Tumor Necrosis Factor Alpha Blocking Agents as Treatment for Ulcerative Colitis Intolerant or Refractory to Conventional Medical Therapy: A Meta-Analysis

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Abstract

Background: Efficacy of tumor necrosis factor alpha (TNF-α) blockers for treatment of ulcerative colitis that is unresponsive to conventional therapy is unclear due to recent studies yielding conflicting results.

Aim: To assess the efficacy and safety of anti-TNF-α agents for treatment of ulcerative colitis patients who were intolerant or refractory to conventional medical therapy.

Methods: Pubmed, Embase, and the Cochrane database were searched. Analysis was performed on randomized controlled trials that assessed anti-TNF-α therapy on ulcerative colitis patients that had previously failed therapy with corticosteroids and/or immunosuppressants. The primary outcome focused on was the frequency of patients that achieved clinical remission. Further trial outcomes of interest included rates of remission without patient use of corticosteroids during the trial, extent of mucosal healing, and the number of cases that resulted in colectomy and serious side effects.

Results: Eight trials from seven studies (n = 2122) met the inclusion criteria and were thus included during analysis. TNF-α blockers demonstrated clinical benefit as compared to placebo control as evidenced by an increased frequency of clinical remission (p < 0.00001), steroid-free remission (p = 0.01), endoscopic remission (p < 0.00001) and a decrease in frequency of colectomy (p = 0.03). No difference was found concerning serious side effects (p = 0.05). Three small trials (n = 57) comparing infliximab to corticosteroid treatment, showed no difference in frequency of clinical remission (p = 0.93), mucosal healing (p = 0.80), and requirement for a colectomy (p = 0.49). One trial compared infliximab to cyclosporine (n = 115), wherein no difference was found in terms of mucosal healing (p = 0.85), colectomy frequency (p = 0.60) and serious side effects (p = 0.23).

Conclusion: TNF-α blockers are effective and safe therapies for the induction and maintenance of long-term remission and prevention of treatment by colectomy for patients with refractory ulcerative colitis where conventional treatment was previously ineffective. Furthermore, infliximab and cyclosporine were found to be comparable for treating acute severe steroid-refractory ulcerative colitis.

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Introduction

Ulcerative colitis (UC) is a chronic disease characterized by diffuse mucosal inflammation within the colon, often with alternating periods of exacerbation and remission. This disease has conventionally been treated with 5-aminosalicylic acid, corticosteroids and oral immunosuppressants (e.g. azathioprine, 6-mercaptopurine) with the goals of achieving clinical or mucosal remission, and/or eliminating long-term corticosteroid use [1]. However, these conventional therapies are in many instances ineffective or cannot be tolerated by the patients. This failure to pervasively treat UC patients is apparent in the frequency of colectomies performed; the cumulative probability of colectomy from the time of diagnosis is 13.1% at 5 years, 18.9% at 10 years, and 25.4% at 20 years [2]. This deficit in widespread, effective treatment of UC patients therefore warrants the development and study of alternative treatments.

One potential alternative therapy is inhibition of tumor necrosis factor alpha (TNF-α) as previous studies have established a correlation between increased production of TNF-α and UC pathophysiology [3–6].
Currently, the anti-TNF-α agents most commonly used for UC treatment are infliximab (IFX) and adalimumab (ADA). Intravenous and subcutaneous administration of IFX and ADA, respectively, has been shown by some studies to be effective for treating moderately to severely active UC [7–10]. However, other studies pertaining to IFX treatment have yielded conflicting results [11]. Another anti-TNF-α agent, golimumab, induces and maintains clinical remission in patients with moderate to severe UC as evidenced by two recent trials [12,13]. The need for alternative UC therapies, as well as the range and conflicting reports found from studies on anti-TNF-α therapeutics, encouraged us to perform a meta-analysis to analyze the efficacy of these agents for UC patients who were intolerant or refractory to conventional medical therapy.

Several systematic reviews and meta-analyses of TNF-α blockers as treatment for UC have been published in recent years [14–17]. However, these failed to fully take into account heterogeneity between the trials analyzed, including differences in the severity of UC in patients studied, drugs administered within the control group, and the point at which patient follow-up concluded. Moreover, the doses of the anti-TNF-α agent varied between different studies that had been included. As expected, these discrepancies skew the results of the previous meta-analyses. Because of this need to account for inconsistencies within previous analyses, as well as include recent findings concerning anti-TNF-α treatment, we conducted a meta-analysis of TNF-α blockers as therapy for UC patients intolerant or refractory to conventional medical treatment. It would be very helpful for decision-making for patients with UC who do not respond well to conventional therapies, encouraging us to perform a meta-analysis to analyze the efficacy of these agents for UC patients who were intolerant or refractory to conventional medical therapy.

