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Barberio, B, Black, CJ, Savarino, EV et al. (1 more author) (2020) Ciclosporin or Infliximab as Rescue Therapy in Acute Glucorticosteroid-refractory Ulcerative Colitis: Systematic Review and Network Meta-Analysis. Journal of Crohn's and Colitis. ISSN 1873-9946

https://doi.org/10.1093/ecco-jcc/jjaa226

Accepted for publication 2nd November 2020

TITLE PAGE

Title: Ciclosporin or Infliximab as Rescue Therapy in Acute Glucorticosteroid-refractory Ulcerative Colitis: Systematic Review and Network Meta-Analysis

Short running head: Ciclosporin vs Infliximab in Ulcerative Colitis: Network Meta-Analysis

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Abbreviations:

CI	confidence interval
IBD	Inflammatory Bowel Disease
UC	Ulcerative Colitis
IFX	Infliximab

Key words: infliximab; ciclosporin; rescue therapy; ulcerative colitis; glucorticosteroid-refractory

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Word count: 3747

ABSTRACT

Background: Despite randomized controlled trials (RCTs) and trial-based meta-analyses, the optimal rescue therapy for patients with acute glucorticosteroid-refractory ulcerative colitis (UC), to avoid colectomy and improve long-term outcomes, remains unclear. We conducted a network meta-analysis examining this issue.

Methods: We searched MEDLINE, EMBASE, EMBASE Classic, and the Cochrane central register to June 2020. We included RCTs comparing ciclosporin and infliximab, either with each other, or with placebo, in patients with glucorticosteroid-refractory UC.

Results: We identified seven RCTs containing 534 patients (415 in head-to-head trials of ciclosporin versus infliximab). Risk of colectomy at ≤1 month was reduced significantly with both treatments, compared with placebo (relative risk (RR) of colectomy with infliximab versus placebo = 0.37; 95% CI 0.21-0.65, RR with ciclosporin versus placebo = 0.40; 95% CI 0.21-0.77). In terms of colectomy between >1 month and <1 year both drugs ranked equally (P-score 0.75). Neither treatment was more effective than placebo in reducing risk of colectomy at ≥1 year. Both ciclosporin and infliximab were significantly more efficacious than placebo in achieving a response. Neither treatment was more effective than placebo for inducing remission, nor more likely to cause serious adverse events than placebo.

Conclusions: Both ciclosporin and infliximab were superior to placebo in terms of response to therapy and avoiding colectomy up to 1 year, with no significant differences in efficacy or safety between the two. Ciclosporin is still a valid option to treat refractory UC patients, especially those who do not respond to previous treatment with infliximab, or as a bridge to other biologic therapies.

INTRODUCTION

Ulcerative colitis (UC) is a chronic inflammatory bowel disease that causes continuous mucosal inflammation of the lower gastrointestinal tract, commencing in the rectum and extending proximally for a variable extent. There is no cure and flares of disease activity occur periodically during a patient's life.[1] The majority of patients with UC have a mild to moderate course, which is generally most active at diagnosis.[2] Nevertheless, approximately 15% of patients experience an aggressive course.[2] In addition, one-in-five patients may require hospitalization due to an acute severe exacerbation of disease activity,[2] of whom 30% will undergo colectomy within 3 months from presentation.[3] Although colectomy rates are declining in Europe and North America, contemporaneous estimates demonstrate that between 1 in 10 and 1 in 20 patients will still undergo colectomy.[4–6] Intravenous glucorticosteroids have been considered first-line management for acute severe UC for almost 50 years,[7] but 30% to 40% of hospitalized patients are refractory to this treatment.[8]

Rescue therapies for patients with acute glucorticosteroid-refractory UC can help avoid colectomy and improve long-term outcomes. Ciclosporin, a calcineurin inhibitor, was first shown to be effective in acute severe glucorticosteroid-refractory UC almost three decades ago.[9] Its use is limited to induction therapy, especially in azathioprine naïve patients, with short-term clinical response rates between 65% and 80% in randomized controlled trials (RCTs).[9,10] For many years this was the only treatment option for this group of patients but, with the advent of infliximab, a chimeric monoclonal antibody targeting tumor necrosis factor-α, and demonstrable evidence for its efficacy in acute severe UC, a second potential rescue therapy became available.[11] To date, two RCTs comparing infliximab with ciclosporin in patients with glucorticosteroid-refractory UC have demonstrated no difference in efficacy or safety between the two treatments.[12,13]

A trial-based meta-analysis, including both observational studies and RCTs, also showed no significant difference between infliximab and ciclosporin in head-to-head trials of the two drugs, although non-randomized studies suggested that infliximab was associated with a better treatment response and a lower risk of colectomy at 12 months.[14] Current data from RCTs, and even meta-analyses of RCTs, therefore suggest the two drugs are in equipoise for the treatment of glucorticosteroid-refractory UC. Network meta-analysis may be able to resolve some of this uncertainty, because the methodology employed allows indirect, as well as direct, comparisons to be made across different RCTs, increasing the number of participants' data available for analysis. In addition, this technique allows a credible ranking system of the likely efficacy of different drugs to be developed, which can aid clinical decision-making. We have therefore conducted a network meta-analysis of all available RCTs comparing ciclosporin and infliximab, either with each other, or with placebo, in patients with glucorticosteroid-refractory UC.

