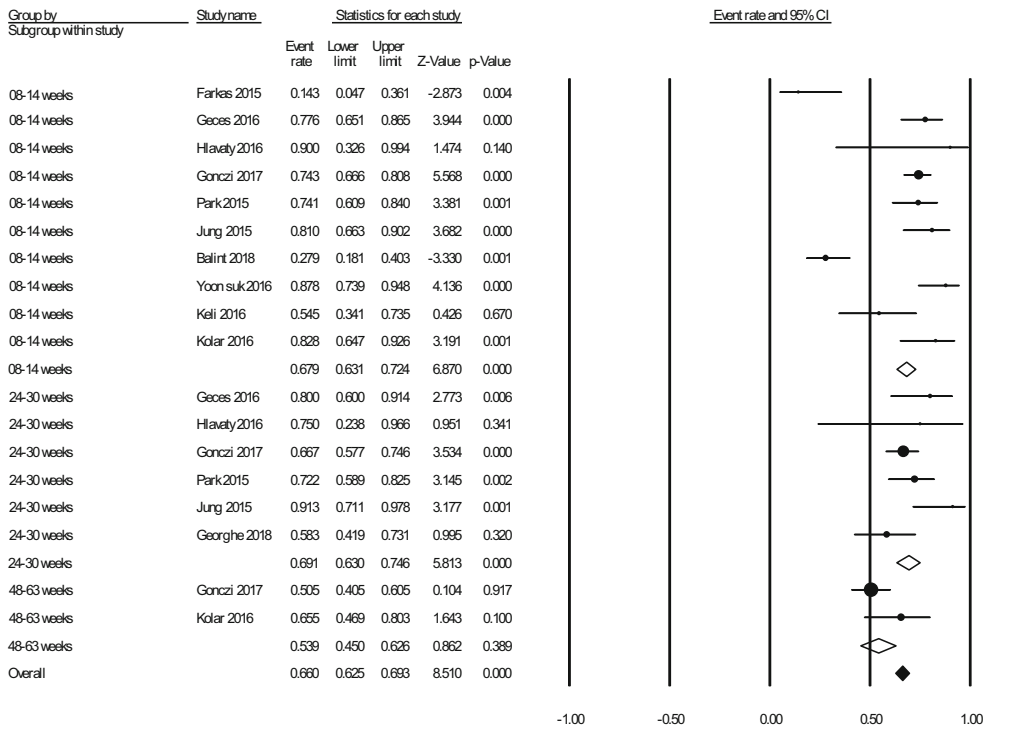
NOS, total score (selection, S (0–4); comparability, C (0–2); outcome, O (0–3)