Methods

Search strategy

The databases Pubmed, Cochrane Library and Embase were searched for studies published between 1991 and July 20, 2013 containing the terms “(infliximab or adalimumab or certolizumab or golimumab or tumor necrosis factor alpha) and (inflammatory bowel disease or ulcerative colitis) and (trial*)”. Furthermore, the reference lists of any studies previously identified as having met the inclusion criteria were manually reviewed to find additional relevant publications.

Study selection

The titles and abstracts of published studies were screened independently by two investigators to determine whether they fulfilled the following inclusion criteria: (i) the studies had to be randomized controlled trials (RCTs) comparing anti-TNF-α therapies (e.g. adalimumab, certolizumab, golimumab, or infliximab) with the administration of a placebo or other intervention, and published in the English language, (ii) the UC patients of any age included had to have UC resistant to conventional therapy of corticosteroids and/or immunosuppressive agents, or refractory to intravenous corticosteroids, and (iii) the patients had to have been given TNF-α blockers at least twice and monitored for at least 12 weeks after the initial dose of TNF-α blocker or control drug. The primary outcome measured was frequency of clinical remission, which was defined by each of the primary studies. Secondary outcomes recorded were the frequency of long-term mucosal healing, steroid-free remission, colectomy and severe side effects. Furthermore, reviews, case reports and abstracts that lacked sufficient information to determine if the above parameters were met were excluded.

Outcome assessment

Unless otherwise defined in the primary study, clinical remission was defined either as a total Mayo score ≤2 with no individual subscore exceeding 1 point, mucosal healing was defined as an endoscopy subscore of 0 or 1. The decision to perform a colectomy was made on clinical grounds. Serious side effects were defined by each primary study.

Data extraction

All data and inclusion decisions were performed independently by two investigators. When there was disagreement between the reviewers, the cases in question were discussed and a decision to include or exclude a study was made by reviewer consensus. The information collected from each study included the type of study, number of patients enrolled in the study, experimental and control therapies used, side effects observed, duration of patient follow-up, patient baseline demographics, patient medical and UC-related history, concomitant therapy received by the patient and the trial outcomes. For instances where a patient dropped out of the study or where data was missing, an intention-to-treat principle was applied and these cases were considered as treatment failure.

Assessment of risk of bias

This data collection and assessment was performed independently by two investigators, wherein any disagreements were resolved by discussion. Risk of bias was assessed as described in the Cochrane handbook [18]: by recording the method of random sequence generation, the method of allocation concealment, whether blinding was implemented, whether incomplete outcome data was reported, whether an intention-to-treat analysis was conducted, and whether there was evidence of selective reporting of outcomes. The quality of the RCTs was assessed by the Jadad scoring system by two independent investigators [19].

Statistical Analysis

The meta-analyses were performed by using relative risk (RR) for dichotomous outcomes. Pooled estimates were presented with 95% confidence intervals (CIs). Sub-analyses were chosen based on the type of control group within the study (placebo or active interventions). Heterogeneity between studies was quantified by calculating $I^2$ where $p<0.10$ was determined significant. Where there was evidence of heterogeneity, a random-effects model was used for pooling. Otherwise, a fixed-effects model was used. Funnel plots were not conducted to investigate publication bias as there were not enough studies included in each comparison to produce a meaningful analysis. All statistical analyses were executed on RevMan 5.2 software. Results were analyzed according to the intention-to-treat principle.

Results

Literature retrieval

The previously described search strategy identified 1911 citations, of which, 1890 were excluded after examination of the title and abstract (Figure 1). 21 articles reporting on the efficacy of anti-TNF-α therapies in UC were then further evaluated [8–13,20–33]. 14 of these 21 articles were excluded: 4 due to use of...
only a single infusion of anti-TNF-α agents [20–23], 3 because the
duration of patient follow-up lasted fewer than 12 weeks [10–12], 4
because the enrolled participants [13,29,30] or outcome(s) assessed
[24] failed to meet the inclusion criteria, 1 because there was no
placebo used [31], and 2 because the papers were published only
as an abstract [32,33].

