Published in final edited form as:
Aliment Pharmacol Ther. 2014 April ; 39(7): 660–671. doi:10.1111/apt.12644.

Systematic review with network meta-analysis: the efficacy of anti-tumour necrosis factor-alpha agents for the treatment of ulcerative colitis.

Stidham RW[1], **Lee TC**[2], **Higgins PD**[1], **Deshpande AR**[3], **Sussman DA**[3], **Singal AG**[4], **Elmunzer BJ**[1], **Saini SD**[1], **Vijan S**[2], **Waljee AK**[1]

[1]Division of Gastroenterology and Hepatology, Department of Internal Medicine, University of Michigan Health System, Ann Arbor, MI, USA.

[2]Division of General Medicine, Department of Internal Medicine, University of Michigan Health System, Ann Arbor, MI, USA.

[3]Division of Gastroenterology, Department of Internal Medicine, University of Miami Miller School of Medicine, Miami, FL, USA

[4]Division of Digestive and Liver Diseases, Department of Internal Medicine, UT Southwestern Medical Center, Dallas, TX, USA

Summary

Background—Antibodies against tumour necrosis factor-alpha (anti-TNF) are effective therapies in the treatment of ulcerative colitis (UC), but their comparative efficacy is unknown.

Aim—To perform a network meta-analysis comparing the efficacy of anti-TNF agents in UC.

Methods—After screening 506 studies, reviewers extracted information on seven studies. Traditional meta-analysis (TMA) was used to compare each anti-TNF agent to placebo. Bayesian network meta-analysis (NMA) was performed to compare the effects of anti-TNF agents to placebo. In addition, sample sizes for comparative efficacy trials were calculated.

Results—Compared to placebo, TMA revealed that anti-TNF agents result in a higher likelihood of induction of remission and response (RR: 2.45, 95% CI: 1.72–3.47 and RR: 1.65, 95% CI: 1.37–1.99 respectively) as well as maintenance of remission and response (RR: 2.00, 95% CI: 1.52–2.62 and RR: 1.76, 95% CI: 1.46–2.14 respectively). Individually, infliximab, adalimumab and goliumumab resulted in a higher likelihood of induction and maintenance for both remission and response. NMA found nonsignificant trends in comparisons of the individual agents. The required sample sizes for direct head-to-head trials between infliximab and adalimumab for induction and maintenance are 174 and 204 subjects respectively.

Authorship

Guarantor of the article: Ryan W. Stidham and Akbar Waljee.

Author contributions: Ryan W. Stidham, Terry C. H. Lee: design, literature search, data collection, data interpretation, writing, figures, critical revision of the manuscript. Peter D. R. Higgins: conception and design, critical revision of the manuscript. Amar R. Deshpande, Daniel A. Sussman, Amit G. Singal, B. Joseph Elmunzer, Sameer D. Saini, Sandeep Vijan: data collection, critical revision of the manuscript. Akbar K. Waljee: conception and design, literature search, data interpretation, figures, critical revision of the manuscript. All authors approved the final version of the manuscript.

Declaration of personal interests: None.

Conclusions—This study demonstrates that, compared to placebo, infliximab, adalimumab and golimumab are all effective for the induction and maintenance of remission in ulcerative colitis. However, network meta-analysis demonstrates that no single agent is clinically superior to the others and therefore, other factors such as cost, safety, route of administration and patient preference should dictate our choice of anti-TNF agents. A randomised comparative efficacy trial between infliximab and adalimumab in UC is of practical size and should be performed.

Introduction

Ulcerative colitis (UC) is a chronic inflammatory disease primarily affecting the colonic mucosa. UC is characterised by a relapsing and remitting course; treatments are aimed at inducing and maintaining disease remission. UC disease activity can result in reduced quality of life, social and occupational disability, and increased health care utilisation.**1, 2** Direct costs of this condition are estimated at US $3.4–8.6 billion and could be as high as US $8.1–14.9 billion when accounting for the total economic impact of UC.**3** Medication use contributes to 25% of the direct costs of UC. However, considering that hospitalisation represents nearly 50% of direct costs and flares of disease activity nearly double the mean economic impact on the individual, improved disease control is likely to reduce the net economic burden of UC.**4**

Antibodies against tumour necrosis factor-alpha (anti-TNF) are effective therapies in the armamentarium used to treat UC. Infliximab is a chimeric monoclonal antibody against soluble and membrane-bound TNF with a murine Fc region. Adalimumab is fully humanised, but has similar action against TNF. A third anti-TNF, golimumab was recently approved in 2013 for moderate-to-severe UC. When assessed in individual randomised controlled trials (RCT), these anti-TNF therapies are approximately twice or more effective than placebo for inducing and maintaining clinical response and remission in UC.**5–10**

The comparative efficacy of individual anti-TNF therapies in UC has not been well studied. In Crohn's disease, the SWITCH randomised clinical trial suggested that at approved standard dosing, adalimumab may be less effective at inducing and maintaining remission than infliximab, although the data are inconclusive.**11** Head-to-head clinical trials among individual anti-TNF therapies have not been performed. Network meta-analysis (NMA) uses the results of direct comparisons to a common comparator (anti-TNF vs. placebo) to simulate comparisons between individual anti-TNF agents, yielding an estimate of comparative efficacy. In the absence of head-to-head RCTs, we employed both traditional and network meta-analyses of infliximab, adalimumab and golimumab clinical trials to assess comparative efficacy between anti-TNF therapies for UC.

Methods

Data sources and search

The study was conducted in accordance with the PRISMA statement.**12** The PubMed and Embase databases were used primarily to identify potentially relevant published, placebo-controlled randomised trials of anti-TNF agents for ulcerative colitis. A search of human studies in these databases from inception through 31 August 2013 was performed using

controlled vocabulary descriptors (Medical Subject Headings and Emtree) and specific keywords to represent the concepts of the inflammatory bowel diseases and therapeutic use of anti-TNF blocking agents. The studies of interest were placebo-controlled randomised, controlled studies; retrospective and observational studies were not included in any of the analyses.

The search was augmented by manual searches of reference lists from potentially relevant papers to identify any additional studies that may have been missed using the computer-assisted strategy. In addition, all available guidelines, systematic reviews and meta-analyses pertaining to the therapeutic use of anti-TNF blocking agents in the inflammatory bowel diseases were reviewed for any additional potentially relevant studies. The search was not limited by language, though a large majority of the manuscripts were originally published in English.

Study selection

Two investigators (TL, RS) independently reviewed the titles of all identified citations to generate a list of potentially relevant articles for further review. The abstracts of these articles were reviewed to identify studies suitable for inclusion in our final analyses. For a manuscript to be eligible for our study, it had to satisfy the following eligibility criteria: (i) studies had to examine the effect of a single anti-TNF agent on induction and/or maintenance of response or remission in UC; (ii) the treatment of interest was an anti-TNF agent; (iii) studies used the standard dosing regimen for the examined anti-TNF agent; (iv) studies could not duplicate data already published previously; (v) studies were published as full manuscripts; (vi) response or remission was defined by a standardised scoring criteria (typically Mayo score for UC); (vii) studies were randomised, placebo-controlled trials with treatment and control arms. Paediatric studies were excluded.