METHODS

Search Strategy and Study Selection

We searched the medical literature using MEDLINE (1946–June 2020), EMBASE and EMBASE classic (1947–June 2020), and the Cochrane central register of controlled trials. We hand-searched conference proceedings (Digestive Diseases Week, American College of Gastroenterology, United European Gastroenterology Week, and the Asian Pacific Digestive Week) between 1990 and 2020 to identify studies published only in abstract form. RCTs examining the effect of first rescue therapy with oral or intravenous ciclosporin or intravenous infliximab in adult patients (> 90% of participants aged >18 years) with acute glucorticosteroid-refractory UC, were eligible for inclusion (Table 1). The first period of cross-over RCTs were eligible for inclusion if they provided outcomes data prior to cross-over. Trials could compare ciclosporin and infliximab with each other, or with a placebo, and had to report one or more of the following outcomes: colectomy rates, response to therapy and/or remission after treatment, and serious adverse events. We considered trials using any dose of ciclosporin or infliximab as eligible.

We identified studies with the terms *ulcerative colitis*, *colitis*, or *acute adj5 severe colitis* (both as medical subject headings and as free text terms). We combined these using the set operator AND with studies identified with the terms: *infliximab* or *anti-TNF* (both as medical subject headings and as free text terms), or the following free text terms: *cyclosporine*, *cyclosporin*, *ciclosporine*, *ciclosporin*, *cyclosporine A*, *cyclosporin A*, *ciclosporine A*, or *ciclosporin A*. There were no language restrictions. We screened the titles and abstracts of all citations identified by our search for potential suitability and retrieved those that appeared relevant, examining them in more detail. We performed a recursive search, using the bibliographies of all eligible articles. We translated foreign language

articles, where required. Where there appeared to be multiple study reports from the same group of subjects, we contacted study authors to clarify this issue. If a study appeared potentially eligible, but did not report the data required, we contacted the first and senior authors to obtain supplementary information, maximizing available studies. We performed eligibility assessment independently. This was done by two investigators (ACF and BB), using pre-designed eligibility forms. We resolved any disagreements by consensus and measured the degree of agreement with a kappa statistic.

Outcome assessment

The primary outcome assessed was the likelihood of undergoing colectomy for all patients treated with oral or intravenous ciclosporin or intravenous infliximab, compared with each other or with placebo, as rescue therapy for acute glucorticosteroid-refractory UC. We assessed this at ≤1 month, between >1 month and <1 year, and ≥1 year. Secondary outcomes included response to therapy and rates of remission after therapy, as well as serious adverse events occurring because of therapy.

Data Extraction

All data were extracted independently by two investigators (ACF and BB) on to a Microsoft Excel spreadsheet (XP professional edition; Microsoft, Redmond, WA) as dichotomous outcomes (colectomy or no colectomy at ≤1 month, between >1 month and <1 year , and ≥1 year, response or no response to therapy, and remission or no remission). In addition, we extracted the following clinical data for each trial, where available: distribution of UC, number of centers, country of origin, dosage and schedule of infliximab or ciclosporin, duration of therapy, definition of response or remission following therapy, and duration of follow-up. We extracted data as intention-to-treat analyses, with all dropouts assumed to be

treatment failures (i.e., underwent colectomy or failed to achieve response or remission), wherever trial reporting allowed this. If the number of dropouts was not clear from the original article, we extracted data only for patients with reported evaluable data.

Quality Assessment and Risk of Bias

We used the Cochrane risk of bias tool to assess the quality of studies.[15] Two investigators (ACF and BB) assessed study quality independently. We resolved disagreements by discussion. We recorded the method used to generate the randomization schedule and conceal treatment allocation, whether participants, personnel, and outcome assessments were blinded, whether there was evidence of incomplete patient outcome data, and whether there was evidence of selective reporting of outcomes.