The remaining 7 studies were used for meta-analysis [8,9,25–
28], 1 study reported on 2 separate trials [8], bringing the total
number of trials analyzed to 8. Of these trials, 2 compared
infliximab or adalimumab treatment to placebo, 3 compared
infliximab treatment to corticosteroid, and 1 compared infliximab
to cyclosporine. The characteristics and trial design of the included
studies were shown in Table 1 and Table 2, respectively.

Methodological quality of included studies

The assessment of the risk of bias was summarized in Figures 2
and Figure 3. Overall, the quality of the studies ranged from
moderate to high (Jadad score ≥3). Two studies were rated at high
risk of bias due to lack of proper blinding controls [25,27]. All data
were analyzed in accordance with the intention-to-treat principle.
Due to an insufficient number of studies to produce a meaningful
analysis, funnel plots were not used to investigate publication bias.

Data synthesis: Clinical remission

The frequency of clinical remission of patients treated with
TNF-α blockers was studied in 6 trials that consisted of 1279
patients. Of these 6 trials, 3 trials were controlled by administering
a placebo. Patients were treated with infliximab in 2 of the trials
and adalimumab in 1. No significant heterogeneity was detected
between these trials ($I^2 = 0\%$, $p = 0.57$). A pooled analysis using
fixed-effects models showed that the TNF-α blocker was signifi-
cantly superior to placebo for maintenance of clinical remission
($RR = 2.29; 95\% [1.73, 3.03], Z = 5.78, p < 0.00001$, Figure 4). In 3
of the trials, infliximab treatment was compared with glucocorticoid.
The control group within these trials consisted of patients given
methylprednisolone in 2 of the trials and prednisolone in the other trial.
There was no significant heterogeneity found among the trials
($I^2 = 0\%$, $p = 0.61$). Based on fixed-effects models, there was no significant difference in
clinical remission rates between the anti-TNF-α agents and
glucocorticoid treatment ($RR = 1.01; 95\% [0.73, 1.42], Z = 0.09,
p = 0.93$, Figure 4).

Data synthesis: Mucosal healing

Mucosal healing was evaluated in 5 trials, consisting of 1345
patients, to determine TNF-α blocker treatment efficacy. Of these, 3
trials compared anti-TNF-α agents with a placebo control.
Patients were given infliximab in 2 trials and adalimumab in the
third trial. No heterogeneity was detected when comparing these 3
trials ($I^2 = 37\%$, $p = 0.20$). A pooled analysis using fixed-effects
models showed the TNF-α blocker was significantly superior to
placebo for healing of the mucosa ($RR = 1.89; 95\% [1.55, 2.31],
p < 0.00001$, Figure 5). Only 1 trial included in our analysis
compared infliximab with prednisolone. This trial found that
infliximab and prednisolone are equally effective as cyclosporine in
sustaining mucosal healing in UC ($RR = 1.04; 95\% [0.70, 1.55], p = 0.85$).

Data synthesis: Steroid-free remission

Of the trials included in our analysis, 3, consisting of 698
patients, reported discontinued corticosteroid use and sustained
steroid-free remission during their study. Of these, infliximab
treatment efficacy was examined in 2 trials and adalimumab in 1
trial. No heterogeneity was detected when comparing the 3 trials
($I^2 = 4\%$, $p = 0.35$). A pooled analysis utilizing fixed-effects models
was conducted. It was shown that the proportion of patients who
achieved steroid-free remission was higher in groups that received
the TNF-α blockers than in the placebo treated groups ($RR = 2.97; 95\% [1.77, 4.96],
p < 0.00001$, Figure 6).

Data synthesis: Colectomy rate

The rate of colectomy was only reported within 3 of the
included trials, which evaluated a total of 863 patients. The data
demonstrated that more patients in the placebo group (36/244)
than in the infliximab group (46/484) had a colectomy, as shown
in Figure 7. This difference in colectomy rate is statistically
significant ($RR = 0.64; 95\% [0.43, 0.97], p = 0.03$, Figure 7),
indicating the benefit of infliximab treatment. In another trial, methylprednisolone was shown that the colectomy rate was
equivalent between those receiving infliximab and those receiving
prednisolone ($RR = 3.00; 95\% [0.14, 65.90], p = 0.49$, Figure 7).
Finally, 1 trial administered cyclosporine within the control group.
This trial found that infliximab is as effective as cyclosporine in
preventing patient colectomy ($RR = 1.22; 95\% [0.57, 2.60],
p = 0.60$, Figure 7).

