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REVIEW ARTICLE

Adalimumab versus infliximab for the treatment of moderate to severe ulcerative colitis in adult patients naïve to anti-TNF therapy: An indirect treatment comparison meta-analysis

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Abstract

Objective: To compare the efficacy of adalimumab and infliximab for the treatment of moderate to severe ulcerative colitis using indirect treatment comparison meta-analysis.
Methods: A systematic review and Bayesian indirect treatment comparison meta-analyses were performed for seven patient-important clinical outcomes at 8 weeks and 52 weeks. Odds ratio (OR) estimates and associated 95% credible intervals (CrIs) were produced.
Results: Five eligible RCTs informed clinical remission, response, mucosal healing, quality of life, colectomy, serious adverse events, and discontinuation due to adverse events at 8 weeks and 52 weeks. At 8 weeks of induction therapy, clinical remission (OR = 0.42, 95% CrI 0.17–0.97), clinical response (OR = 0.45, 95% CrI 0.23–0.89) and mucosal healing (OR = 0.46, 95% CrI 0.25–0.86) statistically favored infliximab. However, after 52 weeks of maintenance therapy OR estimates showed no significant difference between infliximab and adalimumab. For serious adverse events and discontinuations due to adverse events, adalimumab and infliximab were similar to placebo. Further, the indirect treatment comparison of adalimumab and infliximab yielded odds ratios close to 1.00 with wide credible intervals.
Conclusion: The findings of this indirect treatment comparison meta-analysis suggest that both infliximab and adalimumab are superior to placebo in the treatment of moderate to moderately severe ulcerative colitis. While infliximab is statistically more effective than adalimumab in the

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induction of remission, response and mucosal healing at 8 weeks, infliximab and adalimumab are comparable in efficacy at 52 weeks of maintenance treatment.

Contents

1. Introduction

Ulcerative colitis (UC) is a chronic inflammatory disease of the colon, which is characterized by mucosal ulceration leading to diarrhea, rectal bleeding, and abdominal pain.[1] The risk of colectomy within the first five years of a diagnosis of ulcerative colitis ranges from 9% to 35%.[2]

Tumor necrosis factor α (TNF-α) is believed to promote the inflammatory response in patients with UC.[3–5] Therefore, TNF inhibitors (or anti-TNFs) play an important role in the treatment of UC. Adalimumab and infliximab are both anti-TNFs approved for the treatment for UC. Adalimumab and infliximab both constitute viable alternatives to conventional UC treatments such as aminosalicylates, corticosteroids, and immunosuppressants when patients do not respond, experience undesirable adverse effects, or become refractory to such interventions.[6–8]

To date, the efficacy of adalimumab and infliximab for treating adults diagnosed with moderate to severe UC has been documented in a number of placebo-controlled randomized clinical trials (RCTs),[7,8] and the efficacy of anti-TNFs in general (not distinguishing between adalimumab and infliximab) has been documented in a number of conventional pair wise meta-analysis.[9–11] However, adalimumab and infliximab have never been compared head-to-head in a RCT, and thus, it is unclear whether one of the two treatments exhibits higher efficacy than the other. In the absence of head-to-head evidence, it is still possible to draw inferences about the relative efficacy of the two anti-TNFs through indirect treatment comparison meta-analysis, a technique that relies on evidence from RCTs that have compared either of the two active interventions to a common comparator (e.g., placebo) to establish relative effectiveness.[12] The objective of the present study was to conduct an indirect treatment comparison meta-analysis of the efficacy of adalimumab and infliximab for the treatment of moderate to severe ulcerative colitis in adult patients with no prior anti-TNF experience.

2. Methods

2.1. Search strategy

Two reviewers (KT, ED) working independently and in duplicate conducted a systematic literature search. Medline, Embase, and EBM Reviews — Cochrane Central Register of Controlled Trials were searched (from inception to October 30, 2013). The search terms included "ulcerative colitis" and the generic and brand names of each of the agents ("adalimumab" or "Humira™" or "infliximab" or "Remicade™"). Searches were limited to RCTs in humans and were not limited by language. Bibliographies of published systematic reviews and relevant RCTs were also searched. Searches were structured in such a way as to accommodate the controlled vocabulary and search language of each database.

2.2. Eligibility

We included RCTs evaluating either adalimumab or infliximab for the treatment of moderate to severe UC in non-hospitalized adult patients (i.e., outpatients), 18 years of age and older, with an inadequate response to conventional treatment (e.g., aminosalicylates, corticosteroids, and immunosuppressants). RCTs reporting outcomes among patients

with no prior anti-TNF experience (i.e., those naïve to anti-TNFs) were included. The placebo and active treatment arms of included trials could each include concomitant therapy treatments such as aminosalicylates, corticosteroids, and immunosuppressants. We included RCTs reporting on at least one of our five efficacy outcomes (clinical remission, clinical response, mucosal healing, the inflammatory bowel disease questionnaire (IBDQ) response, and colectomy) and reported outcomes at 8 weeks or later. Only RCTs where adalimumab and infliximab had been administered for at least 6 weeks were considered. Trials that did not have a placebo control were excluded.