Data Synthesis and Statistical Analysis

We performed a network meta-analysis using the frequentist model with the statistical package netmeta (version 0.9-0), in R (version 3.6.3) to compare (directly and indirectly) the efficacy and safety of each treatment of interest across studies. We reported the results according to the PRISMA extension statement for network meta-analyses.[16] Network meta-analysis results usually give a more precise estimate of the relative efficacy and safety than results from standard pairwise analyses,[17,18] and allows treatments to be ranked in terms of efficacy to help inform clinical decisions.[19]

We examined the symmetry and geometry of the data by producing a network plot, with node sizes corresponding to the number of study participants, and connection sizes corresponding to the number of studies for each treatment. We planned to generate comparison-adjusted funnel plots to evaluate publication bias and small-study bias for all available treatment comparisons versus placebo, where sufficient studies (≥10) existed.[20] For

each treatment, we generated a pooled relative risk (RR) with 95% confidence intervals (CIs) to summarize the effect of each comparison tested, using a random effects model as a conservative estimate. We used the RR of colectomy, the RR of failure to achieve response to therapy, and the RR of failure to achieve remission as our measures of treatment efficacy, where if the RR is less than 1 and the 95% CI does not cross 1, there is a significant benefit of one treatment over another, or over placebo.

We assessed global statistical heterogeneity across all comparisons using the I^2 measure with the netmeta statistical package. The I^2 measure of heterogeneity ranges from 0% to 100%; a value of 25-49% indicates low heterogeneity, 50-74% indicates moderate heterogeneity, and 75% and above indicates high heterogeneity.[21] We ranked treatments according to their P-score, which is a value between 0 and 1. P-scores are based solely on the point estimates and standard errors of the network estimates. They measure the extent of certainty that one treatment is better, according to any given endpoint, than another treatment as an average over all other competing treatments.[22] The higher the P-score, the greater the probability of the treatment being ranked as best,[22] but the magnitude of the P-score should also be considered because, as the mean value of the P-score is always 0.5, if individual treatments cluster around this value, it is likely that they have similar efficacies. However, when interpreting the results, it is also important to take the RR and corresponding 95% CI for each comparison into account, rather than relying on rankings alone.[23] In our primary analysis, we pooled data from all included RCTs for the likelihood of undergoing colectomy at first point of follow-up, using an intention-to-treat analysis.

RESULTS

The literature search identified 1140 citations, of which 1122 were excluded on review of the title and abstract (Figure 1). We therefore identified 18 articles that appeared to be relevant to the study question. In total, nine of these articles,[9,24,25,11,26,12,27,28,13] reporting on seven separate RCTs and containing 534 subjects with acute glucorticosteroid-refractory UC, fulfilled the eligibility criteria. Three trials, reported in four papers, compared infliximab with placebo in 99 patients,[24,25,11,26] three trials, reported in four articles, compared ciclosporin with infliximab in 415 patients,[12,27,28,13] and one trial compared ciclosporin with placebo in 20 patients.[9] Agreement between investigators for assessment of study eligibility was perfect (kappa statistic = 1.00). Patients were allocated to active therapy or placebo as described in Supplementary Table 1. Detailed characteristics of the seven individual RCTs are provided in Table 2. All trials, except one,[28] were published in full. Risk of bias for all included trials is reported in Supplementary Table 2; none were at low risk of bias. There were too few studies to assess for publication bias, or other small study effects, in any of our analyses.

Colectomy

All seven RCTs, including 534 patients, reported data regarding colectomy rates ≤1 month after starting therapy.[9,24,25,11,12,28,13] There were 481 (90.1%) patients randomized to active treatment. There was no heterogeneity between studies (I^2 = 0%), and risk of colectomy at ≤1 month was reduced by a similar magnitude with both treatments, compared with placebo (RR of colectomy at ≤1 month with infliximab = 0.37; 95% CI 0.21 to 0.65, P-score 0.82, RR with ciclosporin = 0.40, 95% CI 0.21 to 0.77, P-score 0.67) (Figure 2A). This means that the probability of infliximab being the most efficacious when all treatments, including placebo, were compared with each other was 82%. On indirect comparison, there was no difference in efficacy between ciclosporin and infliximab (RR = 0.92; 95% CI 0.62 to

1.38) (Figure 2B).

Five RCTs, including 484 patients, reported data regarding colectomy between >1 month and <1 year after starting treatment.[24,25,11,12,13] There were 440 (90.9%) patients randomized to active treatment. Both drugs were ranked equally (RR of colectomy between >1 month and <1 year = 0.42; 95% CI 0.25 to 0.70 for infliximab, and RR = 0.42; 95% CI 0.23 to 0.77 for ciclosporin, P-score 0.75 for both (Supplementary Figure 1A), with no heterogeneity between studies (I^2 = 0%), and no difference between infliximab and ciclosporin on indirect comparison (RR = 1.00; 95% CI 0.72 to 1.39) (Supplementary Figure 1B).

Data regarding colectomy rates at ≥1 year were reported by four RCTs, including 460 patients, of whom 439 received active treatment.[26,27,28,13] When data were pooled there was no statistical heterogeneity between studies (I^2 = 0%), but neither treatment was more effective than placebo in terms of reducing the risk of colectomy at ≥1 year (RR of colectomy with infliximab at ≥1 year = 0.66; 95% CI 0.41 to 1.05, P-score 0.87, RR with ciclosporin = 0.72; 95% CI 0.43 to 1.21, P-score 0.55) (Figure 3A). Again, there was no difference between infliximab and ciclosporin on indirect comparison (RR = 0.91; 95% CI 0.72 to 1.15) (Figure 3B).