Data synthesis: Serious side effects

Serious side effects were reported in 6 of the trials, consisting of
2088 patients. Within these trials, the frequency of serious side
effects was 16.9% in the anti-TNF-α group, 20.0% in the placebo
group and 24.7% in cyclosporine group. Of these, 4 trials
administered a placebo as a control and 1 used cyclosporine.
Significant heterogeneity was not detected when comparing these
trials ($I^2 = 34\%$, $p = 0.19$). A pooled analysis using fixed effects
models showed the occurrence of serious side effects was
equivalent between TNF-α and placebo receiving patients
($RR = 0.83; 95\% [0.69, 1.00], Z = 1.98, p = 0.05$, Figure 8). Also,
no significant difference was found between the anti-TNF-α group

Figure 1. Study flow diagram.
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recipients and the cyclosporine recipients in terms of serious side effects (RR = 0.63; 95% [0.30, 1.34], Z = 1.19, p = 0.23, Figure 8).

Discussion

Refractory UC treatment is one of the most challenging aspects in the clinical practice of luminal gastroenterology. UC patients who have frequent disease relapse, despite receiving the optimal conventional medical treatments, have few remaining non-surgical options. However, TNF-α inhibition offers a possible alternative therapy for UC patients who are treatment refractory or intolerant to corticosteroids and/or immunosuppressants. In the present study, we analyzed RCTs studying the efficacy of TNF-α blockers where the duration of patient follow-up continued for at least 12 weeks post initial treatment. We found that TNF-α blockers are effective and relatively safe therapies for maintaining long-term remission and preventing colectomy in patients with refractory UC. Of the available TNF-α blockers, infliximab and cyclosporine are comparable when used as rescue therapy in acute severe steroid-refractory UC.

UC is a chronic inflammation of the colon with states of disease that can range from dormant to refractory. Conventional therapy against UC includes a wide range of drugs, such as aminosalicylic acids, thiopurines, and corticosteroids. However, these agents fail to adequately control the disease in a large proportion of UC patients and are associated with many adverse side effects [34,35]. It has now been recognized that treatment goals should go beyond just controlling the symptoms of UC. Rather, UC treatment should aim to rapidly induce steroid-free remission, and achieve complete mucosal healing, while minimizing serious complications and side effects [36]. Due to the introduction of newer biological therapies, such as anti-TNF-α, these treatment goals are within the realm of possibility.

Of the developed anti-TNF-α therapies, infliximab, adalimumab and golimumab have been approved by the Food and Drug Administration (FDA) for the treatment of UC. The efficacy of such agents in steroid-refractory UC was first shown in a controlled pilot study [23]. Later, however, a larger placebo controlled trial (n = 43) failed to support the efficacy of infliximab in active glucocorticoid resistant cases [11]. Subsequently,

| Table 1. Baseline characteristics of included studies. |
|----------------|-----------|----------|--------------|------------------|
| Study          | Case (n)  | Mean age (years) | Duration (years) | Co-therapy permitted |
| Armuzzi 2004   | 20        | 36.3            | -              | NR               |
| Gavalas 2007   | 24        | 47.8            | 58             | AZA, Steroids, 5-ASA |
| Laharie 2012   | 115       | 37.5            | 52.2           | AZA, Antibiotics, nutritional; CS tapered. |
| Ochsenkühn 2004 | 13       | 37.4            | 46.2           | Mesalazine, sulfasalazine, antibiotics, or anti-diarrheal drugs at stable doses |
| Rutgeerts 2005 ACT1 | 364 | 41.9           | 74             | CS alone or in combination with AZA or MP  |
| Rutgeerts 2005 ACT2 | 364 | 40.0           | 71.7           | CS alone or in combination with AZA or MP and 5-ASA Double-blind, RCT (6) |
| Sandborn 2009  | 728       | 41.0            | 60.0           | CS and/or AZA or 6-MP and/or 5-ASA Double-blind, RCT (6) |
| Sandborn 2012  | 294       | 40.4            | 59.5           | CS and/or AZA or 6-MP; CS tapered Double-blind, RCT (4) |

Note: NR, Not reported; AZA, Azathioprine; 5-ASA, 5-aminosalicylates; CS, corticosteroids; MP, mercaptopurine; RCT, randomized controlled trial.