Data extraction

Two authors (TL and RS) independently extracted data from the included studies via manual review. Discrepancy between data extracted was resolved via consensus. The following data points were extracted for each study: first author; year of publication; number of centres involved (if multi-centre); drug studied, dosage and dose interval; blinding and randomisation; clinical endpoints (induction or maintenance of either clinical response or remission); the presence or absence of concomitant glucocorticoid or immunosuppressive exposure; prior anti-TNF agent exposure status; length of follow-up; the presence of a drug washout period; the numbers of patients in the treatment and control arms; the number of patients in each arm who achieved induction of response, induction of remission, maintenance of response or maintenance of remission; the study's measurement of the primary outcome. Of note, for each study, we used the number of patients randomised for the intention-to-treat sample size.

Clinical endpoints

We extracted data to evaluate four clinical endpoints: (i) Induction of Remission – defined by the Mayo Score**13** or Ulcerative Colitis Symptom Score**13** within 8 weeks of the initiation of the treatment; (ii) Induction of Response – defined as a decrease by at least 3

points and/or 30 per cent from baseline in the total Mayo score, with an accompanying decrease in the subscore for rectal bleeding of at least 1 point or an absolute subscore for rectal bleeding of 0 or 1; (iii) Maintenance of Remission – induction of remission (as above) maintained for minimum of 52 weeks; (iv) Maintenance of Response – induction of response (as above) maintained for minimum of 52 weeks.

Quality assessment

Two investigators (AD, DS) critically appraised and quality rated all eligible studies. The randomised controlled trials were assessed by criteria set forth by the Evidence-Based Gastroenterology Steering Group (EBGSG).**14** These criteria were: (i) concealed random allocation; (ii) blinding of patients and caregivers; (iii) equal use of co-interventions for the treatment and placebo groups; (iv) complete follow-up of study patients; and (v) use of an intention-to-treat analysis. Discrepancies in quality assessment were also resolved by consensus.

Data synthesis and analysis

The outcomes analysed included induction and maintenance of clinical response or remission in UC. Traditional meta-analysis was used to calculate indirect comparisons between anti-TNF drugs. Bayesian network meta-analysis (NMA) was used to perform both direct and indirect comparisons between different anti-TNF drugs, using placebo as the common comparator.

Traditional meta-analysis was used for the direct pairwise comparisons of each anti-TNF vs. placebo and was performed using random-effects meta-analysis techniques in Stata 13.0 (StataCorp, College Station, TX, USA). The differences between random effects and fixed effects were also evaluated when only a single study for a particular drug was evaluated. The Cochran Q test (χ^2) and I^2 inconsistency statistic (the percentage of total variation across studies that are due to heterogeneity rather than chance) were used to assess for statistical heterogeneity between trials.**15** When heterogeneity was present, meta-influence analysis and Galbraith plot assessment were performed to identify responsible outlier studies. Pooled relative risks (RRs) and their 95% confidence intervals (95% CIs) were estimated for the various anti-TNFs.

To compare the efficacy of the anti-TNF agents, a Bayesian network meta-analysis (NMA) was performed with the GeMTC GUI statistical package.**16** This form of meta-analysis allows for the analysis of both direct and indirect comparisons and generates estimates of effect (with 95% credible intervals) for all possible pairwise comparisons despite not being evaluated directly in a head-to-head fashion in the included clinical trials. The technique of NMA, in this situation, allows for the formation of indirect comparisons between anti-TNF agents using placebo as a common comparator. In addition, the analysis allows for the ranking of different interventions to evaluate the comparative efficacy. For each individual analysis, simulations were repeated 50 000 times to allow convergence and an additional 50 000 simulations were performed to produce the probability statements. Convergence of iterations was evaluated using Gelman–Rubin–Brooke statistic. For this analysis, Markov

chain Monte Carlo simulations were utilised to estimate posterior distributions and a non-informative uniform prior distribution of effect sizes and precision was used.

Sensitivity analyses

To assess the robustness of the results, separate traditional meta-analyses were repeated after: (i) eliminating statistical heterogeneity by removing outlier studies, (ii) excluding studies that used the UCSS instrument to assess the outcome measure and (iii) excluding the studies that continued maintenance therapy on those that responded to the induction therapy to address any variations in the study design.

Based on the results of this NMA, sample sizes for between-drug comparative efficacy studies were calculated with the *sampsi* command in Stata 13.1, assuming 80% power and a two-sided alpha of 0.05. If these direct head-to-head trials were used to inform NMAs, Thorlund *et al.* have discussed additional methods to evaluate the power and precision (sample size) in NMAs.**17**

Results

Literature search

A flow diagram depicting the search and selection process is provided in Figure 1. Initial searches of the Medline and Embase databases yielded 486 citations. A manual search of the PubMed.gov database for pertinent systematic reviews, meta-analyses and guidelines identified four summary documents, (a review of which yielded 20 additional citations), totalling 506 citations. Title review of these two groups of citations yielded 376 unique potentially relevant articles. Abstract and/or brief manuscript review of these articles yielded 12 manuscripts appropriate for detailed evaluation. Seven of the remaining manuscripts were included in the final analysis. Note that there were six individual manuscripts included, but Rutgeerts *et al.* 2005 reported the results of two separate randomised, controlled trials and therefore each trial was included as a separate study. The remaining five articles were excluded because they did not meet eligibility criteria, as detailed in the flow diagram. There was 100% agreement between reviewers regarding final study selection.

Characteristics of included studies

Characteristics of the included studies are listed in Table 1 and efficacy data in Table 2. The seven studies in six manuscripts meeting eligibility criteria included a total of 1823 subjects for induction and 1070 subjects for maintenance.**5–10** No comparative efficacy studies were identified; all included studies compared placebo to various anti-TNF therapies. Three studies compared infliximab to placebo. Among these, three studies and two studies evaluated remission and response, respectively as an endpoint for induction ($n = 529$) and one study evaluated remission and response as an endpoint for maintenance ($n = 242$). Two studies compared adalimumab to placebo, of which both evaluated remission and response as an endpoint for induction ($n = 778$) and 1 evaluated remission and response as an endpoint for maintenance ($n = 518$). Two studies compared golimumab to placebo, of which 1 evaluated remission and response as an endpoint for induction ($n = 516$) and the other evaluated remission and response as an endpoint for maintenance ($n = 310$).

Testing for heterogeneity between eligible studies

Pooled analysis of the effects of infliximab, adalimumab and golimumab on induction (remission and response) and maintenance (remission and response) demonstrated significant statistical heterogeneity in only one situation, i.e. the induction of remission among infliximab studies (I^2 = 72.8%, P = 0.025). Meta-influence analysis and visual inspection of Galbraith plots revealed that Rutgeerts 2005 (ACT 2)**9** was responsible for this heterogeneity and was likely due to the high placebo rates.

Meta-analysis results

Induction of remission and response—Compared to placebo, traditional meta-analysis revealed that anti-TNF agents result in a 2.45-fold higher likelihood of induction of remission and 1.65-fold higher likelihood of induction of response compared to placebo (RR: 2.45, 95% CI: 1.72–3.47 and RR: 1.65, 95% CI: 1.37–1.99 respectively). Individually, infliximab resulted in a 2.76-fold higher likelihood of inducing remission and 2-fold higher likelihood of inducing response compared to placebo (RR: 2.76, 95% CI: 1.29–5.90 and RR: 2.00, 95% CI: 1.64–2.44 respectively). Adalimumab resulted in a 1.87-fold higher likelihood of inducing remission and 1.36-fold higher likelihood of inducing response compared to placebo (RR: 1.87, 95% CI: 1.27–2.75 and RR: 1.36, 95% CI: 1.13–1.64 respectively). Golimumab resulted in a 3-fold higher likelihood of inducing remission and 1.75-fold higher likelihood of inducing response compared to placebo (RR: 3.00, 95% CI: 1.75–5.14 and RR: 1.75, 95% CI: 1.40–2.19 respectively). (Figure 2a, b).