Response to Therapy

Five RCTs, including 459 patients, reported response to therapy with ciclosporin, infliximab, or placebo.[9,24,25,12,13] There were 427 (93%) patients randomized to active treatment. When data were pooled there was no statistical heterogeneity between studies (I^2 = 0%). Both, ciclosporin and infliximab were significantly more efficacious than placebo (RR of failure to respond to therapy with ciclosporin = 0.46; 95% CI 0.28 to 0.76, P-score 0.83, RR with infliximab = 0.48 95% CI 0.30 to 0.77, P-score 0.67). (Figure 4A). On indirect

comparison, there was no difference in efficacy between ciclosporin and infliximab (RR of failure to respond to therapy with ciclosporin versus infliximab = 0.96; 95% CI 0.79 to 1.16) (Figure 4B).

Remission

Data regarding remission rates were reported in three RCTs, including 188 patients, of whom 168 (89.4%) were randomized to active treatment (71 patients ciclosporin and 97 infliximab).[25,12,28] Again there was no significant heterogeneity between studies (I^2 = 0%). Neither treatment was more effective than placebo in terms of inducing remission (RR of failure to achieve to achieve remission with ciclosporin = 0.85; 95% CI 0.50 to 1.45, P-score 0.63, RR with infliximab = 0.87; 95% CI 0.56 to 1.34, P-score 0.59) (Supplementary Figure 2A). Again, on indirect comparison, there was no difference in efficacy between ciclosporin and infliximab (Supplementary Figure 2B).

Serious Adverse Events

All seven RCTs reported data concerning serious adverse events during treatment.[9,24,25,11,12,28,13] There were very low levels of statistical heterogeneity observed (I^2 = 8.6%). Neither drug was more likely to cause serious adverse events than placebo (RR of serious adverse events with ciclosporin = 0.54; 95% CI 0.16 to 1.85, P-score 0.78, RR with infliximab = 0.63; 95% CI 0.20 to 1.98, P-score 0.54) (Supplementary Figure 3A). Again, there were no differences between the two drugs on indirect comparison (RR = 0.85; 95% CI 0.49 to 1.48) (Supplementary Figure 3B).

DISCUSSION

Clinical guidelines recommend either ciclosporin or infliximab as rescue therapy in patients with UC who do not respond to systemic glucorticosteroids within 3 to 5 days.[29] These are rapidly effective agents and the decision regarding which one to choose as rescue therapy in daily practice is often guided by center preference and the physician's personal experience, as well as by patient age and comorbidities. To our knowledge, this is the first network meta-analysis of all available RCTs comparing ciclosporin and infliximab, either with each other, or with placebo, in patients with acute glucorticosteroid-refractory UC, and supports these recommendations. We found that risk of colectomy at ≤1 month was reduced significantly with both treatments, compared with placebo. In terms of colectomy between >1 month and <1 year after commencing treatment, both drugs were ranked equally, with almost identical estimates of efficacy, and identical P-scores. Neither treatment was more effective than placebo in terms of reducing the risk of colectomy at ≥1 year. Both ciclosporin and infliximab were significantly more efficacious than placebo in achieving a clinical response, and performance was similar. Conversely, neither treatment was more effective than placebo in terms of inducing remission. Finally, regarding the tolerability of these treatments, neither drug was more likely to cause serious adverse events than placebo. Data for individual adverse events were scarce, which precluded any meaningful analysis of this endpoint in our study.

The literature search, eligibility assessment, and data extraction for this network meta-analysis were undertaken independently by two reviewers, with any discrepancies resolved by consensus. We used an intention-to-treat analysis, with all dropouts assumed to have failed therapy, and pooled data with a random effects model, in order to reduce the likelihood that any beneficial effect of either ciclosporin or infliximab in glucorticosteroid-refractory UC has been overestimated. We extracted data during long-term follow-up, beyond 12

months, wherever these data were reported, and contacted authors of individual studies to obtain supplementary data and maximize the number of eligible RCTs in the network for each analysis. We also conducted a subgroup analysis including only trials that reported data concerning colectomy rates at <1 month, between 1 month and 1 year, and ≥1 year, in order to assess which of these drugs reduced the risk of colectomy in the longer term. Finally, there was very low or no heterogeneity between studies in all our analyses, although with only seven RCTs there would be reduced power to detect this.