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| Table 2. Trial design of included studies. |
|----------------|-----------|----------|--------------|------------------|
| Study          | Participants(UC) | Intervention | Control | Follow-up | Outcome |
| Armuzzi 2004   | Steroid-dependent | Infliximab | Methylprednisolone | 9.8±1.1 months | Clinical remission; colectomy rate |
| Gavalas 2007   | Steroid-dependent | Infliximab | Methylprednisolone | 21 months | Clinical remission |
| Laharie 2012   | Not respond to intravenous steroid | Infliximab | Ciclosporin | 98 days | Mucosal healing; colectomy rate; safety; serious adverse events. |
| Ochsenkühn 2004 | Refractory to 5-aminosalicylates. | Infliximab | Prednisolone | 13 weeks | Clinical remission; mucosal healing |
| Rutgeerts 2005 ACT1 | Not respond to conventional therapy | Infliximab | Placebo | 54 weeks | Clinical remission; mucosal healing; steroid-free remission; serious adverse events. |
| Rutgeerts 2005 ACT2 | Not respond to conventional therapy | Infliximab | Placebo | 30 weeks | Clinical remission; mucosal healing; steroid-free remission; serious adverse events. |
| Sandborn 2009  | Not respond to conventional therapy | Infliximab | Placebo | 54 weeks | Colectomy rate; serious adverse events. |
| Sandborn 2012  | Not respond to conventional therapy | Adalimumab | Placebo | 54 weeks | Clinical remission; mucosal healing; steroid-free remission; serious adverse events. |

Note: UC, Ulcerative colitis.
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increasingly controlled trials were designed to assess the effect of infliximab and adalimumab on refractory UC. Two recent well controlled trials showed that golimumab could induce a clinical response, as evidenced by clinical remission and mucosal healing in patients with active UC [12,13]. Unfortunately, both trials were excluded in our analyses due to a failure to follow-up with patients for at least 12 weeks after the initial treatment [12] and the enrolled patients are those who were response to golimumab therapy [13], respectively. Therefore, only infliximab and adalimumab were pooled for analysis within this study.

The rigorous inclusion criteria employed during our literature search returned 8 trials described in 7 published studies (n = 1922) that were hence pooled for meta-analysis. Among these studies, infliximab and adalimumab were compared to a placebo controlled group in 3[8,28] and 1 trial[s] [9], respectively. The patients in the first 3 trials were randomized to receive infliximab at doses of 5 or 10 mg/kg via intravenous, or the matched placebo at weeks 0, 2, and 6, and then every 8 weeks[8,28]. The patients in the fourth trial[s] were randomly assigned to receive subcutaneous injections of 160 mg adalimumab at week 0, 80 mg at week 2 and then 40 mg EOW beginning at week 4, or the matched placebo[9]. These studies concluded that anti-TNF-α therapy was slightly a little superior than administration of a placebo for treatment of UC patients in terms of clinical remission, mucosal healing, steroid-free remission, and reduction of colectomy rate, without causing serious side effects. Therefore, TNF-α blockers are an effective and relatively safe therapy to maintain long-term remission and avoid colectomy for patients who are not responsive to conventional treatment. Additionally, 3 small trials (n = 57) compared infliximab to steroid treatment. There were no statistically significant difference found in terms of frequency of clinical remission, mucosal healing and colectomies. However, this conclusion is unreliable due to the low number of patients in these trials. Moreover, one RCT trial (n = 115) compared infliximab to cyclosporine for use as rescue therapy for acute severe UC patients who were not responsive to intravenous steroid treatment. It was found that these drugs were comparable for rate of clinical remission, mucosal healing, colectomies rate and serious side effects. This result confirmed the conclusions from a previous meta-analysis, which pooled six retrospective cohort studies but did not include RCTs [37].

Besides the efficacy, the possible side effects of TNF-α blocker treatment were of interest when conducting this study. The main
### Figure 4. Pooled outcome for clinical remission in patients exposed to TNF-α blocker vs. controls.

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| Study or Subgroup | TNF-α blocker | Control | Total | Weight | Risk Ratio M-H, Fixed, 95% CI |
|-------------------|---------------|---------|-------|--------|-----------------------------|
| Rutgeerts 2005 ACT 1 | 112           | 243     | 355   | 40.1   | 2.53 [1.70, 3.79]           |
| Rutgeerts 2005 ACT 2 | 124           | 37     | 161   | 12.5   | 1.71 [1.27, 2.30]           |
| Sandborn 2012     | 62            | 246     | 308   | 4.0    | 1.62 [1.13, 2.33]           |
| Subtotal (95% CI) | 298           | 97      | 395   | 37.1   | 1.89 [1.55, 2.31]           |
| Heterogeneity: Chi² = 3.19, df = 2 (P = 0.20); I² = 37% |
| Test for overall effect: Z = 6.23 (P < 0.00001) |