Network meta-analysis of agents for induction of remission did not show significant differences between agents (RR: 2.08 for infliximab vs. adalimumab, 95% CrI: 0.32–12.03; RR: 1.18 for infliximab vs. golimumab, 95% CrI: 0.13–10.63; and RR: 1.75 for adalimumab vs. golimumab, 95% CrI: 0.17–16.86). While trends favoured infliximab over both adalimumab and golimumab, the 95% credible interval crossed 1 and was therefore not statistically significant. Infliximab was ranked the most effective drug in 55% of the simulations, while golimumab was favoured in 36% and adalimumab in 9%.

Similarly, the network meta-analysis of agents for the induction of response demonstrated no statistically significant differences between agents (RR: 2.15 for infliximab vs. adalimumab, 95% CrI: 0.73–5.80; RR: 1.48 for infliximab vs. golimumab, 95% CrI: 0.38–4.69; and RR: 1.46 for golimumab vs. adalimumab, 95% CrI: 0.42–5.38). Again, trends favoured infliximab over both adalimumab and golimumab; however, the 95% credible interval crossed 1 and was therefore not statistically significant. Infliximab was ranked the most effective drug in 80% of the simulations, while golimumab was favoured in 17% and adalimumab in 3%.

Maintenance of remission and response

Compared to placebo, traditional meta-analysis revealed that anti-TNF agents result in a 2.00-fold higher likelihood of maintenance of remission and 1.76-fold higher likelihood of maintenance of response compared to placebo (RR: 2.00, 95% CI: 1.52–2.62 and RR: 1.76, 95% CI: 1.46–2.14 respectively). Individually, infliximab resulted in a 2.10-fold higher likelihood of maintaining remission and 2.29-fold higher likelihood of maintaining response

compared to placebo (RR: 2.10, 95% CI: 1.31–3.36 and RR: 2.29, 95% CI: 1.52–3.45 respectively). Adalimumab resulted in a 2.06-fold higher likelihood of maintaining remission and 1.68-fold higher likelihood of maintaining response compared to placebo (RR: 2.06, 95% CI: 1.26–3.38 and RR: 1.68, 95% CI: 1.21–2.33 respectively). Golimumab resulted in a 1.86-fold higher likelihood of maintaining remission and 1.61-fold higher likelihood of maintaining response compared to placebo (RR: 1.86, 95% CI: 1.19–2.90 and RR: 1.61, 95% CI: 1.22–2.13 respectively – Figure 2C, D).

Network meta-analysis of agents for maintenance of remission did not show significant difference between agents (RR: 1.18 for infliximab vs. adalimumab, 95% CrI: 0.19–8.02, RR: 1.22 for infliximab vs. golimumab, 95% CrI: 0.18–8.43, RR: 1.04 for adalimumab vs. golimumab, 95% CrI: 0.16–6.96). While trends favoured infliximab over both adalimumab and golimumab, the 95% credible interval crossed 1 and was therefore not statistically significant. Infliximab was ranked the most effective drug in 45% of the simulations, while adalimumab was favoured in 28% and golimumab in 26%.

Finally, the network meta-analysis of agents for the maintenance of response demonstrated no statistically significant difference between agents (RR: 1.70 for infliximab vs. adalimumab, 95% CrI: 0.17–16.59, RR: 1.47 for infliximab vs. golimumab, 95% CrI: 0.15–14.43, RR: 1.14 for adalimumab vs. golimumab, 95% CrI: 0.11–10.92). While trends favoured Infliximab over both adalimumab and golimumab, the 95% credible interval crossed 1 and was therefore not statistically significant. Infliximab was ranked the most effective drug in 61% of the simulations, while golimumab was favoured in 22% and adalimumab in 17%.

Direct comparison sample size estimations

Using data generated by our NMA, the required sample sizes for direct comparative efficacy trials between anti-TNF agents were calculated (Table 3). Comparison of infliximab to adalimumab with 90% power would require 174 and 204 subjects to determine whether superiority exists between these agents for induction and maintenance respectively. Direct comparison of infliximab to golimumab would require 214 and 1870 subjects to determine superiority for induction and maintenance, respectively.

Publication bias

The funnel plot asymmetry test for publication bias was negative for all outcomes using the Harbord test ($P = 0.44$) for induction of remission; ($P = 0.64$) for induction of response; ($P = 0.59$) for maintenance of remission; ($P = 0.27$) for maintenance of response.

Sensitivity analyses

The sensitivity analyses did not substantively change the results. Specifically, excluding outlier studies [$n = 1$, Rutgeers 2005 (ACT 2**9**)], studies that use the UCSS instrument to assess the outcome measure ($n = 1$, Probert 2003**8**), and studies that continued maintenance therapy on those that responded to the induction therapy ($n = 1$, Sandborn *et al.***10**) in separate sensitivity traditional meta-analyses did not substantively affect composite treatment effects.

Discussion

This study demonstrates that anti-TNF agents, as a class, are more effective than placebo for both inducing and maintaining clinical response and remission in UC. However, the comparative efficacy of competing agents and the potential superiority of infliximab for ulcerative colitis remains a debated issue. Our study is the first to compare these agents through a network meta-analysis. We found that there is no clear evidence of the superiority of any agent over the others, although there was a trend towards higher rates of remission and response with infliximab.

There are no head-to-head randomised comparisons of anti-TNF agents; however, observational and nonrandomised studies support similar efficacy among anti-TNF therapies.**18–20** Retrospective studies performed in Crohn's disease and rheumatoid arthritis also failed to demonstrate any difference in efficacy between adalimumab and infliximab. For example, studies from the Netherlands and using US Medicare claims data found that CD patients receiving infliximab or adalimumab had similar rates of steroid avoidance, surgery and hospitalisation.**21, 22**

Sample size estimated using data generated by our NMA, demonstrated that while some comparative efficacy trials would require impractical sample sizes (adalimumab vs. golimumab induction, 13 562), others are quite feasible (infliximab vs. adalimumab induction, 174). These sample size estimates suggest that differential efficacy between golimumab and adalimumab may be small, but that important information could be gained from a direct comparative efficacy trial between infliximab and adalimumab, and should be performed. The results of such a trial could be used to help patients make more informed decisions about the optimal choice of agents.

In the meantime, given the lack of head-to-head trials and the lack of clear evidence of clinical superiority of one TNF agent in our analysis, providers should base their choice of TNF agent on other factors including cost, safety, route of administration and patient preferences. There are a limited number of studies on comparative cost effectiveness of anti-TNF agents. One study in CD suggested that adalimumab could result in significant cost savings of US$7000 over a 1-year period compared to infliximab.**23** Similar savings were observed in the United Kingdom without significant increases in hospitalisation, surgery or diagnostic studies and procedures, despite allowing for adalimumab dose escalation where clinically indicated.**24** Generally, safety is believed to be comparable between the anti-TNF therapies, and this has recently been comprehensively evaluated in a multiple meta-analysis for various side effects such as the risk of melanoma,**25** opportunistic infections**26** and lymphoma.**27, 28** In addition, there is data to suggest that infliximab may have higher rates of intolerance and allergy.**29** Survey studies report that patient choice of anti-TNF drug is most influenced by route of administration, with a preference for subcutaneous therapies over infusion-based therapies.**30, 31** In the absence of demonstrated variation in efficacy, economics, safety and patient preference may argue for considering subcutaneous therapies prior to infusion-based therapies when selecting anti-TNF therapy for UC.