There are some limitations of this study. Our conclusions are limited by the quality of the included trials, as none was at low risk of bias. Therefore, the results of the network meta-analysis should be interpreted with caution. It is well known that trials that do not report their methodology in sufficient detail tend to overestimate the efficacy of the intervention studied.[30] However, for some of the RCTs included in the network meta-analysis, particularly head-to-head trials of infliximab versus ciclosporin, it would have been very difficult to mask patients to the intervention they were assigned to, due to the difference in the methods of administration of the interventions. For instance, after continuous intravenous induction for up to 7 days, ciclosporin was then administered by mouth, unlike infliximab whose initial administration is as a single intravenous infusion in the acute phase. On a related note, the use by some trials of a single infliximab infusion, together with the fact that most trials of infliximab used a dose of 5mg/kg, may have underestimated efficacy. Multiple infusions are associated with a reduced likelihood of colectomy,[31] and accelerated dosing also appears to be more effective than standard induction.[32] A wide range of measures of treatment efficacy were used, and they were reported at various timepoints in the studies, one of which was conducted in the previous century. Likewise, data regarding colectomy were reported at different intervals across the studies, although we tried to standardize this as much as possible. However, in spite of our efforts, this may mean that transitivity, where indirect

comparisons are based on the assumption that any patient included in the network could have, theoretically, been recruited to any of the trials and assigned to any of the treatments, is violated.

Two RCTs of very similar design, the CYSIF and CONSTRUCT studies, published in 2012 and 2016 respectively, showed that there was no difference in outcomes including clinical response, colectomy, or serious adverse events between ciclosporin and infliximab in acute glucorticosteroid-refractory UC.[12,13] Subsequently, a meta-analysis including both observational studies and RCTs of infliximab versus ciclosporin found that, when only non-randomized studies were analyzed, there was a significantly lower colectomy rate at 12 months with infliximab (OR 0.42, 95% CI 0.22-0.83).[14] However, such observational cohort studies, especially retrospective ones, do not provide as robust evidence as prospective RCTs. There might be biases in relation to disease severity, prior drug exposures, drug failures, or comorbidities that could impact on the clinician's choice of therapy. When the results of RCTs were pooled in this trial-based meta-analysis there was no difference in efficacy between ciclosporin and infliximab. The two treatments have therefore remained in equipoise since the results of both the CYSIF and CONSTRUCT trials, and even this subsequent meta-analysis. This is where our network meta-analysis may be helpful, because it allows the inclusion of more randomized trials, comparing either of the drugs of interest with placebo, thereby increasing the number of patients contributing data to the analysis, and it also allows the ranking of treatments.

Our analyses demonstrated that risk of colectomy at ≤1 month and between >1 month and <1 year after starting treatment was reduced with both treatments, compared with placebo. Neither drug was more effective than placebo in terms of reducing the risk of colectomy beyond 1 year. Another meta-analysis evaluating long-term outcomes of ciclosporin and infliximab in patients with acute severe UC in observational studies and

RCTs reported a significantly higher colectomy-free survival rate with infliximab compared with ciclosporin.[33] This difference was only seen within the first 3 years after rescue therapy and was found in observational studies of infliximab but, importantly, not in RCTs.

It is well known that ciclosporin is associated with significant adverse events such as nephrotoxicity, neurotoxicity, and opportunistic infections.[34] Accordingly, it should not be used in patients with hypercholesterolemia, infection, or kidney failure.[35] However, infliximab is also associated with potentially severe adverse events including an increased risk of opportunistic infection and infusion reactions,[36] and there are concerns about its use in elderly patients.[37] Both the aforementioned meta-analyses found that there were no significant differences between infliximab and ciclosporin in terms of drug-related adverse events, serious adverse events, or mortality.[14,33] Our results also demonstrated no significant differences between the two drugs in terms of serious adverse events.

Generally, patients with glucorticosteroid-refractory UC are hospitalized for at least 1 week, and the time to response to therapy, impact of treatment on length of hospital stay, and associated treatment costs is a further important issue to consider. Interestingly, economic analyses suggest that the use of infliximab may substantially reduce the total length of hospital stay, as well as in-hospital costs.[38,39] However, the total treatment costs are higher in infliximab-treated patients,[38] and are likely to remain so, even with the advent of biosimilars.

In conclusion, this systematic review and network meta-analysis has demonstrated small differences in ranking between infliximab and ciclosporin for most endpoints we studied, including likelihood of serious adverse events, response to therapy, and colectomy, but no significant differences between efficacy of the drugs themselves on direct or indirect comparison. In the biologic era, an inclination towards use of infliximab is natural, particularly as it only needs to be administered as a single infusion initially, when utilized as rescue therapy. However, validated risk prediction models to accurately identify patients at

high risk of disease-related versus treatment-related complications, and how different treatments modify these risks, is vital to assist in choosing a tailored therapy. In addition, ciclosporin would obviously be an option in those patients who have failed therapy with infliximab previously, as a bridge to infliximab itself, or even other biologic therapies with a slower onset of action in patients with acute glucorticosteroid-refractory UC, such as vedolizumab.[40]

ACKNOWLEDGEMENTS

We thank Dr. Fabrizio Bossa and Dr. Daniela Scimeca for answering our queries about their study.