2.3. Study selection

Two researchers (KT, ED) working independently, in duplicate, scanned all abstracts and obtained the full text publications potentially matching the inclusion criteria. After obtaining these full text publications, the same two researchers independently assessed eligibility. Where required, a third investigator (EM) provided arbitration.

2.4. Data extraction

We extracted data on the following key efficacy outcomes: clinical remission (defined as Mayo score ≤ 2 with no individual subscore >1 or as a Seo index <120 points), clinical response (defined as decrease from baseline in the total Mayo score by ≥ 3 points and at least 30% with an accompanying decrease in rectal bleeding subscore of ≥ 1 point or an absolute rectal bleeding subscore of 0 or 1), mucosal healing (defined as an endoscopy subscore of 0 or 1), IBDQ response (defined as a positive change of ≥ 16 points in IBDQ response), and colectomy. We also extracted data on two key safety outcomes: serious adverse events and discontinuation due to adverse events. The efficacy outcome data were extracted for the time points of 8 to 12 weeks and 52 to 54 weeks. We also extracted sustained clinical remission and sustained response, that is, remission at 52 to 54 weeks conditional on remission at 8 to 12 weeks, and the same for response. The safety outcome data were extracted at latest observed time point. Lastly, we extracted data for all relevant trial characteristics and intervention characteristics (e.g., adalimumab and infliximab doses). Data on all outcomes and baseline characteristics were extracted for patients with no prior experience to anti-TNFs. However, when data was not reported separately for this population group (i.e., adverse events in ULTRA-2), data was extracted for the entire patient cohort.

2.5. Assessment of similarity between trials

A key assumption of indirect treatment comparison meta-analysis is that trials across comparisons are similar with respect to their designs and enrolled patient populations. The similarity of trial designs was assessed with respect to enrolment procedure, patient eligibility criteria, and outcome definitions. The similarity of patient populations was assessed with respect to the extracted baseline characteristics. These assessments were all descriptive in nature. Heterogeneity between trials within each RCT informed comparison (i.e., adalimumab vs placebo and infliximab vs placebo) as valid and reliable estimation is not possible with a very small number of trials (i.e., 2–3 per comparison, see Table 1).[13]

2.6. Analysis

We performed Bayesian indirect treatment comparison meta-analysis to estimate the relative efficacy of adalimumab versus infliximab. The Bayesian analyses were performed using WinBUGS v1.4.3.[14] We also obtained estimates of adalimumab versus placebo and infliximab versus placebo. The analysis considered only Food and Drug Administration (FDA) approved doses of adalimumab (initial dose of 160 mg, a second dose two weeks later of 80 mg, and a maintenance dose of 40 mg every other week) and infliximab (5 mg/kg at week 0, 2, and 6, and then at every 8 weeks).

Given that a degree of heterogeneity was expected between RCTs and across comparisons, a random-effects model of indirect treatment comparison meta-analysis was employed.[16,17] However, in the face of few RCTs, heterogeneity estimation becomes highly unreliable. Therefore, we

Table 1 Characteristics of the included randomized clinical trials.

Trial	Intervention	Setting	Blinded period	No. pts	Patient setting and severity	Outcomes of interest assessed
ULTRA 2 Sandborn et al. 2012[6]	Adalimumab	Europe and North America	52 weeks	295	Outpatients, moderate–severe UC	Remission, response, mucosal healing, IBDQ response
ULTRA 1 Reinisch et al. 2011[7]	Adalimumab	International	8 weeks	390	Outpatients, moderate–severe UC	Remission, response, mucosal healing
ACT 1 Rutgeerts et al. 2005[8]; Feagan et al. 2007[21]; Sandborn et al. 2009[20]	Infliximab	International	54 weeks	364	Outpatients, moderate–severe UC	Remission, response, mucosal healing, IBDQ response, colectomy
ACT 2 Rutgeerts et al. 2005[8]; Feagan et al. 2007[21]; Sandborn et al. 2009[20]	Infliximab	International	30 weeks	364	Outpatients, moderate–severe UC	Remission, response, mucosal healing, IBDQ response, colectomy

IBDQ, inflammatory bowel disease questionnaire.

decided a priori to stabilize the heterogeneity estimation by using heterogeneity variance priors empirically established by Turner et al. [18] In situations where only one trial was available per comparison (i.e., adalimumab versus placebo and infliximab versus placebo), heterogeneity could not be estimated; therefore a fixed-effect model Bayesian indirect treatment comparison meta-analysis was used.