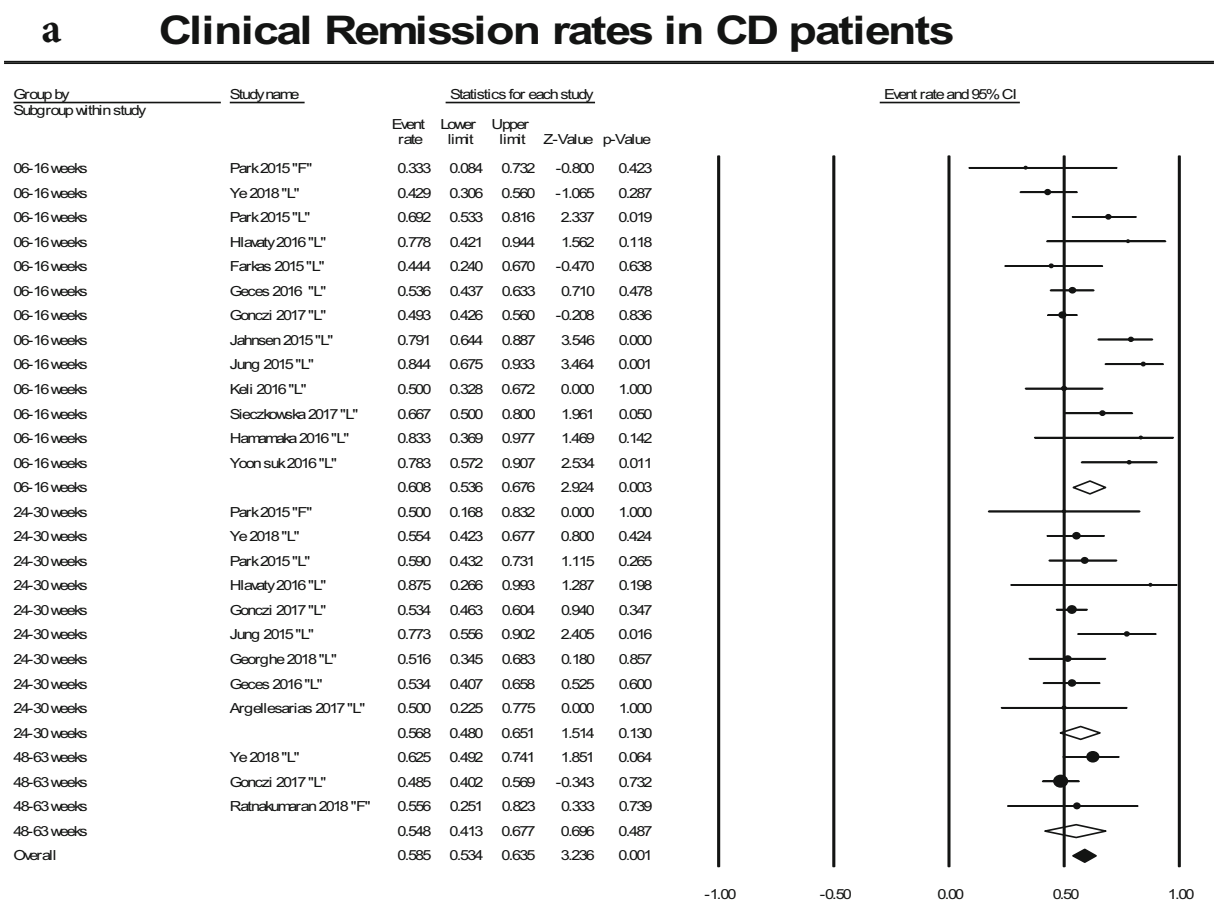
Fig. 2 **a** Forest plot of the clinical response rates in CD patients, **b** forest plot of the clinical response rates in UC patients

