

The efficacy and safety of infliximab and calcineurin inhibitors in steroid-refractory UC patients: A meta-analysis

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Abstract

Background: Infliximab (IFX) and calcineurin inhibitors (cyclosporine [CYS] and tacrolimus [TAC]) were considered as rescue therapy in steroid-refractory ulcerative colitis (UC). The objective of our study was to perform a meta-analysis evaluating the short-term and long-term efficacy and safety of IFX and calcineurin inhibitors in steroid-refractory UC.

Methods: We systematically searched the databases from inception to September 2020 that evaluated IFX, CYS, and TAC in steroid-refractory UC. The primary outcome was the response rates, remission rates, mucosal healing rates, and colectomy rates after therapy initiation. The secondary outcomes were the rates of adverse events (AE), serious adverse events (SAE), and mortality. Odds ratios (OR) with 95% confidence intervals (CIs) were calculated.

Results: Nineteen studies comprising 1323 Acute severe ulcerative colitis (ASUC) patients were included in the meta-analysis. Among the non-randomized studies, a significantly higher therapeutic response rate was seen with IFX treatment, with a pooled OR of 3.15 (95% CI 2.26–4.40). Among non-randomized studies, IFX was associated with a significantly lower first-year OR (0.46 [95% CI 0.27–0.79]), second-year (OR 0.53 [95% CI 0.28–0.97]), third-year (OR 0.43 [95% CI 0.24–0.75]) colectomy rate. But the randomized controlled trials (RCTs) did not suggest any difference between IFX and CYS as rescue therapies for steroid-refractory UC. There were no significant differences among IFX, CYS, and TAC in the rates of AE, SAE, or mortality.

Conclusion: Our meta-analysis suggested a better treatment response rate and lower risk of colectomy in the first, second and third year, with IFX, compared with CYS in steroid-refractory UC patients. There was no significant difference among IFX and calcineurin inhibitors in AE, SAE, and mortality.

Keywords: Colectomy, cyclosporine, infliximab, meta-analysis, tacrolimus, ulcerative colitis

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INTRODUCTION

Ulcerative colitis (UC) is a common type of inflammatory bowel disease that is characterized by the course of remission and relapse.^[1] To induce remission, most patients with mild UC are initially treated with 5-aminosalicylates (5-ASA) or corticosteroids.^[2] However, as approximately 30% of moderate to severe UC patients are steroid-resistant or

steroid-dependent,^[3] these UC patients often need to be treated with antitumor necrosis factor- α (anti-TNF- α) agents or calcineurin inhibitors.^[4] Rescue therapies such as anti-TNF- α and calcineurin inhibitors for steroid-refractory UC patients can help avoid colectomy and improve short-term and long-term outcomes.

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IFX is a chimeric Immunoglobulin G (IgG) 1 monoclonal antibody designed to bind TNF- α . It has now become an alternative treatment in UC. In clinical trials (ACT1 and ACT2), IFX was shown to be superior to placebo at achieving and maintaining clinical remission.^[5] However, some potentially severe adverse events (SAE) such as opportunistic infections, reactivation on latent tuberculosis, or infusion reactions may occur in some UC patients.^[6]

Calcineurin inhibitors, such as cyclosporine (CYS) and tacrolimus (TAC), are immunosuppressive agents, which can be used to induce remission in steroid-refractory UC.^[7,8] CYS is a calcineurin and cytochrome P450 inhibitor immunosuppressant blocking the transcription of cytokine genes (interleukin-2 and -4) in activated T cells, thereby reducing the intestinal inflammation of UC patients.^[5] CYS was demonstrated to be an effective remission-inducing therapy for steroid-refractory UC in a clinical trial,^[6] but is associated with significant side effects such as opportunistic infections and nephrotoxicity. Therefore,

strict drug-level monitoring of CYS is required in the management of UC patients.^[7] TAC is a newly developed calcineurin inhibitor that inhibits the transcription of interleukin-2 and interferon-gamma in T lymphocytes.^[8] TAC has a 30-fold to 100-fold greater immunosuppressive effect *in vitro* and a 10-fold to 20-fold greater effect *in vivo* than CYS, as well as more reliable intestinal absorption. Therefore, it is considered that TAC is more effective against steroid-refractory UC than CYS. Because UC is a chronic disease with the risk of repeating aggravation and remission, it is important to select appropriate remission-inducing therapy with a long-lasting remission effect.

Although IFX and calcineurin inhibitors are recognized as important therapeutic agents for UC, the mechanism of action of IFX and calcineurin inhibitors are completely different. Therefore, it is difficult to determine which medication is more appropriate in steroid-refractory UC. A number of studies compared the efficacy and