For all outcomes, odds ratios with associated 95% credible intervals (CrIs) were calculated for the comparisons of adalimumab versus infliximab, adalimumab versus placebo, and infliximab versus placebo. For clinical remission and clinical response at 8 and 52 weeks, the expected proportions in the placebo, adalimumab, and infliximab groups were calculated. The placebo proportions were obtained by pooling across all trials, whereas the adalimumab and infliximab proportions were obtained by linking the proportions to the estimated odds ratios in the Bayesian (logistic regression) model.[19]

3. Results

3.1. Evidence-base

Five publications representing four RCTs met the inclusion criteria (two of these RCTs assessed adalimumab[6,7] and two assessed infliximab.[8,20,21]) Table 1 lists the characteristics of each of the included RCTs. Eleven publications were excluded following full-text review.[15,22–31] Reasons for excluding these publications are presented in Table A of the Appendix. A schematic of the study selection process is provided in Fig. 1.

Data for all considered outcomes, except for colectomy, were available for both adalimumab and infliximab, and thus indirect treatment comparisons were possible for these outcomes. All trials provided data on one or more of the 8 week efficacy outcomes,[6–8,15,21] whereas two trials provided randomized data for the 52 week efficacy outcomes (and sustained efficacy outcomes).[6,8] Sustained efficacy in one trial (ULTRA 2) was additionally conditional on 30 week efficacy. Four trials provided randomized data on the safety outcomes (at last observed time point), whereas two provided data for the 52 week safety outcomes.[6,8] Note, the 52 week results from the ULTRA 1 trial was not included given that patients that did not have a response in the placebo were allowed to cross-over to adalimumab; one trial reported results for hospitalized patients, and of the considered efficacy and safety outcomes, this trial reported on 8 week remission.[15]

3.2. Assessment of similarity between trials

Table 1 presents the characteristics included in each RCT, and Table 2 presents the demographic characteristics of patients included in each RCT. Overall the study settings were similar for four trials ULTRA 1, ULTRA 2, ACT 1, and ACT 2 (with the exception of the anti-TNF intervention). However, some potentially important differences should be noted. First, in ULTRA 1 (Reinisch et al., 2011), patients that had been enrolled before an important protocol amendment were also considered included in the safety outcome reporting,[7] and in ULTRA 2, safety outcomes were not reported separately for anti-TNF-naïve (60% patients) and anti-TNF-exposed responders (40% of patients).[6] For the 52 week outcomes, the ULTRA 2 and ACT 2 trials differed in patient follow-up. The ACT 2 trial randomized patients to a 52 week course of infliximab or placebo and did not allow any modifications to the assigned intervention (or placebo) during the 52 weeks. The ULTRA 2 trial allowed patients with inadequate response at 12 weeks or later to either switch to adalimumab (if originally randomized to placebo) or escalate their dose (if originally randomized to adalimumab). However, patients who chose to switch were analyzed using 'non-responder imputation', which assumes that patients would have remained non-responders had they continued the full 52 weeks of treatment. For the sustained outcomes, ACT 2 also required sustained remission/response at the 30 week time point in addition to the 8 and 54 week time points.

The patient baseline characteristics were also similar for these four studies. Particularly, the proportion of males, age, weight, baseline disease duration, baseline Mayo score, the proportion of patients on the concomitant medications, and the proportion of patients with total/extensive UC versus distal/left-sided UC were highly similar across these four trials. For baseline C-reactive protein (CRP), the mean values were similar but the median values were slightly higher for the ACT 1 and ACT 2 trials. The proportion of patients with CRP elevation were also slightly higher in ACT 1 and ACT 2 than in ULTRA 2 (not reported in ULTRA 1), however, the threshold determining elevation was also

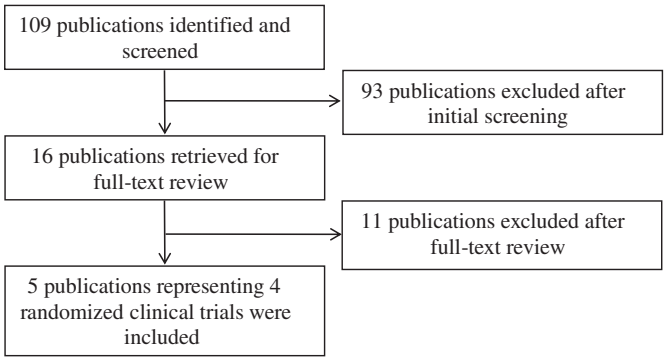

Figure 1 Schematic of the publication selection process.

Table 2 Baseline patient characteristics of the included randomized clinical trials.