a Clinical Response rates in CD patients



b Clinical Response rates in UC patients





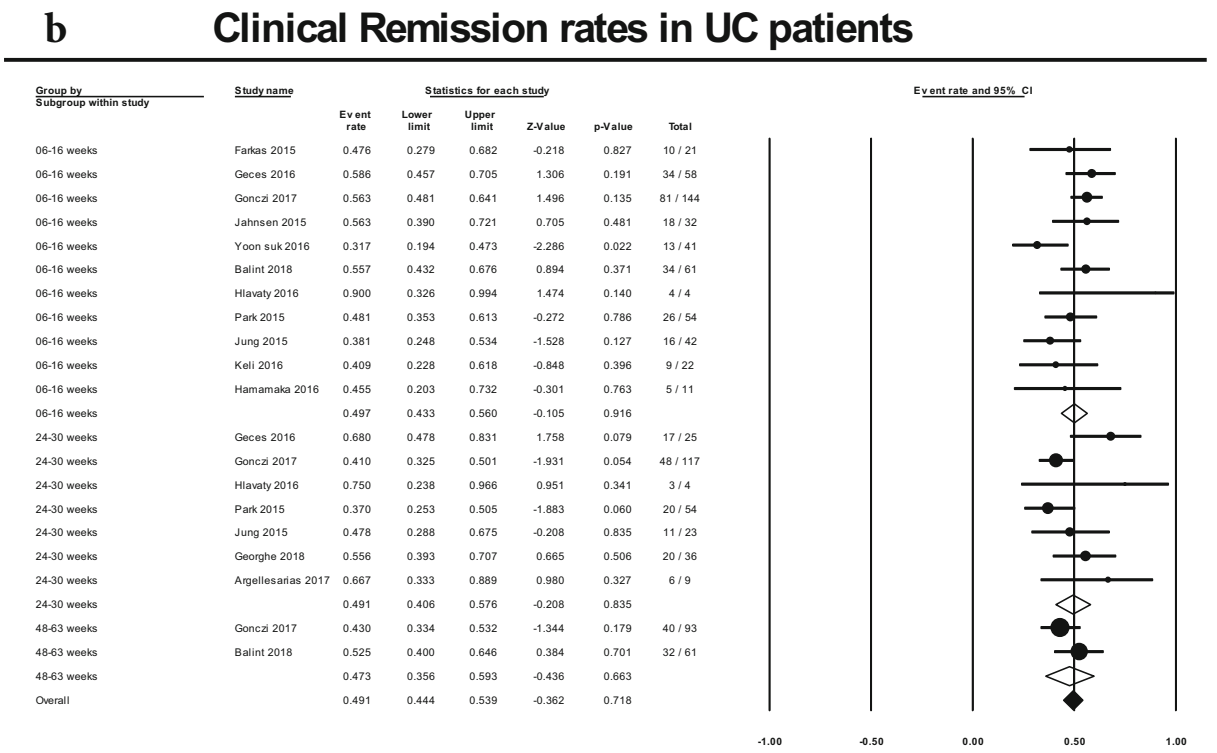


Fig. 3 **a** Forest plot of the clinical remission rates in CD patients, **b** forest plot of the clinical remission rates in UC patients