Table 1 The characteristics of included studies

Author	Year	Country	Type	Age (years)	Male (%)	Disease duration	Extensive colitis (%)	Drug intervention	Quality of evidence
Kitayama ^[9]	2020	Japan	Retrospective	46.5 (32-60.25)	51.3	61 (24-132) months	64.7	TAC vs IFX	moderate
Matsumoto ^[10]	2017	Japan	Retrospective	37 (14-78)	34	4.7 (0-18.0) years	75	TAC vs IFX	moderate
Endo ^[11]	2016	Japan	Retrospective	24 (12-59)/30 (12-67)	64.2	4 (0.6-32)/3.8 (0.1-18) years	66.3	TAC vs IFX	moderate
Inaba ^[12]	2016	Japan	Retrospective	-	-	-	-	TAC vs IFX	very low
Protic ^[13]	2014	Switzerland	Retrospective	39.5 (16-90)	61.8	5.0 (0-35) years	64.5	TAC vs IFX	low
Laharie ^[14]	2018	France	RCT	36 (26-51)/39 (26-50)	36	2.5 (0.5-7.3)/0.8 (0.1-4.4) years	57	CYS vs IFX	moderate
Williams ^[15]	2016	UK	RCT	39.3 \pm 15.5/39.8 \pm 15	63	-	43	CYS vs IFX	low
Laharie ^[16]	2012	France	RCT	36 (26-52)/39 (26-50)	52	2.4 (0.4-7.1)/1.0 (0.2-4.4) years	57	CYS vs IFX	moderate
Ordas ^[17]	2017	Spain	Retrospective	40 (13-83)/36 (9-83)	58	20.0 (0-351)/37.5 (0-260) months	76	CYS vs IFX	low
Duijvis ^[18]	2016	Netherlands	Retrospective	35.5 \pm 15.4/37.7 \pm 13.6	56	34.5 (8.3-107.3)/48.0 (14.5-144.8) months	49	CYS vs IFX	low
Kim ^[19]	2015	Korea	Retrospective	44 (15-71)/56 (22-72)	65	121.4 (0-216)/76.3 (0-192) months	47	CYS vs IFX	low
Naves ^[20]	2014	Spain	Retrospective	38 (27-56)/42 (30-50)	60	42 (2-93)/37 (4-96) months	70	CYS vs IFX	low
Protic ^[13]	2014	Switzerland	Cohort study	39 (16-90)	62	5.0 (0-35)/4.0 (0-22) years	65	CYS vs IFX	moderate
Nelson ^[21]	2014	USA	Retrospective	41 (18-85)/34 (21-61)	58	2.5 (0-30)/2.0 (0-17) years	63	CYS vs IFX	very low
Lynch (2008) ^[22]	2013	UK	Cohort study	38 (28-49)/40 (29-52)	57	-	NA	CYS vs IFX	very low
Lynch (2010) ^[22]	2013	UK	Cohort study	36 (26-57)/40 (28-55)	57	-	NA	CYS vs IFX	very low
Croft ^[23]	2013	Australia	Cohort study	26 (20-43)/28 (20-37)	51	3.57 (0.77-8.2)/0.34 (0.03-2.82) years	74	CYS vs IFX	moderate
Dean ^[24]	2012	New Zealand	Retrospective	25 (16-85)/31 (15-56)	46	36 (0-360)/12 (0-168) months	38	CYS vs IFX	low
Mocciaro ^[25]	2012	Italy	Retrospective	37 \pm 16.6/34.9 \pm 13.7	46	36 (1-588)/48 (4-348) months	75	CYS vs IFX	moderate
Sjoberg ^[26]	2012	Sweden	Retrospective	38 (17-60)/32 (17-72)	55	-	78	CYS vs IFX	moderate
Daperno ^[27]	2004	Italy	Retrospective	43.2 (15.3-89.1)	58	-	61	CYS vs IFX	very low

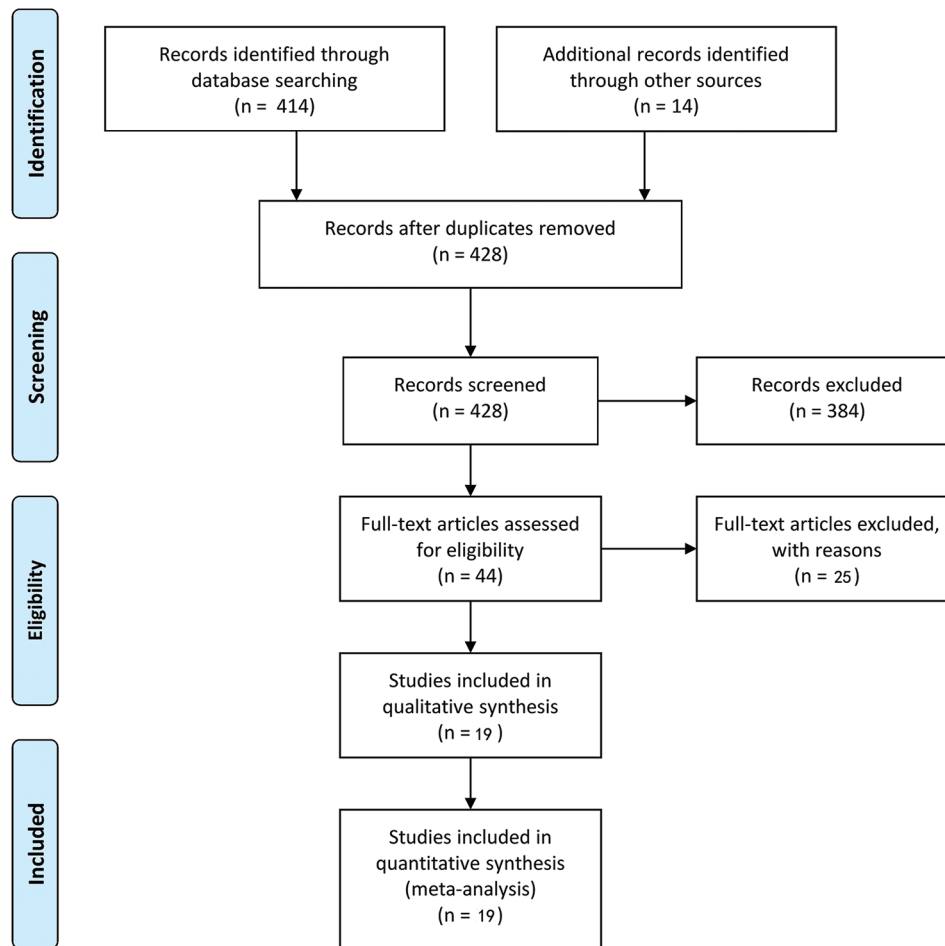


Figure 1: A flow diagram of articles retrieved and inclusion progress through the stage of meta-analysis

safety of IFX and calcineurin inhibitors in patients with steroid-refractory UC. However, their results were not consistent. To summarize the pertinent data, we performed a systematic review and meta-analysis to compare the efficacy and safety of IFX and calcineurin inhibitors in steroid-refractory UC.