DISCLOSURES: Brigida Barberio: none. Christopher J. Black: none. Edoardo V Savarino: has received lecture or consultancy fees from Takeda, Merck & Co, Bristol-Myers Squibb, Abbvie, Amgen, Novartis, Fresenius Kabi, Sandoz, Sofar, Janssen. Alexander C. Ford: none.

SPECIFIC AUTHOR CONTRIBUTIONS: BB, CJB, EVS and ACF conceived and drafted the study. BB and ACF collected all data. BB, CJB and ACF analyzed and interpreted the data. BB and ACF drafted the manuscript. All authors commented on drafts of the paper. All authors have approved the final draft of the manuscript.

GUARANTOR OF THE ARTICLE: ACF is guarantor.

FUNDING: none

ETHICS COMMITTEE APPROVAL

Not required.

DATA AVAILABILITY STATEMENT: The data underlying this study is available within the manuscript and supplementary materials

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FIGURE LEGENDS

Figure 1. Flow Diagram of Assessment of Studies Identified in the Network Meta-analysis.

Figure 2: Network Meta-analysis of Likelihood of Colectomy at <1 Month.

Figure 3: Network Meta-analysis of Likelihood of Colectomy at ≥1 Year.

Figure 4: Network Meta-analysis of Failure to Achieve a Response to Therapy.

Figure 1. Flow Diagram of Assessment of Studies Identified in the Network Meta-analysis.

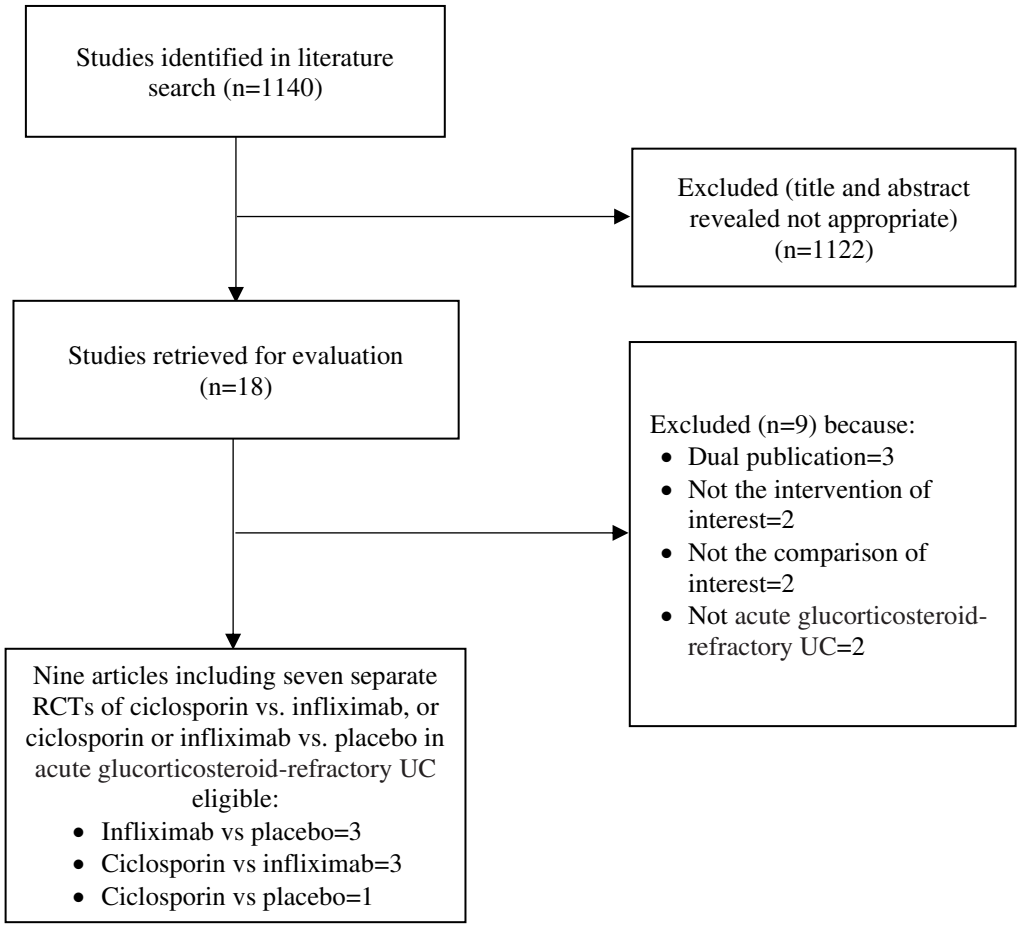
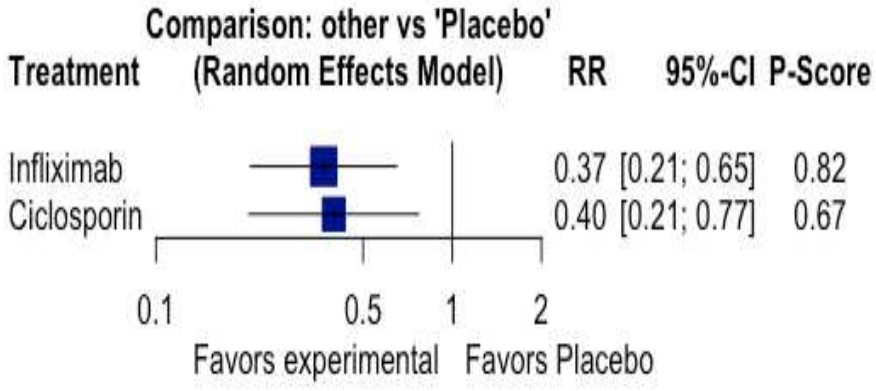