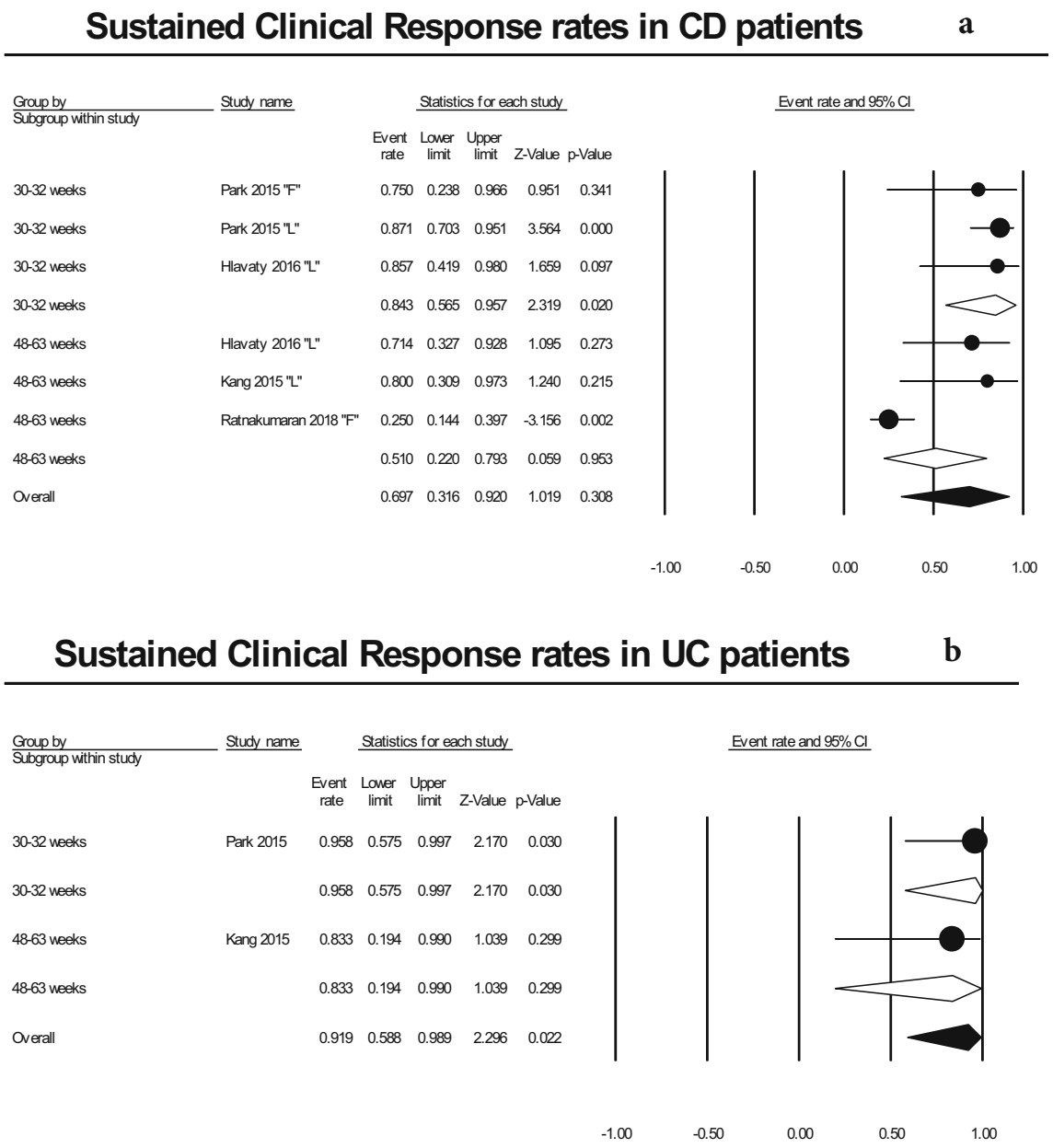


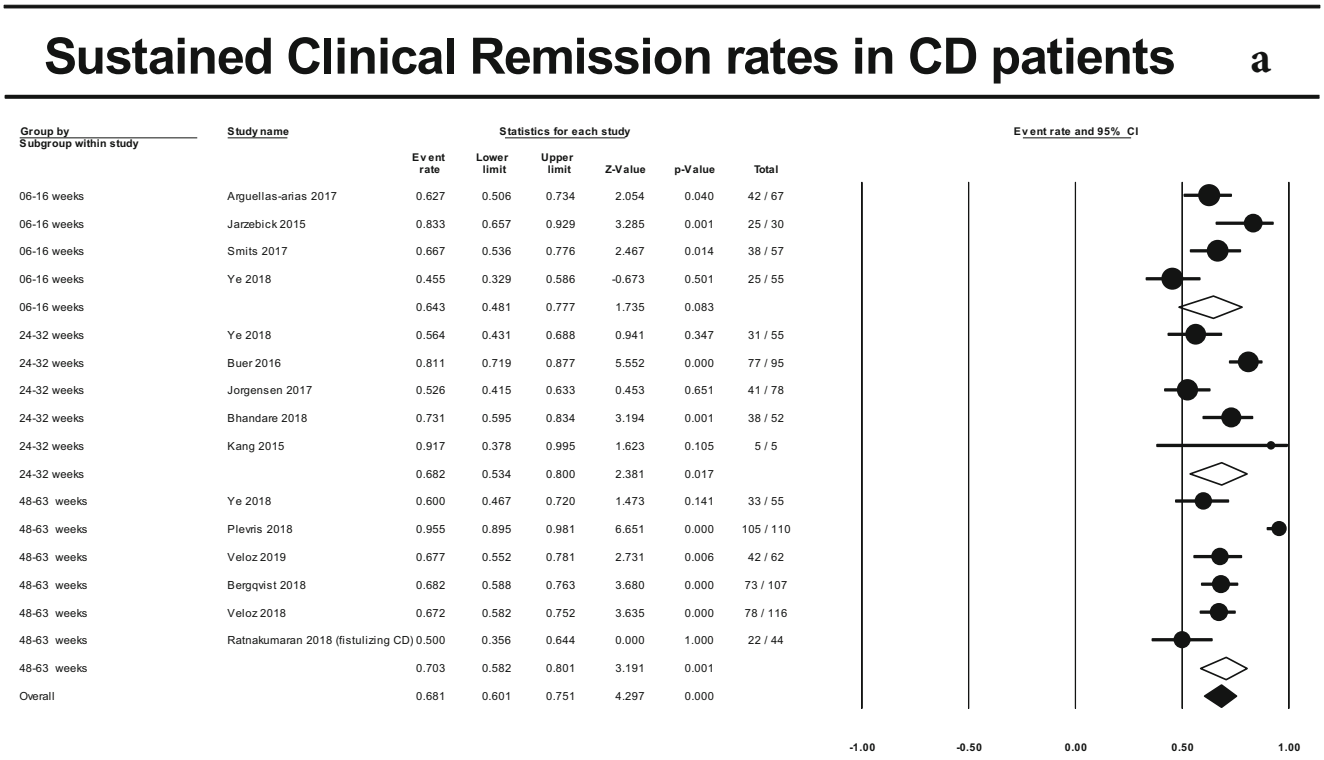
Fig. 4 **a** Forest plot of the sustained clinical response rates in CD patients, **b** forest plot of the sustained clinical response rates in UC patients

several extra-intestinal IBD complications. Regulatory authorities require comprehensive and extensive comparability programs to approve biosimilars which are not costly compared with IFX.