METHODS

Literature search

We comprehensively and systematically searched the databases including Medline (OvidSP), Web of Science, PubMed, Cochrane Library, and EMBASE for eligible studies from inception to August 2019. Language restrictions were not used. The search strategy used the following terms: “Infliximab,” “IFX,” “anti-TNF,” “Calcineurin inhibitors,” “cyclosporine,” “cyclosporin,” “tacrolimus,” “TAC,” “ulcerative colitis,” “UC,” “colitis.” References and reviews of the related literature were searched manually.

The studies discussed a population of patients with steroid-refractory UC who received IFX or calcineurin

inhibitors as salvage therapy. The primary outcomes were therapeutic response rates, therapeutic remission rates, mucosal healing rates, and colectomy rates after therapy initiation. Secondary outcomes were the rates of adverse events (AE), SAE, and mortality.

Study selection

Articles were first screened by two independent reviewers (CD and QC) based on the title and abstract. The full text of a potentially eligible study was then assessed independently. Disagreements were resolved by discussion (MJ). A study was included if it met the inclusion criteria as follows: (1) UC patients being refractory to IV or oral steroid treatment; (2) IFX and calcineurin inhibitors were used as salvage therapy after 3–7 days of steroid treatment; (3) the response rates, the remission rates, mucosal healing rates, colectomy rates, the rates of AEs, SAE, and mortality were assessed.

Data extraction and quality assessment

The two investigators (QC and MJ) who performed the database searches also independently extracted the relevant

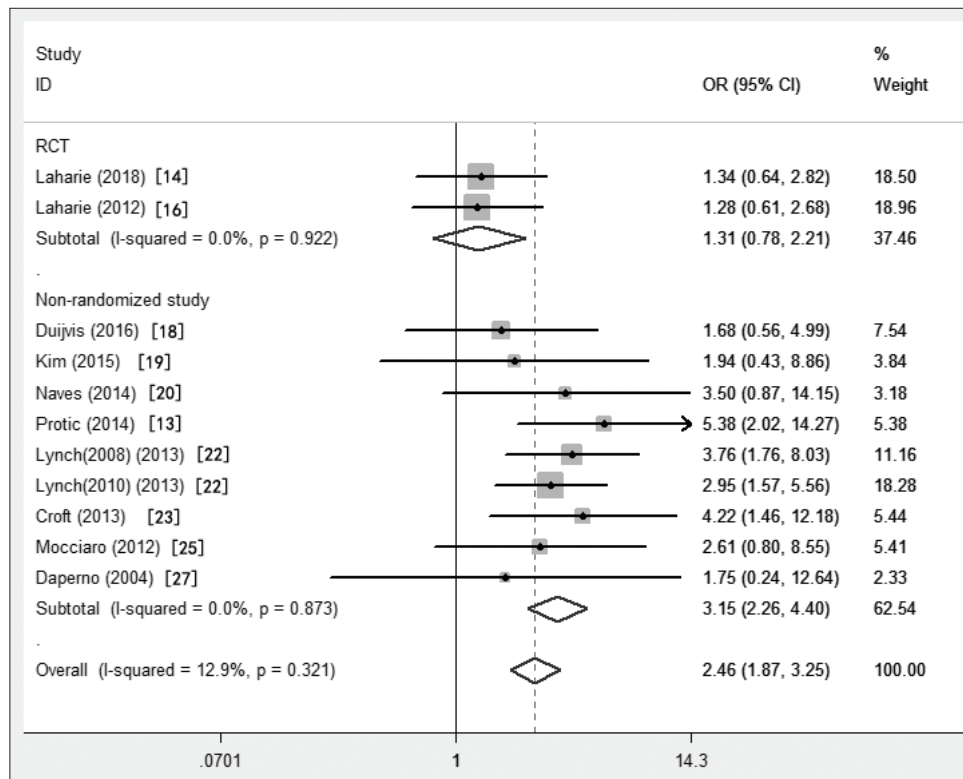


Figure 2: Forest plot of all studies reporting treatment response rate of IFX vs CYS

data. The retrieved data included information on authors, publication year, country, study type, age, male to female ratio, disease duration, the rates of extensive colitis, and drug intervention.

The methodological quality of the included observational studies was independently assessed by two authors (MJ and CD) using the Newcastle-Ottawa scale (NOS). The NOS comprises three key domains: selection and comparability of the groups, and the ascertainment of the outcome. And the methodological quality of the included RCTs was independently assessed by two authors (MJ and CD) using the Cochrane Collaboration scale. This approach requires studies to be assessed across six domains that are subject to potential bias, including sequence generation, allocation concealment, blinding, incomplete outcome data, selective outcome reporting, and other sources of bias. In case of disagreement, a consensus was reached by consultation with the senior reviewer (MJS). We then used the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system to determine the quality of evidence. GRADE uses several domains including design, consistency, precision, directness, and publication bias to rate the quality of evidence as high, moderate, low, or very low.

Data synthesis and statistical analysis

Meta-analysis of aggregate patient data was conducted by combining the odds ratios (OR) of individual studies into

a pooled OR using a random-effects model or fixed-effects model. We tested for heterogeneity using the I^2 -test. The I^2 -test describes the percentage of variability in effect estimates that is due to heterogeneity rather than chance, wherein an I^2 -test $>50\%$ suggests significant heterogeneity. If heterogeneity was observed among the studies, the random-effects model was used to estimate the pooled OR. Otherwise, the fixed-effects model was adopted. For assessment of publication bias, we performed funnel plots and calculated Bgger's regression intercept for studies that report therapeutic response. A two-tailed P value <0.05 was considered statistically significant. We performed statistical analysis on Stata (version 12).