Several limitations of this study impact interpretation of the reported results. In both NMAs and TMAs, statistical and clinical heterogeneity should be evaluated and this process includes assessing study quality and evaluating bias.

In our meta-analysis, the literature search only identified placebo-controlled RCTs, without any head-to-head comparisons; nonetheless there were notable variations in study design and conduct. For example, we included the study from Probert *et al.*, which used the UCSS tool in place of the full Mayo score to measure disease activity. However, sensitivity analysis did not reveal any significant change in the point estimate if this study was not included. Similarly, the golimumab study was performed with a different maintenance study methodology compared to the infliximab and adalimumab studies. In the golimumab maintenance study, only patients who responded to initial induction were re-randomised to golimumab or placebo. Excluding the golimumab study from the TMA did not significantly change the results but did limit the analysis to only 2 studies.

Heterogeneity in placebo remission rates between ACT-1 and 2 (14.9–16.5% at week 8 and 54), and ULTRA-1 and 2 (8.5–9.3%), suggest that variations in study conduct or design were present, and these were evaluated in sensitivity analysis. Heterogeneity in placebo rates remains a prevalent issue in inflammatory bowel disease research with no clear consensus on a single mechanism but include selection of patients, clinical characteristics, timing of clinical evaluation and inter-observer variation as suggested by Renna *et al.***32** Others have proposed alternative endpoints in the evaluation of inflammatory bowel disease trials, but this has not been widely adopted.**33**

One additional concern for NMAs is that, while we assume that studies can be combined, these assumptions must hold true over the entire network, including evaluation of the indirect comparisons between existing studies. Unfortunately, in our study, the validity of this assumption could not be evaluated, as head-to-head trials between anti-TNFs do not exist. Financial and market incentives will likely prevent head-to-head trials between anti-TNF agents for the foreseeable future, which makes this NMA the only comparative data we are likely to have. More complex assumptions do exist for NMAs, but these are not statistically based and rely on expert consensus.**34, 35**

Further, the Bayesian-driven approach used in this network meta-analysis assumed non-informative priors for treatment effects and assumed a homogenous variance between studies, which is the most common approach in NMA.**36** These unbiased assumptions are considered the most conservative approach, but may reduce the probability of identifying significant differences between treatments. Thorlund *et al.* have suggested that using informative priors to estimate variance may lead to more precise analyses and thereby increase the probability that statistically significant differences may be found between treatments.**37** The decision of whether to use informative or non-informative priors for network meta-analysis and mixed treatment comparisons remains controversial. However, a recent report by the Agency for Healthcare Research and Quality (AHRQ) evaluated various studies that used mixed treatment comparisons and concluded that based on the current literature they do not believe that there is enough data to support using informative priors.**38** Therefore, we used the more conservative approach of non-informative priors in this study,

which may have limited our study's ability to detect significant differences between the therapies. This is the primary bias in our approach, in that by choosing a conservative approach, we make it less likely to have a type I error (false positive finding) and more likely to have a type II error (false negative or absence of a difference).

Taking all this into account, NMAs provide estimates of the relative treatment effects in addition to 95% credible intervals. This in turn can be used to calculate the probability of how efficacious the therapy is compared to the other therapies as detailed above. In conclusion, infliximab, adalimumab and golimumab are all effective agents to induce and maintain clinical response in ulcerative colitis. However, network meta-analysis demonstrates that no single agent is clinically superior to the others and therefore, other factors such as cost, safety, route of administration and patient preferences should dictate our choice of anti-TNF therapy as we await the results of comparative efficacy trials. A network meta-analysis in the absence of head-to-head studies may not be able to detect small differences between anti-TNF therapies that do exist (type II error). We have excluded large therapeutic differences with the NMA.

Acknowledgements

Declaration of funding interests: Crohn's and Colitis Foundation of America (Stidham), Veterans Affairs HSR&D Career Development Awards (Waljee, Saini). The content is solely the responsibility of the authors and does not necessarily represent the official views of the VA.

References

1. Reinisch W, Sandborn WJ, Bala M, et al. Response and remission are associated with improved quality of life, employment and disability status, hours worked, and productivity of patients with ulcerative colitis. Inflamm Bowel Dis 2007; 13: 1135–40 [PubMed: 17476675]
2. Vogelaar L, Spijker AV, van der Woude CJ. The impact of biologics on health-related quality of life in patients with inflammatory bowel disease. Clin Exp Gastroenterol 2009; 2: 101–9. [PubMed: 21694833]
3. Cohen RD, Yu AP, Wu EQ, Xie J, Mulani PM, Chao J. Systematic review: the costs of ulcerative colitis in Western countries. Aliment Pharmacol Ther 2010; 31: 693–707. [PubMed: 20064142]
4. Bassi A, Dodd S, Williamson P, Bodger K. Cost of illness of inflammatory bowel disease in the UK: a single centre retrospective study. Gut 2004; 53: 1471–8. [PubMed: 15361497]
5. Reinisch W, Sandborn WJ, Hommes DW, et al. Adalimumab for induction of clinical remission in moderately to severely active ulcerative colitis: results of a randomised controlled trial. Gut 2011; 60: 780– 7. [PubMed: 21209123]
6. Sandborn WJ, van Assche G, Reinisch W, et al. Adalimumab induces and maintains clinical remission in patients with moderate-to-severe ulcerative colitis. Gastroenterology 2012; 142: 257–65.e1–3. [PubMed: 22062358]
7. Sandborn WJ, Feagan BG, Marano C, et al. Subcutaneous golimumab induces clinical response and remission in patients with moderate-to-severe ulcerative colitis. Gastroenterology 2014; 146: 85–95. [PubMed: 23735746]
8. Probert CS, Hearing SD, Schreiber S, et al. Infliximab in moderately severe glucocorticoid resistant ulcerative colitis: a randomised controlled trial. Gut 2003; 52: 998–1002. [PubMed: 12801957]
9. Rutgeerts P, Sandborn WJ, Feagan BG, et al. Infliximab for induction and maintenance therapy for ulcerative colitis. N Engl J Med 2005; 353: 2462–76. [PubMed: 16339095]
10. Sandborn WJ, Feagan BG, Marano C, et al. Subcutaneous golimumab maintains clinical response in patients with moderate-to-severe ulcerative colitis. Gastroenterology 2014; 146: 96–109. e1. [PubMed: 23770005]