	ULTRA 2		ULTRA 1			ACT 1			ACT 2		
	Sandborn et al. 2012[6]		Reinisch et al. 2011[7]			Rutgeerts et al. 2005[8]; Feagan et al. 2007[21]; Sandborn et al. 2009[20]			Rutgeerts et al. 2005[8]; Feagan et al. 2007[21]; Sandborn et al. 2009[20]		
	Placebo	ADA 160 mg	Placebo	ADA 80 mg	ADA 160 mg	Placebo	INF 5 mg/kg	INF 10 mg/kg	Placebo	INF 5 mg/kg	INF 10 mg/kg
No. patients randomized	246	248	130	130	130	121	121	122	123	121	120
Male sex	61.8%	57.3%	63.1%	60.0%	63.8%	59.5%	64.5%	59.0%	57.7%	62.8%	56.7%
Age (years)	41.3[a]	39.6[a]	37.0[b]	40.0[b]	36.5[b]	41.4[a]	42.4[a]	41.8[a]	39.3[a]	40.5[a]	40.3[a]
Weight (kg)	77.1[a]	75.3[a]	78.7[a]	76.8[a]	75.5[a]	76.8[a]	80.0[a]	76.9[a]	76.1[a]	78.4[a]	79.6[a]
Disease duration (years)	8.5[a]	8.1[a]	5.4[b]	6.9[b]	6.1[b]	6.3[a]	5.9[a]	8.4[a]	6.5[a]	6.7[a]	6.5[a]
Mayo score	8.9[a]	8.9[a]	8.7[a]	9.0[a]	8.8[a]	8.4[a]	8.5[a]	8.4[a]	8.5[a]	8.3[a]	8.3[a]
Concomitant therapy											
Corticosteroids	56.9	60.5	68.5	56.9	54.6	65.3	57.9	59.8	48.8	49.6	55.0
Aminosalicylates	63.0	58.9	75.4	76.2	80.8	70.2	67.8	70.5	72.4	76.0	75.8
Azathioprine	32.5	37.5	NR	NR	NR	29.8	37.2	36.1	28.5	33.9	30.8
Immunosuppressants	NR	NR	NR	NR	NR	43.8	54.5	48.4	43.9	43.0	41.7
C-reactive protein (CRP)											
Mean (SD) (mg/dL)	1.3 (3.7)	1.5 (3.2)	NR	NR	NR	1.7 (2.7)	1.4 (1.9)	1.6 (2.3)	1.6 (2.9)	1.3 (2.3)	1.4 (2.2)
Median (mg/dL)	0.4	0.4	0.3	0.6	0.3	0.8	0.9	1.0	0.6	0.8	0.6
% elevated	47.2[c]	45.7[c]	NR	NR	NR	62.2[d]	65.0[d]	66.9[d]	59.5[d]	63.3[d]	53.8[d]
Disease location											
Total/extensive	48.8%	48.4%	56.2%	53.8%	46.2%	45.0%	47.1%	44.6%	41.7%	40.7%	37.5%
Distal/left-sided	51.2%	51.6%	43.8%	46.1%	53.8%	55.0%	52.9%	55.4%	58.3%	59.3%	62.5%

Note: Baseline characteristics for the Sandborn et al. 2012 (ULTRA 2) trial were not stratified by prior anti-TNF experience in the source publication and are therefore presented for the entire population. NR, not reported; NA, not applicable; ADA, adalimumab; INF, infliximab.

[a] Mean.
[b] Median.
[c] C-reactive protein elevation threshold of 0.494 mg/dL.
[d] C-reactive protein elevation threshold of 0.6 mg/dL.

higher in the ACT 1 and ACT 2 trials, and thus, would result in a higher proportion of elevations.

3.3. Indirect treatment comparison meta-analysis

The results of the direct and indirect treatment comparison meta-analyses for all efficacy outcomes are presented in Table 3, and Table B in the Appendix presents the number of events for each outcome, as reported in the individual RCTs. The derived proportions of clinical remission and clinical response at 8 weeks and 52 weeks are presented in Fig. 2, and Table C in the Appendix presents these proportion estimates with their associated 95% CrIs. The results for the two safety outcomes are presented in Table 4, and Table D in the Appendix presents the number of event for each safety outcome, as presented in the individual RCTs.

When compared with placebo, adalimumab and infliximab both yielded statistically significant improvements over placebo for the majority of the efficacy outcomes (the exceptions were adalimumab for mucosal healing at 8 weeks, adalimumab for sustained remission, and infliximab for colectomy at 52 weeks; see Table 3). Indirect treatment comparison meta-analyses of adalimumab versus infliximab are shown in Table 3. At 8 weeks, adalimumab was statistically less effective than infliximab in producing clinical remission (OR = 0.42, 95% CrI 0.17–0.97), clinical response (OR = 0.45, 95% Cri 0.23–0.89), and mucosal healing (OR = 0.46, 95% CrI 0.25–0.84). However, at 52 weeks adalimumab was not statistically different from infliximab for achieving clinical remission (OR = 0.72, 95% CrI 0.31–1.76), clinical response (OR = 0.54, 95% CrI 0.24–1.13) or mucosal healing (OR = 0.51, 95% CrI 0.23–1.11) (Table 3). Similarly, for sustained clinical remission, adalimumab was not statistically different from infliximab (OR = 0.52, 95% CrI 0.16–1.20). However, adalimumab was associated with statistically lower odds of sustaining response compared with infliximab (OR = 0.53, 95% CrI 0.24–0.98).