RESULTS

Study characteristics

Figure 1 shows 428 articles available after the initial search. After reading the titles and abstracts and reviewing the full texts, 19 publications including 1,323 steroid-refractory UC patients were included in the meta-analysis.^[9-27] There were 616 patients treated with IFX, 536 patients treated with CYS, and 171 patients treated with TAC. The clinical characteristics of the included studies are listed in Table 1. There are 4 cohort studies, 14 retrospective studies, and 3 RCTs. The diagnostic criteria of UC used in these studies were the

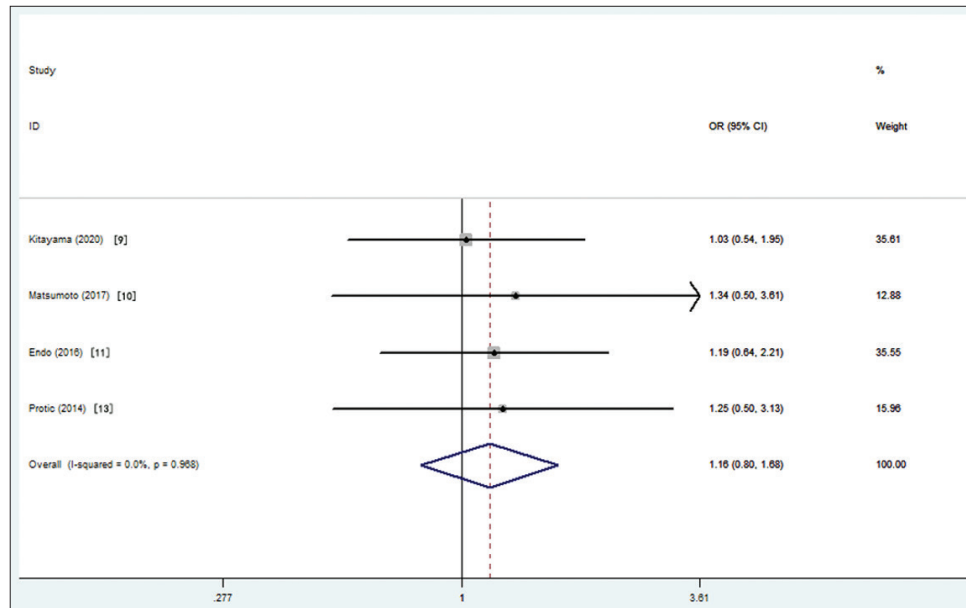


Figure 3: Forest plot of all studies reporting treatment response rate of IFX vs. TAC

Truelove and Witts criteria, the Montreal severity score, the Mayo and the Lichtiger scores.

Standard 5 mg/kg dose of IFX was administered in multiple IV infusions (at 0, 2, and 6 weeks) following the induction protocol. Then IFX was administered every 8 weeks. In most of the studies, the standard 2 mg/kg/day IV CYS regimen was applied while, oral CYS was used for induction of remission only in two studies. TAC was administered orally at an initial dose of 0.05 or 0.1 mg/kg/day. The dosage was adjusted to reach a whole-blood trough level of 10–15 ng/mL (a high trough level), and this level was maintained for 2 weeks. Subsequently, the trough level was adjusted to 5–10 ng/mL (a low trough level), and TAC was continued for up to 3 months for the purpose of remission induction.

Therapeutic response rates

Eleven studies (two RCTs and nine non-randomized studies) reported a therapeutic response rate and included 470 patients who received IFX, and 536 patients who received CYS. The pooled OR for therapeutic response rate among two RCTs was 1.31 (95% CI 0.78–2.21, $P = 0.922$, $I^2 = 0\%$) [Figure 2]. The pooled response rate in RCTs was 46.4% for those receiving IFX and 39.8% for those receiving CYS. Among non-randomized studies, a significantly higher therapeutic response rate was seen with IFX treatment, with a pooled OR of 3.15 (95% CI 2.26–4.40, $P = 0.873$, $I^2 = 0\%$) [Figure 2]. The pooled response rate in non-randomized studies was 73.5% in the group receiving IFX and 51.2% in the CYS group.

Four retrospective studies reported a therapeutic response rate and included 146 patients who received IFX and 171 patients who received TAC. The pooled OR for therapeutic response rate for steroid-refractory UC was 1.16 (95% CI 0.80–1.68, $P = 0.968$, $I^2 = 0\%$) [Figure 3].

Therapeutic remission rates

Four retrospective studies reported a therapeutic remission rate and included 121 patients who received IFX and 172 patients who received TAC. The pooled OR for therapeutic remission rate for steroid-refractory UC was 1.08 (95% CI 0.75–1.55, $P = 0.774$, $I^2 = 0\%$) [Figure 4].

Mucosal healing rates

Two retrospective studies reported mucosal healing rates and included 60 patients who received IFX and 56 patients who received TAC. The pooled OR for mucosal healing rate for steroid-refractory UC was 0.90 (95% CI 0.44–1.85, $P = 0.389$, $I^2 = 0\%$) [Figure 5].

Colectomy rates

Ten studies (two RCTs and eight non-randomized studies) reported the 3-month colectomy rates and included 518 patients who received IFX and 768 patients who received CYS. The pooled OR for 3-month colectomy rates among two RCTs was 0.95 (95% CI 0.60–1.50, $P = 0.476$, $I^2 = 0\%$) [Supplemental Figure 1]. Among the non-randomized studies, no statistically significant difference could be detected between the two groups in 3-month colectomy rate, with a pooled OR of 0.58 (95% CI 0.29–1.17, $P = 0.01$, $I^2 = 62.2\%$) [Supplemental Figure 2].