11. Van Assche G, Vermeire S, Ballet V, et al. Switch to adalimumab in patients with Crohn's disease controlled by maintenance infliximab: prospective randomised SWITCH trial. Gut 2012; 61: 229–34. [PubMed: 21948942]
12. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. BMJ 2009; 339: b2700.
13. Schroeder KW, Tremaine WJ, Ilstrup DM. Coated oral 5-aminosalicylic acid therapy for mildly to moderately active ulcerative colitis. A randomized study. N Engl J Med 1987; 317: 1625–9. [PubMed: 3317057]
14. Schoenfeld P, Cook D, Hamilton F, Laine L, Morgan D, Peterson W. An evidence-based approach to gastroenterology therapy. Evidence-Based Gastroenterology Steering Group. Gastroenterology 1998; 114: 1318–25. [PubMed: 9609770]
15. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ 2003; 327: 557–60. [PubMed: 12958120]
16. GeMTC: network meta-analysis software. Available at: http://drugis.org/gemtc.
17. Thorlund K, Mills EJ. Sample size and power considerations in network meta-analysis. Syst Rev 2012; 1: 41. [PubMed: 22992327]
18. Kaymakcalan Z, Sakorafas P, Bose S, et al. Comparisons of affinities, avidities, and complement activation of adalimumab, infliximab, and etanercept in binding to soluble and membrane tumor necrosis factor. Clin Immunol 2009; 131: 308–16. [PubMed: 19188093]
19. Nesbitt A, Fossati G, Bergin M, et al. Mechanism of action of certolizumab pegol (CDP870): In vitro comparison with other anti-tumor necrosis factor α agents. Inflamm Bowel Dis 2007; 13: 1323–32. [PubMed: 17636564]
20. Vos ACW, Wildenberg ME, Duijvestein M, Verhaar AP, van den Brink GR, Hommes DW. Anti-tumor necrosis factor-α antibodies induce regulatory macrophages in an Fc region-dependent manner. Gastroenterology 2011; 140: 221–30. [PubMed: 20955706]
21. Kestens C, van Oijen MG, Mulder CL, et al. Adalimumab and infliximab are equally effective for Crohn's disease in patients not previously treated with anti-tumor necrosis factor-alpha agents. Clin Gastroenterol Hepatol 2013; 11: 826–31. [PubMed: 23376000]
22. Osterman MT, Haynes K, Delzell E, et al. Comparative effectiveness of infliximab and adalimumab for Crohn's Disease. Clin Gastroenterol Hepatol 2013; doi:10.1016/j.cgh.2013.06.010 .
23. Sussman DA, Kubiliun N, Mulani PM, et al. Comparison of medical costs among patients using adalimumab and infliximab: a retrospective study (COMPAIRS). Inflamm Bowel Dis 2012; 18: 2043–55. [PubMed: 22241679]
24. Choi GKH, Collins SDE, Greer DP, et al. Costs of adalimumab versus infliximab as first-line biological therapy for luminal Crohn's disease. J Crohns Colitis 2013; doi:10.1016/j.crohns.2013.09.017 .
25. Singh S, Nagpal SJ, Murad MH, et al. Inflammatory Bowel disease is associated with an increased risk of melanoma: a systematic review and meta-analysis. Clinical Gastroenterol Hepatol 2014; 12: 210–8.
26. Ford AC, Peyrin-Biroulet L. Opportunistic infections with anti-tumor necrosis factor-alpha therapy in inflammatory bowel disease: meta-analysis of randomized controlled trials. Am J Gastroenterol 2013; 108: 1268–76. [PubMed: 23649185]
27. Siegel CA, Marden SM, Persing SM, Larson RJ, Sands BE. Risk of lymphoma associated with combination anti-tumor necrosis factor and immunomodulator therapy for the treatment of Crohn's disease: a meta-analysis. Clinical Gastroenterol Hepatol 2009; 7: 874–81.
28. Williams CJ, Peyrin-Biroulet L, Ford AC. Systematic review with meta-analysis: malignancies with anti-tumour necrosis factor-alpha therapy in inflammatory bowel disease. Aliment Pharmacol Ther 2014; 39: 447–458. [PubMed: 24444171]
29. Du Pan SM, Dehler S, Ciurea A, et al. Comparison of drug retention rates and causes of drug discontinuation between anti-tumor necrosis factor agents in rheumatoid arthritis. Arthritis Rheum 2009; 61: 560–8. [PubMed: 19405000]

30. Chilton F, Collett RA. Treatment choices, preferences and decision-making by patients with rheumatoid arthritis. Musculoskeletal Care 2008; 6: 1–14. [PubMed: 17726671]

31. Scarpato S, Antivalle M, Favalli EG, et al. Patient preferences in the choice of anti-TNF therapies in rheumatoid arthritis. Results from a questionnaire survey (RIVIERA study). Rheumatology (Oxford) 2010; 49: 289–94. [PubMed: 19920093]

32. Renna S, Camma C, Modesto I, et al. Meta-analysis of the placebo rates of clinical relapse and severe endoscopic recurrence in postoperative Crohn's disease. Gastroenterology 2008; 135: 1500–9. [PubMed: 18823987]

33. Rangwalla SC, Waljee AK, Higgins PDR. Voting with their feet (VWF) endpoint: a meta-analysis of an alternative endpoint in clinical trials, using 5-ASA induction studies in ulcerative colitis. Inflamm Bowel Dis 2009; 15: 422–8. [PubMed: 19058232]

34. Glenny AM, Altman DG, Song F, et al. Indirect comparisons of competing interventions. Health Technol Assess 2005; 9: 1–134.

35. Song F, Loke YK, Walsh T, Glenny AM, Eastwood AJ, Altman DG. Methodological problems in the use of indirect comparisons for evaluating healthcare interventions: survey of published systematic reviews. BMJ 2009; 338: b1147.

36. Coleman CI, Phung O, Cappelleri JC, et al. Use of Mixed Treatment Comparisons in Systematic Reviews [Internet]. Rockville, MD: Agency for Healthcare Research and Quality (US), 2012.

37. Thorlund K, Druyts E, Aviña-Zubieta JA, Wu P, Mills EJ. Why the findings of published multiple treatment comparison meta-analyses of biologic treatments for rheumatoid arthritis are different: an overview of recurrent methodological shortcomings. Ann Rheum Dis 2013; 72: 1524–35. [PubMed: 23087184]

38. AHRQ. Methods Research Report - Findings of Bayesian Mixed Treatment Comparison Meta-Analyses: Comparison and Exploration Using Real-World Trial Data and Simulation. 2013: 1–143.