For the safety outcomes, adalimumab and infliximab were equally likely to result in a serious adverse event or discontinuation due to an adverse event when compared with placebo. None of the safety outcome comparisons was statistically significant (Table 4).

4. Discussion

The results of this indirect treatment comparison meta-analysis show a statistical benefit of infliximab over adalimumab for producing clinical remission, clinical response and mucosal healing at 8 weeks. At 52 weeks the estimated relative odds of maintaining these outcomes were similarly higher with infliximab. However, due to the lower proportion of patients maintaining these outcomes at 52 weeks as well as limited evidence (only two RCTs), results were not statistically different.

There are several advantages and drawbacks to this meta-analysis. First, no published systematic review or meta-analysis has previously compared infliximab and adalimumab using indirect treatment comparison or Bayesian multiple treatment comparison techniques. These techniques are the only reliable statistical methods for comparing interventions that have not been evaluated head-to-head in randomized clinical trials.[12] Further, indirect treatment comparison meta-analysis is now widely embraced by health technology assessment agencies across the world,[19] and several studies have validated this approach.[32–35] Thus, the indirect treatment comparison meta-analyses presented in this article are the first to establish comparative effectiveness of adalimumab versus infliximab for the treatment of ulcerative colitis.

Table 3 Bayesian indirect treatment comparison odds ratio estimates and 95% credible intervals from the efficacy analysis.

Outcome	Indirect treatment comparison of Adalimumab versus Infliximab OR (95% CrI)	Placebo comparisons	
		Adalimumab OR (95% CrI)	Infliximab OR (95% CrI)
Results at 8 weeks			
Clinical remission	0.42 (0.17–0.97)	2.22 (1.23–3.98)	5.26 (2.94–9.99)
Clinical response	0.45 (0.23–0.89)	1.87 (1.18–2.97)	4.15 (2.53–6.82)
Mucosal healing	0.46 (0.25–0.84)	1.51 (0.96–2.39)	3.26 (2.21–0.84)
IBDQ response	0.84 (0.48–1.50)	1.98 (1.24–3.18)	2.36 (1.72–3.25)
Colectomy	–	–	4.86 (1.37–17.2)
Results at 52 weeks			
Clinical remission	0.72 (0.31–1.76)	1.99 (1.08–3.89)	2.73 (1.50–5.14)
Clinical response	0.54 (0.25–1.13)	1.81 (1.09–3.05)	3.39 (1.94–6.06)
Mucosal healing	0.50 (0.23–1.11)	1.91 (1.12–3.31)	3.77 (2.12–6.89)
IBDQ response	–	1.73 (1.02–2.92)	–
Colectomy	–	–	1.32 (0.78–2.25)
Results sustained			
Sustained remission	0.52 (0.16–1.20)	1.81 (0.77–4.23)	3.49 (1.51–8.08)
Sustained response	0.53 (0.24–0.98)	2.08 (1.20–3.60)	3.89 (2.11–7.16)

Note: For the indirect treatment comparison, odds ratios smaller than 1.00 indicate relatively lower number of events in the adalimumab group (i.e., favors infliximab). For the placebo comparisons, odds ratios larger than 1.00 indicate relatively higher number of events in the adalimumab and infliximab groups. All analyses are based on anti-TNF naïve patient data only (i.e., anti-TNF-IR patients from ULTRA were not included).
IBDQ, inflammatory bowel disease questionnaire; OR, odds ratio; CrI, credible interval.