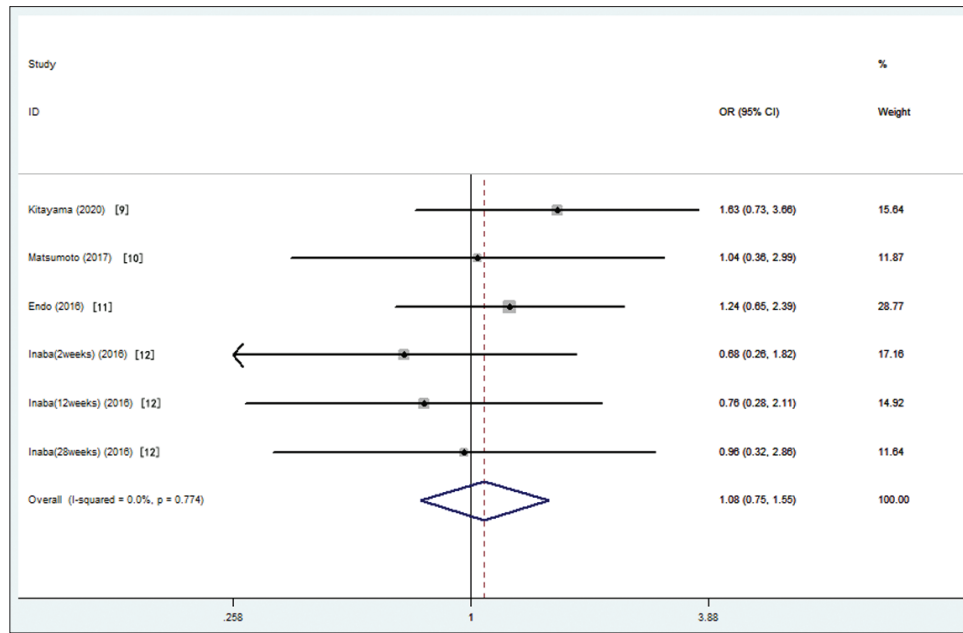


Figure 4: Forest plot of all studies reporting treatment remission rate of IFX vs. TAC

Fourteen studies (3 RCTs and 11 non-randomized studies) reported first-year colectomy rates and included 797 patients who received IFX and 1,091 patients who received CYS. The pooled OR for first-year colectomy rates among three RCTs was 0.74 (95% CI 0.52–1.07, $P = 0.597$, $I^2 = 0\%$) [Supplemental Figure 1]. Among the non-randomized studies, a significantly lower first-year colectomy rate was seen with IFX treatment, with a pooled OR of 0.46 (95% CI 0.27–0.79, $P = 0.00$, $I^2 = 69\%$) [Supplemental Figure 2].

Six studies (two RCTs and four non-randomized studies) reported second-year colectomy rates. The pooled OR for second-year colectomy rates among two RCTs was 0.71 (95% CI 0.47–1.06, $P = 0.907$, $I^2 = 0\%$) [Supplemental Figure 1]. Among the non-randomized studies, a significantly lower second-year colectomy rate was seen with IFX treatment, with a pooled OR of 0.53 (95% CI 0.28–0.97, $P = 0.556$, $I^2 = 0\%$) [Supplemental Figure 3].

Seven studies (two RCTs and five non-randomized studies) reported third-year colectomy rates. The pooled OR for third-year colectomy rates among two RCTs was 0.75 (95% CI 0.50–1.12, $P = 0.696$, $I^2 = 0\%$) [supporting information Figure 1]. Among the non-randomized studies, significantly lower third-year colectomy rate was seen with IFX treatment, with a pooled OR of 0.43 (95% CI 0.24–0.75, $P = 0.04$, $I^2 = 60.2\%$) [Supplemental Figure 3].

Three non-randomized studies reported fourth-year colectomy rates. Among these studies, no statistically significant difference could be detected between the two groups in fourth-year colectomy rate, with a pooled OR of 0.79 (95% CI 0.37–1.69, $P = 0.845$, $I^2 = 0\%$) [Supplemental Figure 3].

Three non-randomized studies reported fifth-year colectomy rates. Among these studies, no statistically significant difference could be detected between the two groups in fifth-year colectomy rate, with a pooled OR of 0.80 (95% CI 0.55–1.16, $P = 0.037$, $I^2 = 69.6\%$) [Supplemental Figure 3].

Two non-randomized studies reported sixth-year colectomy rates. Among these studies, no statistically significant difference could be detected between the two groups in sixth-year colectomy rate, with a pooled OR of 1.74 (95% CI 0.78–3.87, $P = 0.161$, $I^2 = 49.2\%$) [Supplemental Figure 3].

Rates of AE, SAE, and mortality

Six studies (one RCT and five non-randomized studies) assessed AE between the IFX group and CYS group. Seventy-six (25.2%) AEs were reported with IFX and ninety-two (33.5%) with CYS. The pooled OR of AEs rate was 0.60 (95% CI: 0.20–1.82, $P = 0.015$) among five non-randomized studies, demonstrating no significant difference between the two groups [Supplemental Figure 4]. Four retrospective studies assessed AEs between the IFX group and TAC group. The pooled OR of AEs rate for steroid-refractory UC was 0.54 (95%

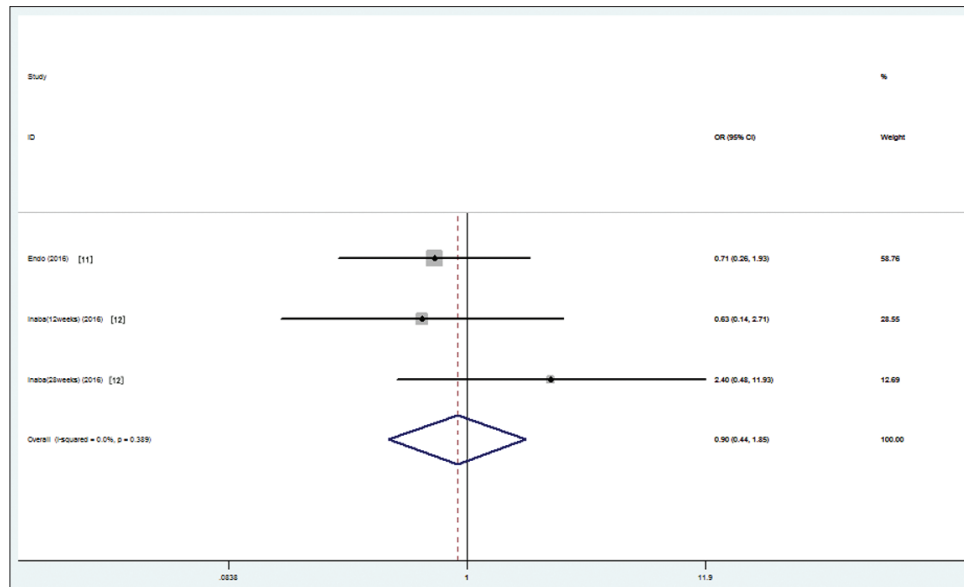


Figure 5: Forest plot of all studies reporting mucosal healing rate of IFX vs. TAC

CI: 0.12–2.40, $P = 0.013$), demonstrating a significant difference between the two groups [Supplemental Figure 5].