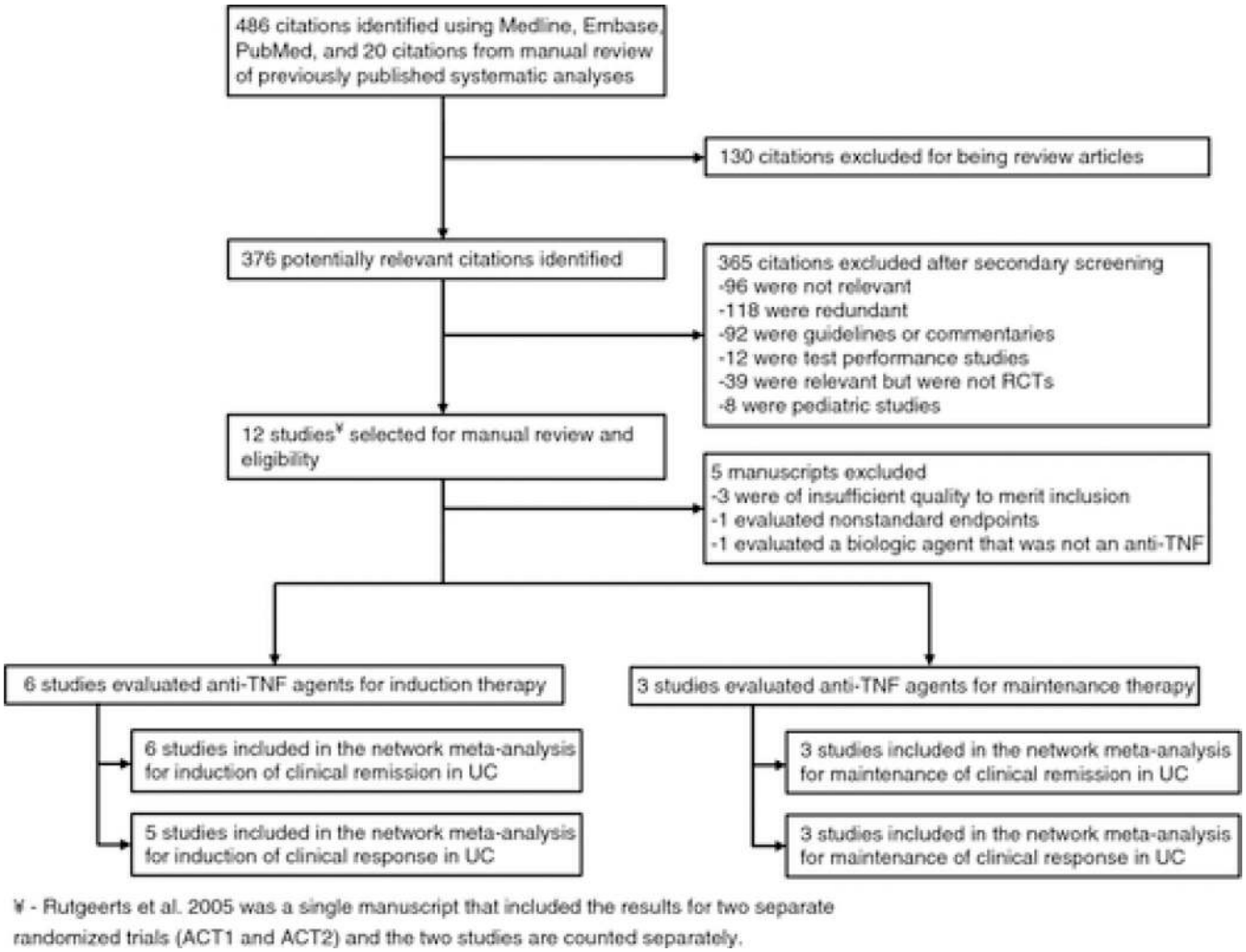
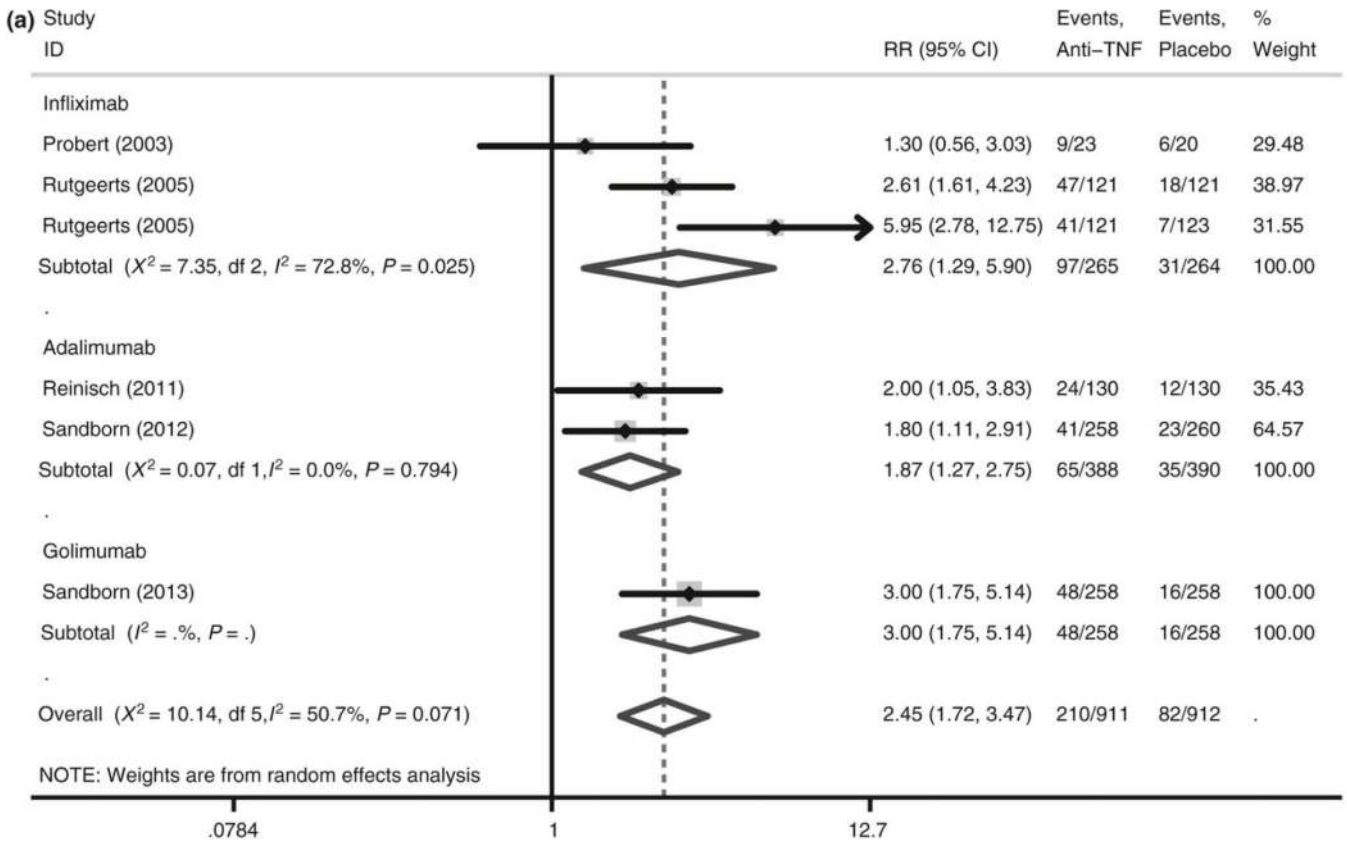
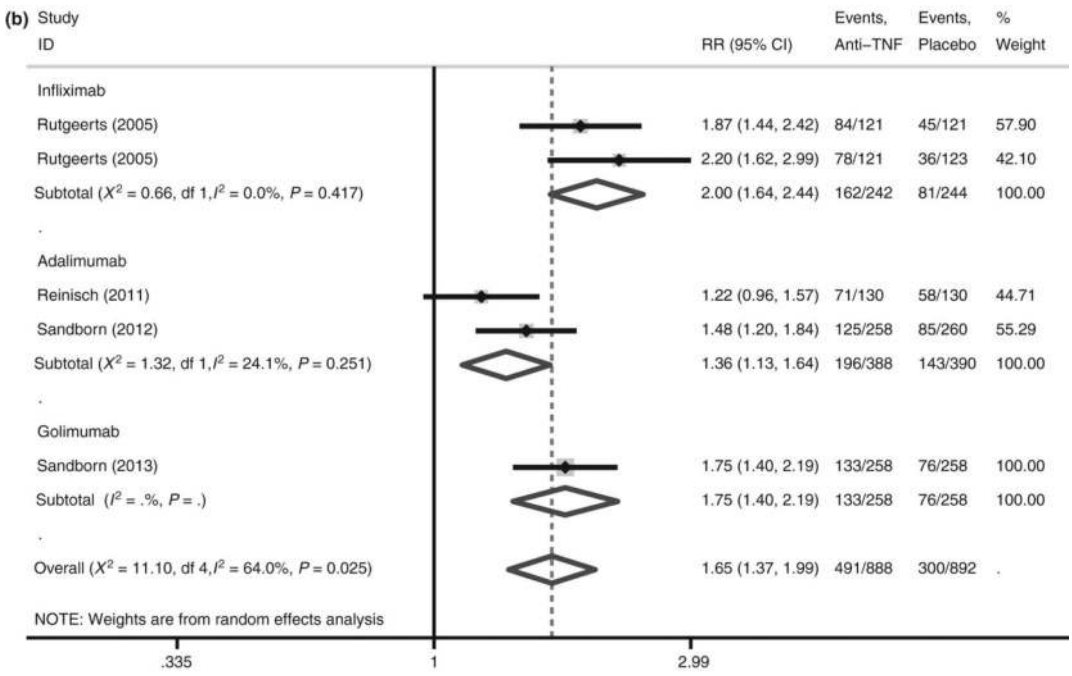
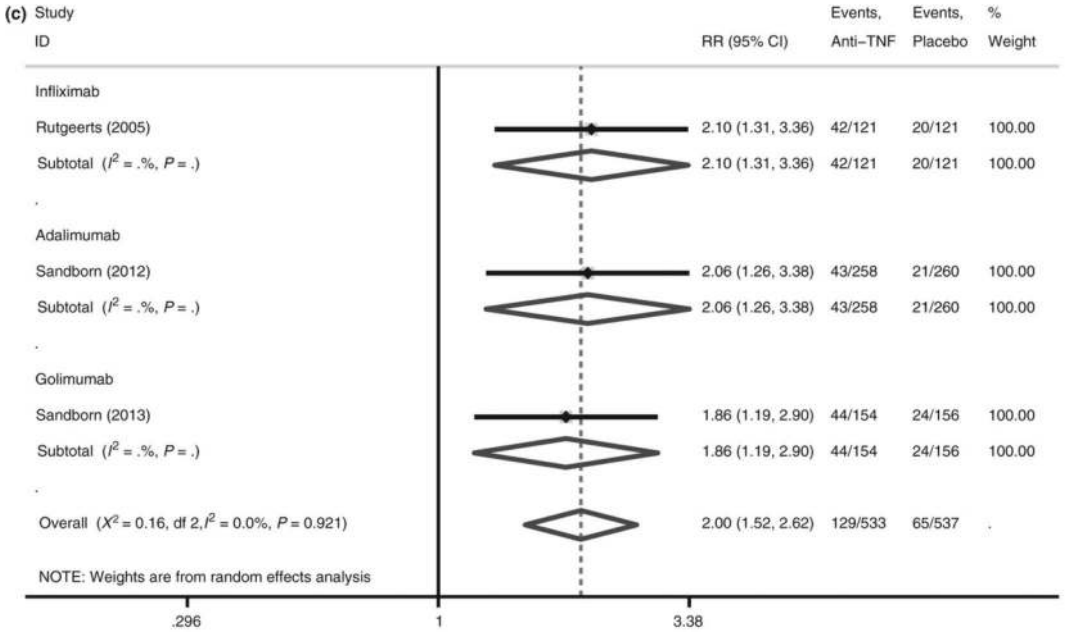