Currently, the rising incidence of IBD combined with the increasing use of biological agents has resulted in a growing economic burden, especially in developing countries. Thus, biosimilar would be an excellent choice for IBD patients, and it represents an opportunity to reduce health care costs while offering a similar level of efficacy and safety to that of their originator biological drug.

Summary of main results

We conducted an updated systematic review and meta-analysis to investigate the safety and efficacy of CT-P13 in the treatment of IBD. All observational studies and clinical trials studies showed statistically significant efficacy of the biosimilar of anti-TNF-a agents. We evaluated the rates of clinical response, clinical remission, and adverse events in IBD patients treated with CT-P13. This review included a total of 32 studies comprising 3464 patients.



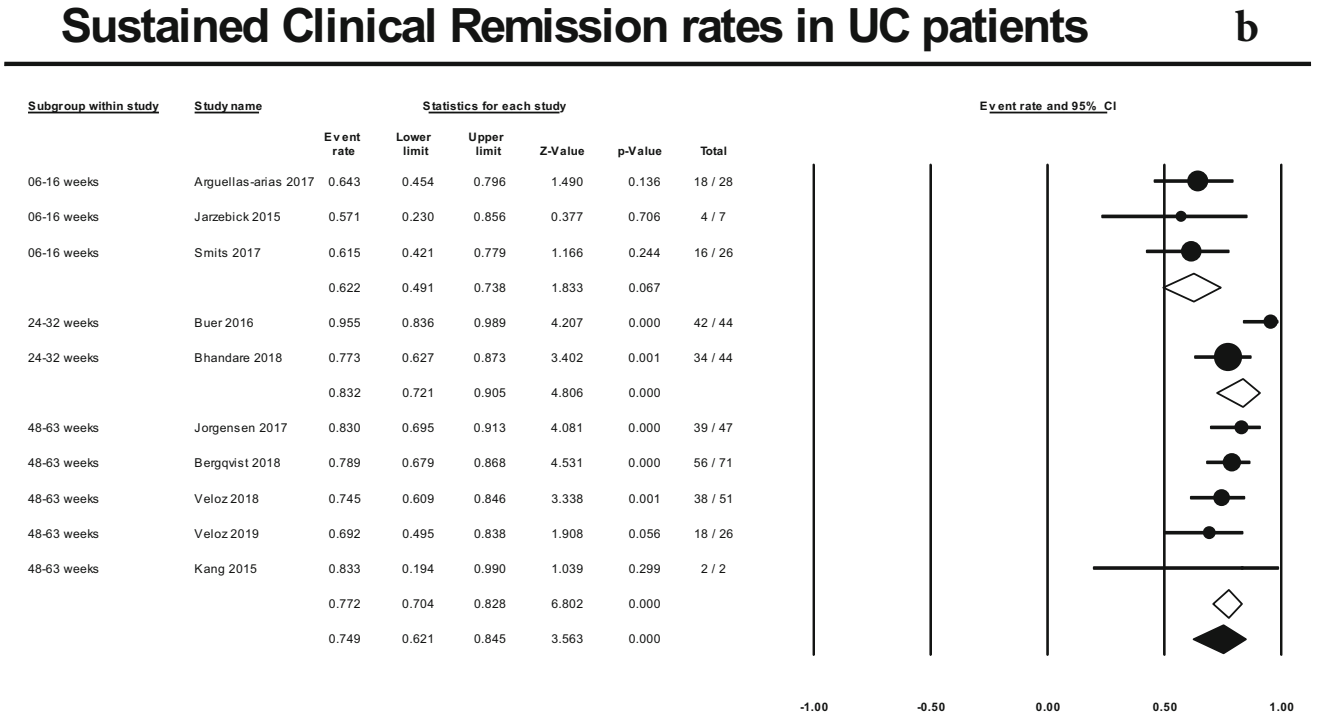


Fig. 5 **a** Forest plot of the sustained clinical remission rates in CD patients, **b** forest plot of the sustained clinical remission rates in UC patients

In CD patients, the pooled estimate demonstrated that CT-P13 had high rates of clinical response at short-term and long-term periods; moreover, low rates of overall adverse events were observed with a rate of around 10% in both naïve and switched patients.