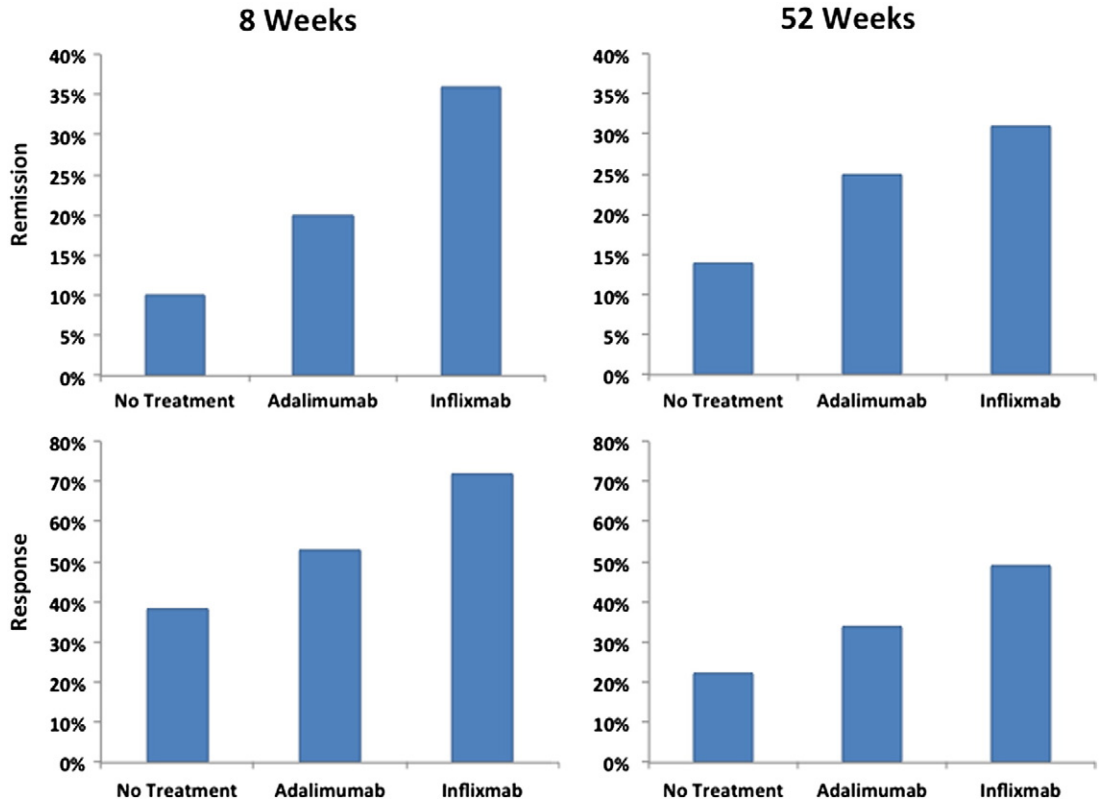

Figure 2 Proportion of patients with expected clinical remissions and clinical responses at 8 weeks and 52 weeks with adalimumab, infliximab, and no treatment, respectively. These proportions are mathematical transformations of the odds ratio estimates. The 8-week difference in proportions between infliximab and adalimumab can be considered statistically significant, whereas the 52-week results should not.

This study employed rigorous eligibility criteria to ensure comparability of trials both within comparisons (i.e., infliximab versus placebo and adalimumab versus placebo) and between comparisons; as such comparability is quintessential for the validity of indirect treatment comparison meta-analysis. However, some differences in trial settings were observed. Safety outcomes from ULTRA 2 were only available for a mix of anti-TNF-naïve and anti-TNF-exposed patients. Since anti-TNF-exposed patients are generally at a more advanced stage of the disease, a relatively larger portion of adverse events may be disease-related rather than treatment-related, and efficacy results could be attenuated. For the efficacy measures, the 'non-responder imputation' in ULTRA 2 may have downward biased both the estimated placebo and adalimumab efficacy at 52 weeks. Lastly, the more rigorous definition of sustained remission/response in the ACT 2 trials may have downward biased efficacy estimates in both the placebo and infliximab groups.

Another limitation of this indirect treatment comparison meta-analysis is the small number of trials and patients available for some of the outcomes. Outcomes at 8 weeks were informed by all trials, but outcomes at 52 weeks were only informed by two trials. Limited reporting of important outcomes such as IBDQ response and colectomy is also a

Table 4 Bayesian indirect treatment comparison odds ratio estimates and 95% credible intervals from the safety analysis.

Outcome	Indirect treatment comparison of Adalimumab versus Infliximab OR (95% CrI)	Placebo comparisons	
		Adalimumab OR (95% CrI)	Infliximab OR (95% CrI)
Results at any time point			
Serious AEs	1.21 (0.53–2.78)	0.79 (0.43–1.42)	0.65 (0.36–1.13)
Discontinuations due to AEs	1.45 (0.49–4.16)	0.67 (0.35–1.30)	0.47 (0.21–1.05)
Results at 52 weeks			
Serious adverse events (AEs)	1.23 (0.43–3.47)	0.98 (0.49–1.95)	0.79 (0.37–1.70)
Discontinuations due to AEs	0.72 (0.20–2.53)	0.65 (0.31–1.33)	0.90 (0.32–2.52)

Note: For the indirect treatment comparison, odds ratios larger than 1.00 indicate relatively higher number of adverse events of discontinuations due to AEs in the adalimumab group (i.e., favors infliximab). For the placebo comparisons, odds ratios smaller than 1.00 indicate relatively lower number of adverse events or discontinuations due to AEs in the adalimumab and infliximab groups.
AE, adverse event; OR, odds ratio; CrI, credible interval.

limiting factor. Safety outcome data retrieved from the adalimumab trials were reported for marginally greater patient cohorts that were not used for the efficacy analysis.