Figure 1.
Flow diagram of the search strategy and included studies in the analysis.







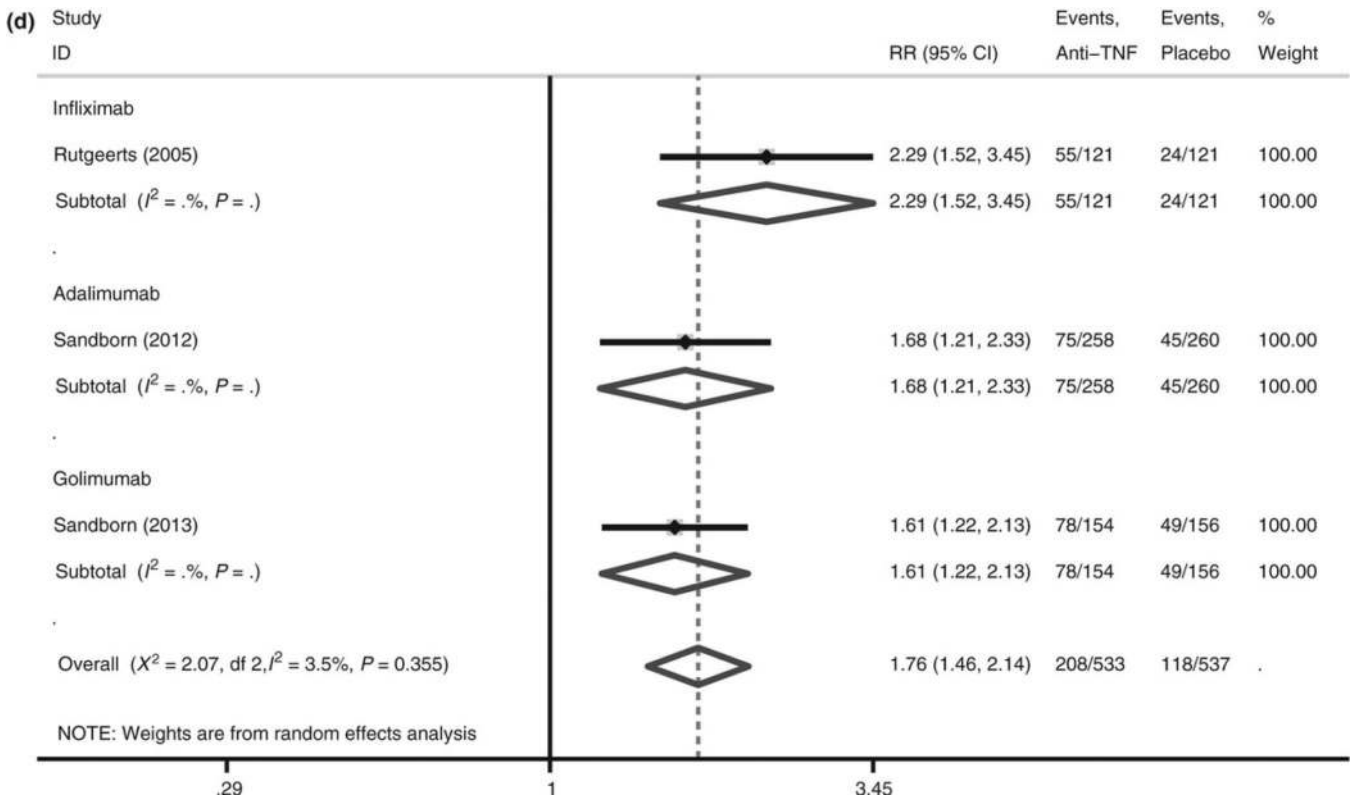


Figure 2.

Panel: Meta-analysis of anti-TNFs for the treatment of ulcerative colitis. (a) Meta-analysis of the induction of remission endpoint. (b) Meta-analysis of the induction of response endpoint. (c) Meta-analysis of the maintenance of remission endpoint. (d) Meta-analysis of the maintenance of response endpoint.

Table 1.