Figure 2: Network Meta-analysis of Likelihood of Colectomy at <1 Month.

A.



B.

Infliximab	**0.93 [0.61; 1.40]**	**0.37 [0.20; 0.68]**
0.92 [0.62; 1.38]	**Ciclosporin**	**0.41 [0.10; 1.75]**
0.37 [0.21; 0.65]	**0.40 [0.21; 0.77]**	**Placebo**

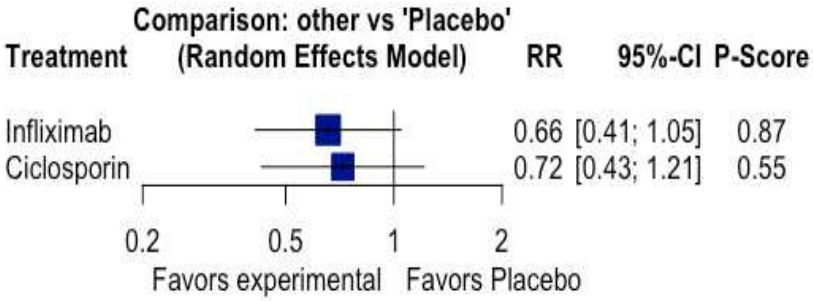
(A) Forest plot showing the relative risk of colectomy at <1 month. The P score is the probability of each treatment being ranked as best in terms of efficacy in the network.

(B) League table of pairwise comparisons in the network meta-analysis for the relative risk of colectomy at <1 month. Relative risk with 95% confidence intervals in parentheses. Comparisons, column versus row, should be read from left to right, and are ordered relative to their overall efficacy. The treatment in the top left position is ranked as best after the network meta-analysis of direct and indirect effects. Boxes

highlighted in light blue indicate significant differences. Direct comparisons are provided above the drug labels, and indirect comparisons are below.

Figure 3: Network Meta-analysis of Likelihood of Colectomy at ≥1 Year.

A.



B.

Infliximab	**0.91 [0.72; 1.15]**	**0.66 [0.41; 1.05]**
0.91 [0.72; 1.15]	**Ciclosporin**	**N/A**
0.66 [0.41; 1.05]	**0.72 [0.43; 1.21]**	**Placebo**

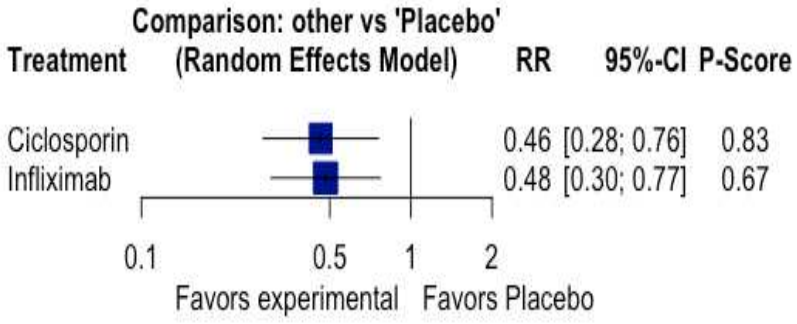
(A) Forest plot showing the relative risk of colectomy at ≥1 year. The P score is the probability of each treatment being ranked as best in terms of efficacy in the network.

(B) League table of pairwise comparisons in the network meta-analysis for the relative risk of colectomy at ≥1 year. Relative risk with 95% confidence intervals in parentheses. Comparisons, column versus row, should be read from left to right, and are ordered relative to their overall efficacy. The treatment in the top left position is ranked as best after the network meta-analysis of direct and indirect effects. Boxes highlighted in light blue indicate significant differences. Direct comparisons are provided above the drug labels, and indirect comparisons are below.

N/A; not applicable, no RCTs making direct comparisons.