There are a number of clinical implications associated with the findings of this indirect treatment comparison. It is important to keep in mind that not all patients will have a favorable response at 8 weeks, and even for those who do, over half may have a loss of response to therapy within one year. Currently, there are no biomarkers available to predict which treatment patients are most likely to respond with, and so, clinicians may want to rely on the reported probabilities (Fig. 2) to inform patients of remission and response rates. Evidence on long-term (52 weeks) comparative efficacy of the two anti-TNFs is limited. While additional placebo comparison trials of adalimumab and infliximab seem a sub-optimal use of resources, further subgroup analyses of the existing trial data, and perhaps a head-to-head trial could provide additional insight. It is also important to note that the lower efficacy of adalimumab may be due to dosing issues. Current ongoing RCTs are exploring other dosing regimens of adalimumab with the aim to attain similar efficacy as infliximab. Lastly, one should not ignore that differences in administration may become the key factor to deciding between the two anti-TNFs. Adalimumab is given subcutaneously every 2 weeks, whereas infliximab administered intravenously, but only every 8 weeks once the loading dose is over. Adalimumab may therefore be preferable to patients due to its less invasive nature, however, adalimumab may also be less preferable due to the inconvenience of receiving treatment every 2 weeks rather than every 8 weeks.

In summary, our findings suggest that at 8 weeks infliximab is more efficacious than adalimumab for attaining clinical remission, response and mucosal healing among patients with moderate to severe ulcerative colitis. Due to a lower proportion of patients maintaining these induction outcomes till 52 weeks, more evidence is needed to confirm that whether the superiority of infliximab is sustained in the long term.

Competing interest

Kristian Thorlund and Edward Mills have previously consulted Merck, Pfizer, Novartis, GSK, Takeda, and UCB Pharma on indirect comparison and systematic reviews. Richard Fedorak has been an Advisory Board Member of Abbott Canada, Axcan, Celltech, Elan/Biogen, Proctor & Gamble, Schering Canada, Shire, UCB Pharma, and Genentech. He has also received research grants and consultation fees from: Abbott, Altana/Nycomed, Axcan, Berlex, Bristol Myers Squibb, Centocor, Elan/Biogen, Ferring, Millenium, Novartis, Otsuka, Proctor & Gamble, Protein Design Labs, Schering, UCB Pharma, and VSL#3 Genentech. John Marshall has been on advisory boards and/or received speaker fees from Abbvie, Aptalis, AstraZeneca, Ferring, Forrest, Innomar, Janssen, Procter & Gamble, Shire, Takeda and Warner-Chilcott. Eric Druyts has no competing interest to declare.

Role of funding

This study was initiated and conducted by the academic researchers. KT and EM approached Janssen Inc. Canada for funding and received funding based on a submitted protocol. Janssen Inc. had no involvement in the choice of analyses past the protocol stage, and had no involvement in the interpretation of the results.

Author contributions

KT conceived the study protocol, extracted the data, performed all statistical analyses, wrote the first draft of the manuscript and contributed to the interpretation. ED contributed to the design of the study, extracted data and contributed to the writing and interpretation. EM, RNF, and JKM contributed to the design, writing and interpretation.

Appendix A

Table A Publications excluded after detailed evaluation.

Study	Principal reason for exclusion
Colombel et al. 2011[23]	Follow-up to Rutgeerts et al. 2005; no relevant data for current meta-analysis
Gustavsson et al. 2010[26]	Follow-up to Jarnerot et al. 2005; no relevant data for current meta-analysis
Oussalah et al. 2008[28]	All patients have an inadequate response to infliximab
Ferrante et al. 2007[24]	Not a placebo controlled study
Reinisch et al. 2007[30]	Follow-up to Rutgeerts et al. 2005; no relevant data for current meta-analysis
Jarnerot et al. 2005[15]	Included only hospitalized patients
Armuzzi et al. 2004[22]	All patients are not inadequate responders to conventional (i.e. steroid) therapy
Ochsenkuhn et al. 2004[27]	All patients are not inadequate responders to conventional (i.e. steroid) therapy
Gornet et al. 2003[25]	Not a placebo controlled study
Probert et al. 2003[29]	Outcomes only provided at 6 weeks
Sands et al. 2001[31]	Outcomes only provided at 2 weeks

Table B Number of events for each efficacy outcome.