Six studies (two RCT and four non-randomized studies) reported on SAE such as opportunistic infections, sepsis, anaphylactic reaction, and hepato- and nephrotoxicity between the IFX group and CYS group. Seventy-four (16.2%) SAEs were reported with IFX and ninety-six (14.7%) with CYS. The rate of SAE was not elevated with IFX compared to that with CYS (OR = 1.38, 95% CI: 0.98–1.94, $P = 0.164$). In the subgroup analysis of non-randomized studies, IFX was associated with a higher SAE rate (OR = 1.73, 95% CI: 1.10–2.72, $P = 0.298$). However, in the subgroup analysis of RCTs, no statistically significant difference could be detected between the two groups (OR = 1.04, 95% CI: 0.62–1.75, $P = 0.174$) [Supplemental Figure 6].

Fourteen studies (3 RCT and 11 non-randomized studies) assessed mortality between IFX group and CYS group. There was no significant difference between the two groups in the rate of mortality (OR: 0.69, 95% CI: 0.30–1.59, $P = 0.464$). At the same time, no statistically significant difference could be detected in the subgroup analysis of RCTs (OR = 1.36, 95% CI: 0.33–5.61, $P = 0.112$) or non-randomized studies (OR = 0.48, 95% CI: 0.16–1.46, $P = 0.643$) [Supplemental Figure 7].

Methodological quality assessment

According to the GRADE system for assessing quality, evidence from RCTs begins with a “high” rating. We downgraded the rating because of the risk of bias in some RCTs, given that patients and clinicians were not blinded, and

due to the impreciseness of the treatment effect. Evidence from non-randomized studies begins with a “moderate” rating. We downgraded the rating to “low” because of the risk of bias in some observational studies. The risk of bias included no data on the selection process, no comparison was performed based on age or extent of disease, and incomplete follow-up without explanation of the loss. The methodological quality of the included studies is listed in Table 1.

Publication bias

A funnel plot was performed for the analysis of publication bias for studies that reported therapeutic response rates. Bgger’s test revealed no evidence of publication bias (Bgger’s t value = 0.31; $P = 0.755$). At the same time, a funnel plot was performed for the analysis of publication bias for studies that reported therapeutic remission rates, mucosal healing rates, colectomy rates, and rates of AEs. Bgger’s test revealed no evidence of publication bias.

DISCUSSION

Steroid-refractory UC is associated with high morbidity and is a great challenge for physicians and surgeons. During UC treatment, early identification of steroid refractoriness and early introduction of salvage treatments are crucial to avoid colectomy and mortality. IFX, CYS, and TAC are the most commonly used salvage treatments. Salvage treatments with IFX, CYS or TAC are of great interest, as approximately 60% of severe UC patients may fail initial therapy following a lack of response to intravenous steroids.^[28] Although the efficacy and safety of IFX, CYS, and TAC are well-established, a few studies have directly compared the efficacy and safety between these three

agents. In order to compare the efficacy and safety of these three agents in these UC patients, we performed a systematic review and meta-analysis. This meta-analysis attempts to provide guidance on the salvage treatments for steroid-refractory UC patients.

Our meta-analysis included three RCTs, fourteen retrospective studies, and four cohort studies, but a discrepancy in the results of this meta-analysis is seen between RCTs and the non-randomized studies. The RCTs did not suggest any difference between IFX and CYS as rescue therapies for steroid-refractory UC. But the non-randomized studies suggested that IFX may be associated with an increased therapeutic response rate and decreased colectomy rate in the first, second, and third years, compared with CYS. However, neither RCTs nor non-randomized studies detect any difference in the rate of AE, SAE, and mortality between the two groups. A recent meta-analysis examining IFX versus CYS for steroid-refractory UC found no difference in the colectomy rates at 3 and 12 months but included only six retrospective trials in their analysis. The long-term outcomes seem to favor IFX, as it is associated with a rate of colectomy in the first, second, and third years, that is significantly lower than that seen with CYS. The observational literature is particularly informative here, as few RCTs data examine this outcome. One potential explanation for this is that oral CYS has not been studied in UC as a maintenance agent. These patients with CYS are often switched to thiopurine (such as AZA) maintenance therapy, which does not have impressive remission rates. In contrast, patients with IFX can continue IFX for maintenance therapy. Theoretically, long-term CYS use has been associated with significant long-term complications including nephrotoxicity, neurotoxicity, and hypertension. However, the rate of AE, SAE, and mortality observed in this meta-analysis was comparable between the two groups. In fact, more UC patients prefer IFX to CYS, citing reasons such as an easier treatment regimen and more tolerable side effects.^[29] CYS is not frequently used in some developing countries outside of academic centers, as it requires expertise in drug-level monitoring.

Our results demonstrated relatively high-pooled response and remission rates in both the IFX and TAC groups, meaning that a large portion of steroid-refractory UC patients could avoid urgent colectomy and could be treated to achieve remission. And, we found that the clinical response, clinical remission, mucosal healing, and AE rates were not significantly different between these UC patients treated with IFX and TAC. The reported AEs to IFX include susceptibility to infection, particularly tuberculosis (TB), reactivation of hepatitis B virus, and development of nonmelanoma skin cancer and

lymphoma. On the other hand, TAC has a narrow therapeutic window. If blood concentrations of TAC are high (≥ 10 ng/mL), serious AEs, such as renal dysfunction, can occur in UC patients. Therefore, when TAC is used in these UC patients, it is essential to prepare an individualized administration plan based on monitoring of the blood concentrations of TAC.