Study characteristics of the included studies for the use of anti-TNFs for the treatment of ulcerative colitis

Study	Drug	Dosage	Interval	Baseline meds allowed	Previous anti-TNF: Ctrl/Tx/Washout	Quality score
Induction of clinical remission in ulcerative colitis						
Reinisch *et al.*[5] (ULTRA-1)	Adalimumab	160 mg, 80 mg, 40 mg, 40 mg SC	Every 2 Weeks	CCS, 5-ASA, MCP, AZA	Not allowed	5
Sandborn *et al.*[6] (ULTRA-2)	Adalimumab	160 mg, 80 mg, 40 mg, 40 mg SC	Every 2 Weeks	CCS, 5-ASA, MCP, AZA	41.1%/39.1%/2-month washout	5
Sandborn *et al.*[7] (PURSUIT-SC)	Golimumab	200 mg, then 100 mg SC	Week 0 and 2	CCS, 5-ASA, MCP, AZA, MTX	Allowed; 12-month washout	5
Probert *et al.*[8]	Infliximab	5 mg/kg IV	Week 0 and 2	CCS, MCP, 5-ASA, AZA	Unknown but allowed; 3-month washout	4
Rutgeerts *et al.*[9] (ACT 1)	Infliximab	5 mg/kg IV	Week 0, 2 and 6	CCS, 5-ASA, MCP, AZA	Not allowed	5
Rutgeerts *et al.*[9] (ACT 2)	Infliximab	5 mg/kg IV	Week 0, 2 and 6	CCS, 5-ASA, MCP, AZA	Not allowed	5
Induction of clinical response in ulcerative colitis						
Reinisch *et al.*[5] (ULTRA-1)	Adalimumab	160 mg, 80 mg, 40 mg, 40 mg SC	Every 2 Weeks	CCS, 5-ASA, MCP, AZA	Not allowed	5
Sandborn *et al.*[6] (ULTRA-2)	Adalimumab	160 mg, 80 mg, 40 mg, 40 mg SC	Every 2 Weeks	CCS, 5-ASA, MCP, AZA	41.1%/39.1%, 2-month washout	5
Sandborn *et al.*[7] (PURSUIT-SC)	Golimumab	200 mg, then 100 mg SC	Week 0 and 2	CCS, 5-ASA, MCP, AZA, MTX	Allowed; 12-month washout	5
Rutgeerts *et al.*[9] (ACT 1)	Infliximab	5 mg/kg IV	Week 0, 2 and 6	CCS, 5-ASA, MCP, AZA	Not allowed	5
Maintenance of clinical response and remission in ulcerative colitis						
Sandborn *et al.*[6] (ULTRA-2)	Adalimumab	40 mg SC	Every 2 Weeks after induction	CCS, 5-ASA, MCP, AZA	41.1%/39.1%/2-month washout	5
Sandborn *et al.*[10] (PURSUIT-M)	Golimumab	100 mg SC	Every 4 Weeks after induction	CCS, 5-ASA, MCP, AZA, MTX	Allowed, 12-month washout	5
Rutgeerts *et al.*[9] (ACT 1)	Infliximab	5 mg/kg IV	Every 8 Weeks after induction	CCS, 5-ASA, MCP, AZA	Not allowed	5

CCS, corticosteroids; 5-ASA, 5-aminosalicylates; MCP. mercaptopurine; AZA. azathioprine; MTX. methotrexate.

Washout in all cases refers to a period free of Anti-TNF agents if previous receipt of Anti-TNF agents was allowed.

Quality Score defined by the Evidence-Based Gastroenterology Steering Group's system (EBGSG). It is a 5-point system used to assess the rigour of randomised controlled trials. The individual points are awarded for (i) concealed random allocation; (ii) blinding of patients and caregivers; (iii) equal use of co-interventions for the treatment and placebo groups; (iv) complete follow-up of study patients; and (v) use of an intention-to-treat analysis. A perfect score of 5 indicates a high quality study and lower scores indicate lower quality studies.

Table 2|

Efficacy data of the included studies for the use of anti-TNFs for the treatment of ulcerative colitis

Study	Drug	Endpoint	Follow-up (weeks)	Results Control (%)	Anti-TNF (%)
Induction of clinical remission in ulcerative colitis					
Reinisch *et al.*[5] (ULTRA-1)	Adalimumab	Clinical remission (Mayo score)	8	12/130 (9.2)	24/130 (18.5)
Sandborn *et al.*[6] (ULTRA-2)	Adalimumab	Clinical remission (Mayo score)	8	23/260 (8.8)	41/258 (15.9)
Sandborn *et al.*[7] (PURSUIT-SC)	Golimumab	Clinical Remission (Mayo score)	6	16/258 (6.2)	48/258 (18.6)
Probert *et al.*[8]	Infliximab	Clinical remission (Mayo score)	6	6/20 (30.0)	9/23 (39.1)
Rutgeerts *et al.*[9] (ACT 1)	Infliximab	Clinical Remission (Mayo score)	8	18/121 (14.9)	47/121 (38.8)
Rutgeerts *et al.*[9] (ACT 2)	Infliximab	Clinical remission (Mayo score)	8	33/123 (26.8)	41/121 (33.9)
Induction of clinical response in ulcerative colitis					
Reinisch *et al.*[5] (ULTRA-1)	Adalimumab	Clinical response (Mayo score)	8	58/130 (44.6)	71/130 (54.6)
Sandborn *et al.*[6] (ULTRA-2)	Adalimumab	Clinical response (Mayo score)	8	85/260 (32.7)	125/258 (48.4)
Sandborn *et al.*[7] (PURSUIT-SC)	Golimumab	Clinical response (Mayo score)	6	76/258 (29.5)	133/258 (51.6)
Rutgeerts *et al.*[9] (ACT 1)	Infliximab	Clinical response (Mayo score)	8	45/121 (37.2)	84/121 (69.4)
Maintenance of clinical remission in ulcerative colitis					
Sandborn *et al.*[6] (ULTRA-2)	Adalimumab	Clinical remission (Mayo score)	52	21/260 (8.1)	43/258 (16.7)
Sandborn *et al.*[10] (PURSUIT-M)	Golimumab	Clinical remission (Mayo score)	52	24/156 (15.4)	44/154 (28.6)
Rutgeerts *et al.*[9] (ACT 1)	Infliximab	Clinical remission (Mayo score)	54	20/121 (16.5)	42/121 (34.7)
Maintenance of clinical response in ulcerative colitis					
Sandborn *et al.*[6] (ULTRA-2)	Adalimumab	Clinical response (Mayo score)	52	45/260 (17.3)	75/258 (29.1)
Sandborn *et al.*[10] (PURSUIT-M)	Golimumab	Clinical response (Mayo score)	52	49/156 (31.4)	78/154 (50.6)
Rutgeerts *et al.*[9] (ACT 1)	Infliximab	Clinical response (Mayo score)	54	24/121 (19.8)	55/121 (45.5)

Remission by Mayo Score defined as total mayo score ≤2 with no individual subscore >1.

Remission by Ulcerative Colitis Symptom Score defined as UCSS ≤2.

Clinical Response by Mayo Score defined as a decrease from baseline in the total Mayo score of at least 3 points and at least 30 per cent, with an accompanying decrease in the subscore for rectal bleeding of at least 1 point or an absolute subscore for rectal bleeding of 0 or 1.

Table 3.

Total number of subjects required for comparative effectiveness RCTs between anti-TNF drugs for UC induction and maintenance

	Total subject number (Induction/Maintenance)		
	Infliximab	**Golimumab**	**Adalimumab**
Infliximab	–	214/1870	174/204
Golimumab	214/1870	–	13 562/420
Adalimumab	174/204	13 562/420	–