Furthermore, in UC patients, the pooled rates showed that CT-P13 was linked with high clinical response rates at short term and long-term periods, and we observed low rates of overall adverse events with a rate of 0.09 in naïve patients and 0.18 in switched patients.

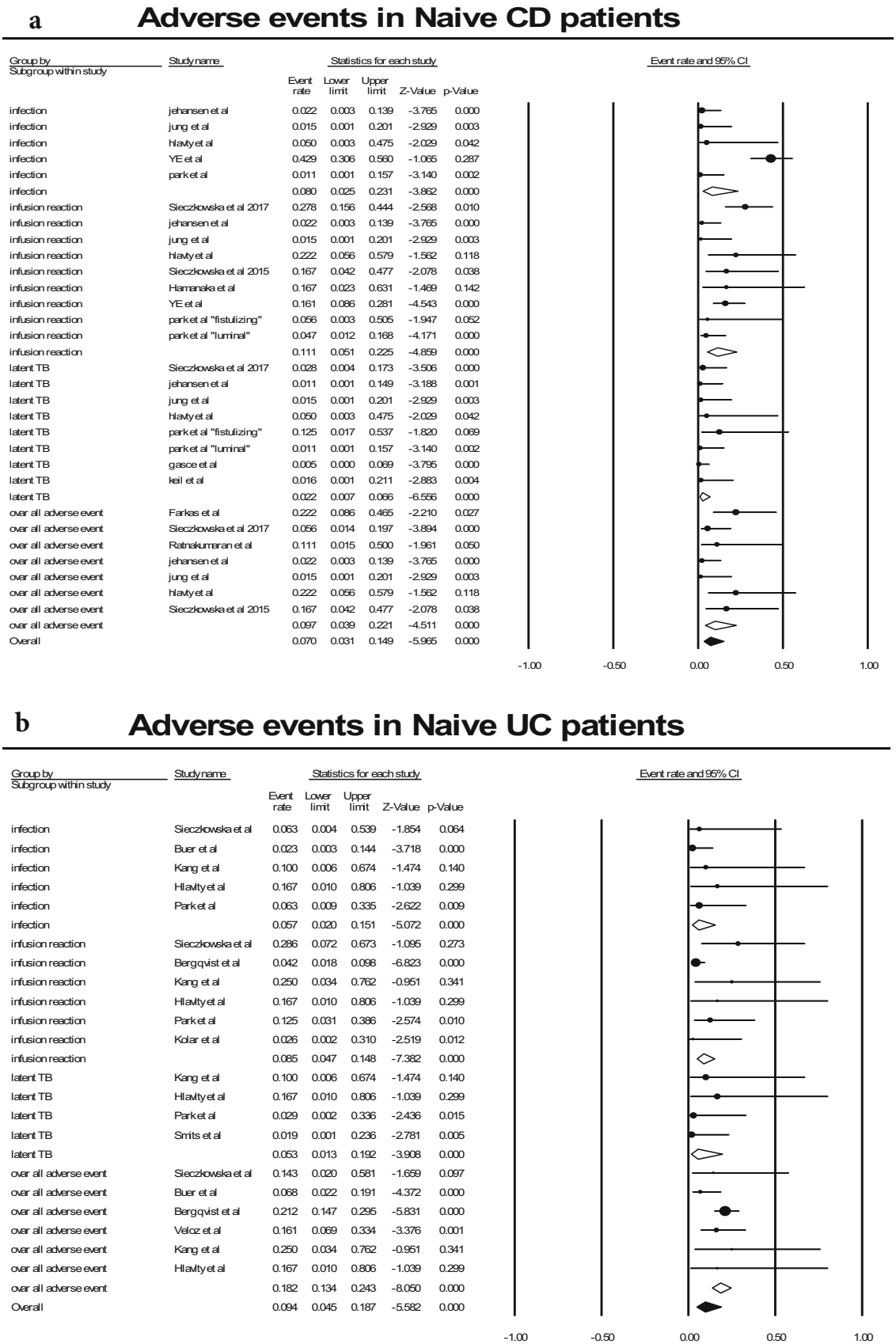
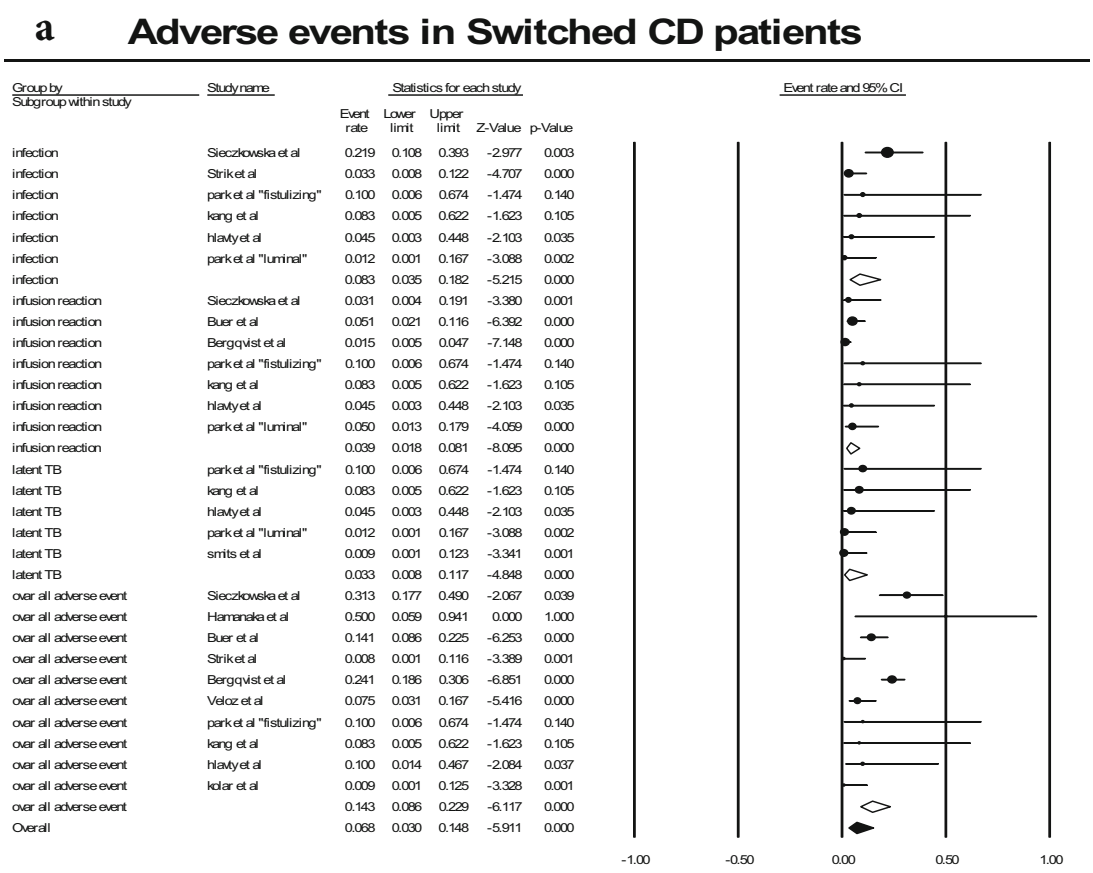