Figure 4: Network Meta-analysis of Failure to Achieve a Response to Therapy.

A.



B.

Ciclosporin	**0.98 [0.81; 1.19]**	**0.22 [0.07; 0.65]**
0.96 [0.79; 1.16]	**Infliximab**	**0.57 [0.34; 0.95]**
0.46 [0.28; 0.76]	**0.48 [0.30; 0.77]**	**Placebo**

(A) Forest plot showing the relative risk of failure to achieve a response to therapy. The P score is the probability of each treatment being ranked as best in terms of efficacy in the network.

(B) League table of pairwise comparisons in the network meta-analysis for the relative risk of failure to achieve a response to therapy. Relative risk with 95% confidence intervals in parentheses. Comparisons, column versus row, should be read from left to right, and are ordered relative to their overall efficacy. The treatment in the top left position is ranked as best after the network meta-analysis of direct and indirect

effects. Boxes highlighted in light blue indicate significant differences. Direct comparisons are provided above the drug labels, and indirect comparisons are below.

Table 1. Eligibility Criteria.

Randomized controlled trials
Adults (>90% of patients aged >18 years) with acute ulcerative colitis (UC) who had failed a course of intravenous or oral steroids prior to treatment with a rescue therapy
Compared infliximab and ciclosporin with each other, or with a placebo, as rescue therapy with outcomes of interest* reported for both trial arms
Subjects not treated previously with infliximab or ciclosporin therapy during the same presentation of acute UC

*Outcomes: colectomy at ≤1 month, between >1 month and <1 year, and ≥1 year, response to therapy, remission after therapy, and serious adverse events.

Table 2. Characteristics of Randomized Controlled Trials of Infliximab or Ciclosporin Vs. Placebo or Each Other in Acute Moderate to Severe UC.

Study and year	Country, and number of centers	Disease distribution	Endpoints reported	Total number of patients	Treatments compared (number of patients in each arm)	Duration of follow up
Lichtiger 1994 [8]	USA, 2 sites	80% pancolitis, 20% left-sided	Response to therapy (Lichtiger score <10 on 2 consecutive days) Colectomy rate at ≤1 month	20	Infusion of ciclosporin 4mg/kg/day (11) versus placebo (9) for up to 2 weeks	1 month
Sands 2001 [23]	USA and Belgium, multiple sites	Not reported	Response to therapy (Truelove and Witts severity score <10 with a 5-point decrease from baseline) Colectomy rate at ≤1 month, and between >1 month and <1 year	11	Single infusion of infliximab 5mg/kg, 10mg/kg, or 20mg/kg (8) versus placebo (3)	3 months

Probert 2003 [24]	UK and Germany, 4 sites	62% pancolitis, 19% left-sided, and 19% proctosigmoiditis or proctitis	Response to therapy (≥1-point decrease in Baron score from baseline) Remission (ulcerative colitis symptom score ≤2) Colectomy rate at ≤1 month, and between >1 month and <1 year	43	Two infusions of infliximab 5mg/kg at 0 and 2 weeks (23) versus placebo (20)	8 weeks
Jarnerot 2005 [10] **and Gustavsson 2010** [25]	Sweden and Denmark, 10 sites	80% pancolitis, 20% proctosigmoiditis or proctitis	Colectomy rate at ≤1 month, between >1 month and <1 year, and ≥1 year	45	Single infusion of infliximab 5mg/kg (24) versus placebo (21)	3 years

Laharie 2012 [11] **and** **Laharie 2017** [26]	Multinational, 27 sites	57% pancolitis, 43% left-sided, proctosigmoiditis, or proctitis	Response to therapy (Lichtiger score <10 points with a 3-point decrease from baseline) Remission (mucosal healing) Colectomy rate at ≤1 month, between >1 month and <1 year, and ≥1 year	115	Infusion of ciclosporin 2 mg/kg/day for 1 week followed by oral ciclosporin until day 98 (58) versus three infusions of infliximab 5mg/kg at 0, 2, and 6 weeks (57)	5 years
Scimeca 2012 [27]	Italy, 1 site	80% pancolitis, 20% left-sided	Remission (Powell-Tuck index ≤3) Colectomy rate at ≤1 month, and ≥1 year	30	Oral ciclosporin 5 mg/kg/day (13) versus three infusions of infliximab 5mg/kg at 0, 2, and 6 weeks (17)	1 year

Williams 2016 [12]	UK, 52 sites	46% pancolitis, 47% left-sided, and 7% proctitis	Response to therapy Colectomy rate at ≤1 month, between >1 month and <1 year, and ≥1 year	270	Infusion of ciclosporin 2 mg/kg/day for 1 week followed by oral ciclosporin for 12 weeks (135) versus three infusions of infliximab 5 mg/kg at 0, 2, and 6 weeks (135)	1 to 3 years