In all eligible studies, there was close therapeutic drug monitoring (TDM) of UC patients receiving CYS and TAC, but no optimization of IFX dosing. Some studies have demonstrated that UC patients with higher IFX levels are more likely to achieve clinical response, remission, and mucosal healing (MH) than those with low or absent trough levels. In the setting of severe UC, there may be a high local intestinal TNF- α level that necessitates higher IFX dosing. The IFX doses used in the included studies were the standard dosing regimen at 5 mg/kg, but aggressive dosing based on drug-level monitoring may result in even more improved patient outcomes. Recent studies have suggested that severe UC patients who undergo two or more infusions of IFX or accelerated IFX induction therapy are at a lower risk of colectomy in the short term, compared with those who receive standard induction therapy.^[30,31] Combination therapy with thiopurines may also lead to better long-term outcomes than in those patients with only IFX therapy.^[32]

In addition, observational data can be potentially informative as they reflect real-world practice. They can offer the outcome data in treated UC patients who may not fit strict inclusion criteria, offer long-term results on efficacy and safety, and provide insights into real-life limitations in managing these patients and using certain therapies.^[14] For example, some studies have not utilized Oxford criteria to assess steroid failure.^[33] The observational studies also varied in their time to steroid non-responsiveness, with steroids administered for a time period between 3 days and 4 weeks.^[16,17,18] This may be more reflective of clinical practice than the strict protocols followed in RCTs.

However, this meta-analysis has several limitations. First, of all eligible studies, only three studies used a randomized controlled design. Unfortunately, the paucity of RCTs in this field necessitates careful examination of observational literature. Observational studies cannot control for all potential confounding factors, including duration of disease, steroid use, concomitant medication, and maintenance therapy.

Second, there is some potential bias in the observational studies that favor IFX. For instance, the study by Croft *et al.*^[23] demonstrates significant improvement in treatment response and colectomy rates with only a single dose of IFX compared with CYS. However, the median duration

of disease in the CYS group was 3.57 years compared with just 0.34 years in the IFX group. The study by Protic *et al.*^[13] also favored IFX for both therapeutic response and the 12-month colectomy rate, but enrolled both moderate and severe steroid-refractory UC. At the same time, there is a switch reported in some cases from the included studies between IFX, CYS, and TAC. The switch can cause difficulty defining the effect of the drug and may affect the short-term and long-term outcomes.

Third, there is also variability in the definition of therapeutic response across studies. Some studies used decreases in validated scores to define therapeutic response, whereas others used more subjective measures like physicians' assessment to determine response. The dosing and target level of CYS was variable among studies, with reported targets that varied from 100 ng/mL to 600 ng/mL. The length of follow-up was also significantly different between studies, with observation periods as short as 1 year in some studies and the longest reported, 8 years, in the study by Duijvis *et al.*^[18] And most studies do not report on the concomitant use of IFX, CYS or TAC-treated patients. At the same time, the definitions of AE and SAE were often mixed together and were unclear in some studies.

In conclusion, despite the limitations mentioned above, our study suggested better treatment response and lower risk of colectomy in the first, second, and third years with IFX, compared with CYS, in steroid-refractory UC patients. But the RCTs did not suggest any difference between IFX and CYS as rescue therapies for steroid-refractory UC. Our meta-analysis also suggested that both IFX and TAC appeared to be effective for steroid-refractory UC; however, no significant difference between IFX and TAC was demonstrated. There was no significant difference among IFX and calcineurin inhibitors in AE, SAE, and mortality. Further RCTs comparing the efficacy and safety of IFX and calcineurin inhibitors in steroid-refractory UC patients are needed in the future.

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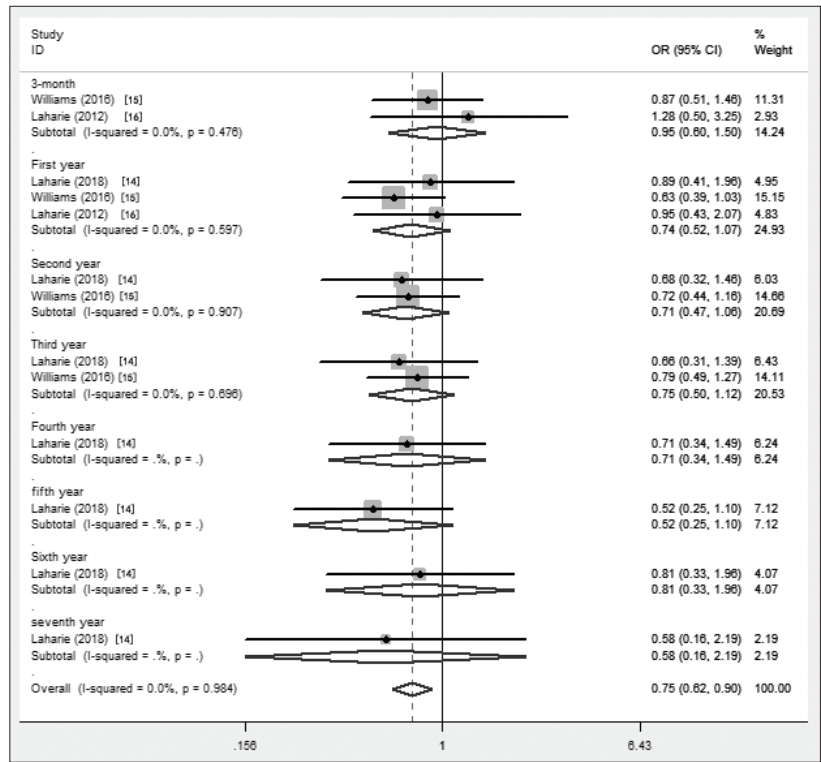
Conflicts of interest

There are no conflicts of interest.