Fig. 6 **a** Forest plot of adverse events in naïve CD patients, **b** shows a forest plot of adverse events in naïve UC patients



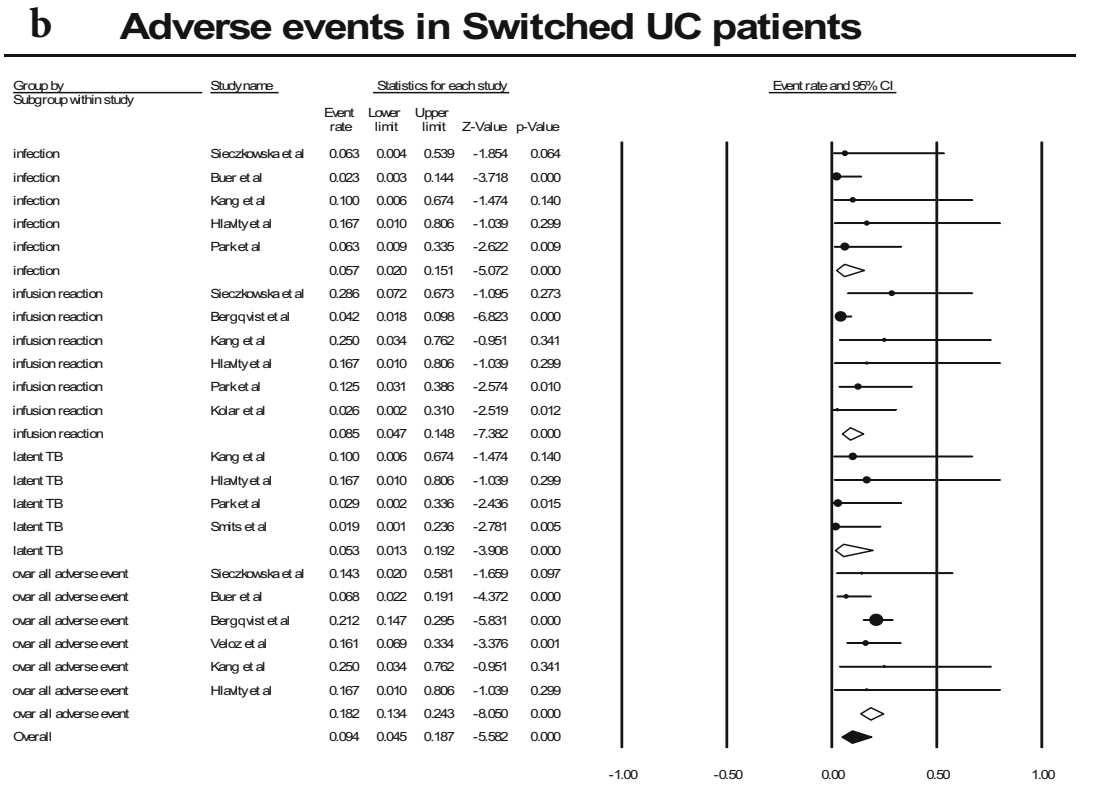


Fig. 7 **a** Forest plot of adverse events in switched CD patients, **b** forest plot of adverse events in switched UC patients

Agreement and disagreement with previous studies

A relevant meta-analysis involving 11 observational studies by Komaki et al. [25] reported high rates of clinical response, around 80%, in IBD patients treated with CT-P13. Despite the various associated limitations such as the low number of observational studies included, the results reported in this 2017 meta-analysis were similar to our analysis.

Another published RCTs, Jorgensen 2017 et al. [26] and Ye 2018 et al. [27] showed that switching from IFX originator to CT-P13 showed the same efficacy in maintaining response. At week 30, CDAI-70, CDAI-100, clinical response rates, and clinical remission rates were similar even after switching to CT-P13 [27]. Furthermore, previous data were conducted on patients switched from IFX originator to CT-P13 reported that switching is safe and effective during the first 12 months, and the loss of response was nearly 15.7%. However, in all these studies, there was no assessment of mucosal inflammation or fecal calprotectin as a biochemical measurement in patients with IBD [23, 28, 29].

Strength points and limitations

Our meta-analysis has several strength points: (1) we determined search methods and performed a comprehensive search using many electronic databases; (2) in our systematic review, we followed PRISMA checklist when reporting this manuscript, and all steps were done in strict correspondence with Cochrane handbook of systematic reviews for interventions; (3) we included large number of studies including observational and RCTs studies assessing the efficacy and safety of the switching from originator IFX to CT-P13; and (4) long-term follow-up was reported.

However, the main limitations of our meta-analysis were that the majority of studies were not able to measure mucosal healing or fecal calprotectin as a sign of remission in patients with IBD [23, 30, 31]. And the limited number of the RCTs which involved a little number of patients and some of the papers did not include a control group that allowed a comparison between originator and biosimilar infliximab [21, 22, 32]. Moreover, the included studies did not provide enough information about the loss of response cause in IBD patients [23, 31]. Most of the included studies lacked the endoscopic measurement after the used drug [33].

Despite the mentioned limitations, our results provide evidence on the efficacy and safety of CT-P13 for IBD patients by showing positive clinical outcomes in 1-year follow-up.

Authors' conclusion In conclusion, our systematic review and meta-analysis support that switching from infliximab originator to CT-P13 biosimilar was safe, well-tolerated, and effective in IBD patients.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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