### Figure 5. Pooled outcome for mucosal healing in patients exposed to TNF-α blocker vs. controls.

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| Study or Subgroup | TNF-α blocker | Control | Total | Weight | Risk Ratio M-H, Fixed, 95% CI |
|-------------------|---------------|---------|-------|--------|-----------------------------|
| Rutgeerts 2005 ACT 1 | 112           | 243     | 355   | 40.1   | 2.53 [1.70, 3.79]           |
| Rutgeerts 2005 ACT 2 | 124           | 37     | 161   | 12.5   | 1.71 [1.27, 2.30]           |
| Sandborn 2012     | 62            | 246     | 308   | 4.0    | 1.62 [1.13, 2.33]           |
| Subtotal (95% CI) | 298           | 97      | 395   | 37.1   | 1.89 [1.55, 2.31]           |
| Heterogeneity: Chi² = 3.19, df = 2 (P = 0.20); I² = 37% |
| Test for overall effect: Z = 6.23 (P < 0.00001) |
side effects that have been recorded are an increased risk of infections, occurrence of autoimmune disorders [28], and risk of lymphoma or other malignancy [9]. In the present study, we found the risk of serious side effects were similar between anti-TNF-α and the control (p<0.00001, Figure 8). Overall, serious side effects occurred in 20% of patients within the placebo group and 16.9% of patients within the anti-TNF-α group. However, the rate of adverse events (AE) for AE’s for combined immunomodulator/
anti-TNF therapy compared to each used as monotherapy beyond conventional treatment is a source of controversy. More studies with larger sample size are needed in future trials to further evaluate the rate serious infection due to the limit sample size in the current ones.

When performing a meta-analysis, caution needs to be used when drawing conclusions based on pooled studies of heterogeneous patient populations. To control for this heterogeneity, only the studies that had enrolled patients refractory to conventional treatment (e.g. steroid-dependent, nonresponsive to intravenous steroid or nonresponsive to conventional therapy) were included. Furthermore, trials of only a single infusion of anti-TNF-α and/or a patient follow up duration of less than 12 weeks were excluded. To statistically control any further heterogeneity in the meta-analysis, we used a random effects model to analyze if there was heterogeneity among the trials. Also, subgroup analyses were performed based on the interventions applied in the control group. It should be noted that the majority of the included studies were judged to be of “moderate to high” quality without publication bias during our analysis.

Despite rigorous inclusion criteria that have been made to reduce the heterogeneity there are still several limitations within this study. First, the duration of patient follow up within the analyzed trials was still variable, ranging from 13 weeks to 54 weeks. Second, UC severity was not uniform upon trial initiation. Some trials enrolled patients that were steroid-dependent/refractory, while others enrolled those nonresponsive to intravenous steroid therapy and/or oral conventional drugs treatment. Third, the co-therapy scheme and dose administered of TNF-α blockers differed between trials. All of these instances of variability could affect the results drawn from our analysis.

In summary, this meta-analysis has updated the UC treatment field and demonstrated that TNF-α blockers were superior for patient treatment as compared to placebo. This conclusion was based on increased achievement of clinical remission and mucosal healing and reduction in the need for colectomy, combined with no significant, severe side effects. Using anti-TNF-α also spares patients the effects of corticosteroid treatment, which is used when the patients have refractory UC nonresponsive to conventional treatment. Additionally, infliximab and cyclosporine are comparable when used as rescue therapy in acute severe steroid-refractory UC, although, more randomized trials are needed to further evaluate the efficacy of these agents. So, in selected patients with moderate to severe active ulcerative colitis who have failed to respond or are poorly responsive to standard pharmacologic forms of treatment with corticosteroids and immunosuppressive agents, therapy with an anti-TNF-α agent may be considered. In addition, it may be necessary to identify biomarkers that indicative of patients who will respond to the TNF-α inhibitor.

Supporting Information

Checklist S1  PRISMA checklist.

Author Contributions

Conceived and designed the experiments: RXL, WGQ, XBZ. Performed the experiments: RXL, ZYW, QL. Analyzed the data: WGQ, YJW, SXD. Contributed reagents/materials/analysis tools: ZYW, QL. Wrote the paper: RXL, WGQ. Provided clinical advice: XBZ, QL.

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