	ULTRA 2 Sandborn et al. 2012[6]		ULTRA 1 Reinisch et al. 2011[7]			ACT 1 Rutgeerts et al. 2005[8]; Feagan et al. 2007[21]; Sandborn et al. 2009[20]			ACT 2 Rutgeerts et al. 2005[8]; Feagan et al. 2007[21]; Sandborn et al. 2009[20]		
	Placebo	ADA 160 mg	Placebo	ADA 80 mg	ADA 160 mg	Placebo	INF 5 mg/kg	INF 10 mg/kg	Placebo	INF 5 mg/kg	INF 10 mg/kg
Randomized, *n*	145	150	130	130	130	121	121	122	123	121	120
Results at 8 weeks											
Clinical remission, *n* (%)	16 (11.0)	32 (21.3)	12 (9.2)	13 (10.0)	24 (18.5)	18 (14.9)	47 (38.8)	39 (32.0)	7 (5.7)	41 (33.9)	33 (27.5)
Clinical response, *n* (%)	56 (38.6)	89 (59.3)	58 (44.6)	67 (51.5)	71 (54.6)	45 (37.2)	84 (69.4)	75 (61.5)	36 (29.3)	78 (64.5)	83 (69.2)
Mucosal healing, *n* (%)	51 (35.2)	74 (49.3)	54 (41.5)	49 (37.7)	61 (46.9)	41 (33.9)	75 (62.0)	72 (59.0)	38 (30.9)	73 (60.3)	74 (61.7)
IBDQ response, *n* (%)	75 (51.7)	102 (68.0)	–	–	–	*	*	*	*	*	*
Colectomy, *n* (%)	–	–	–	–	–						
Results at 52 weeks											
Clinical remission, *n* (%)	18 (12.4)	33 (22.0)	–	–	–	20 (16.5)	42 (34.7)	42 (34.4)	–	–	–
Clinical response, *n* (%)	35 (24.1)	55 (36.7)	–	–	–	24 (19.8)	55 (45.5)	54 (44.3)	–	–	–
Mucosal healing, *n* (%)	28 (19.3)	47 (31.3)	–	–	–	22 (18.2)	55 (45.5)	57 (46.7)	–	–	–
IBDQ response, *n* (%)	31 (21.4)	48 (32.0)	–	–	–	–	–	–	–	–	–
Colectomy, *n* (%)						**	**	**	**	**	**
Results sustained from 8 weeks to 52 weeks											
Clinical remission, *n* (%)	9 (6.2)	16 (10.7)	–	–	–	–	–	–	8 (6.6)	24 (19.8)	25 (20.5)
Clinical response, *n* (%)	24 (16.6)	44 (29.3)	–	–	–	–	–	–	17 (14.0)	47 (38.8)	45 (36.9)

	ACT 1 and ACT 2 Feagan et al. 2007[21]		
	Placebo	INF 5 mg/kg	INF 10 mg/kg
Randomized, *n*	244	242	242
Results at 8 weeks			
IBDQ response, *n* (%)	*121 (49.6)	*169 (69.7)	*164 (67.8)

	ACT 1 and ACT 2 Sandborn et al. 2009[20]		
	Placebo	INF 5 mg/kg	INF 10 mg/kg
Randomized, *n*	244	242	242
Results at 52 weeks			
Colectomy, *n* (%)	** 36 (15)	**28(11)	**18 (7)

Note: Events for ULTRA 2 trial are presented for those with no prior anti-TNF experience.
* in the first table refers to the second table.
** in the first table are refers to the third table.

Table C Expected proportion of clinical remissions and clinical responses derived from the Bayesian indirect treatment comparison.

Outcome	Placebo (control)	Adalimumab	Infliximab
Results at 8 weeks			
Clinical remission	10% (7%–14%)	20% (11%–33%)	37% (23%–55%)
Clinical response	38% (32%–44%)	53% (40%–66%)	72% (59%–82%)
Results at 52 weeks			
Clinical remission	14% (11%–18%)	25% (14%–41%)	31% (18%–47%)
Clinical response	22% (18%–28%)	34% (22%–49%)	49% (34%–65%)

Table D Number of events for each safety outcome.

	Sandborn et al. 2012 (ULTRA 2)[6]		Reinisch et al. 2011[7]			Rutgeerts et al. 2005 (ACT 1)[8]			Rutgeerts et al. 2005 (ACT 2)[8]		
	Placebo	ADA 160 mg	Placebo	ADA 80 mg	ADA 160 mg	Placebo	INF 5 mg/kg	INF 10 mg/kg	Placebo	INF 5 mg/kg	INF 10 mg/kg
Randomized, *n*	260*	257*	223**	130	223**	121	121	122	123	121	120
Results at 8 weeks											
Serious adverse events, *n* (%)	–	–	17 (13.1)	9 (6.9)	19 (14.6)	–	–	–	–	–	–
Discontinuation due to AEs, *n* (%)	–	–	5 (3.8)	6(4.6)	4 (3.0)	–	–	–	–	–	–
Results at 30 weeks											
Serious adverse events, *n* (%)	–	–	–	–	–	–	–	–	24 (19.5)	13 (10.7)	11 (9.2)
Discontinuation due to AEs, *n* (%)	–	–	–	–	–	–	–	–	12 (10.0)	2 (1.6)	5 (4.2)
Results at 52 weeks											
Serious adverse events, *n* (%)	32 (12.3)	31 (12.1)	–	–	–	31 (25.6)	26 (21.5)	29 (23.8)	–	–	–
Discontinuation due to AEs, *n* (%)	34 (13.1)	23 (8.9)	–	–	–	11 (9.1)	10 (8.3)	11 (9.0)	–	–	–

* Patient population consists of both anti-TNF naïve and anti-TNF-inadequate responders.
**Patient population consists of patients from the original protocol and the amended protocol (the latter which the efficacy results are based on).

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