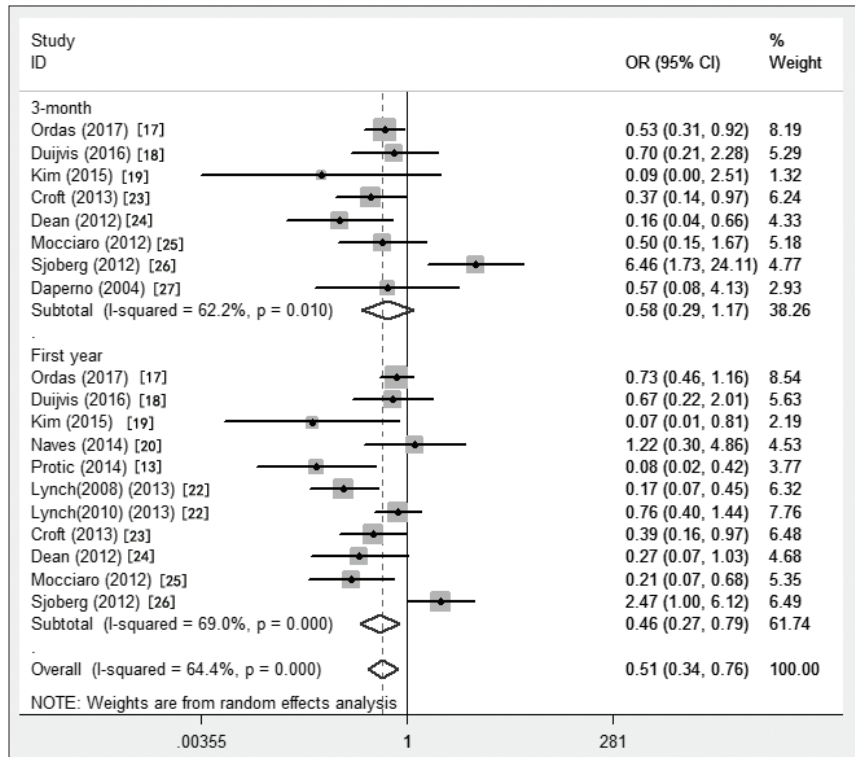
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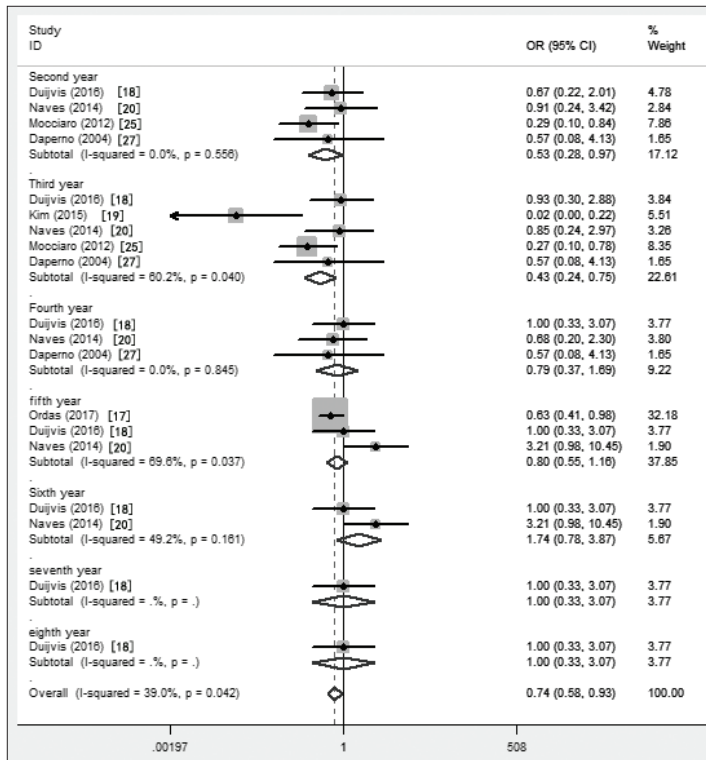
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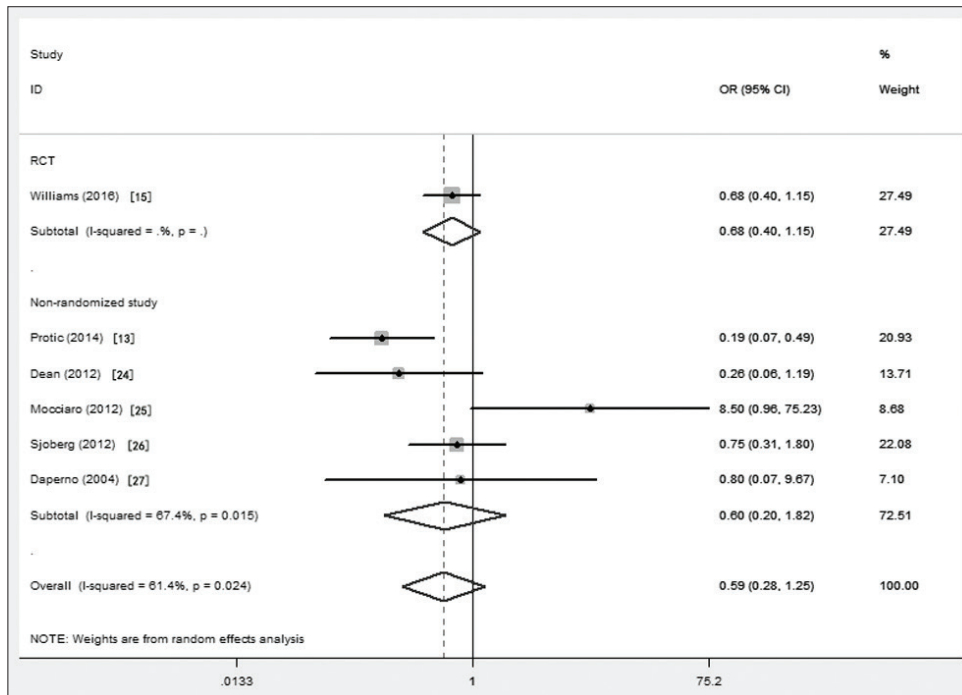
Supplemental Figure 1: Forest plot of all RCT studies reporting colectomy rates of IFX vs. CYS from 3 months to 7th year



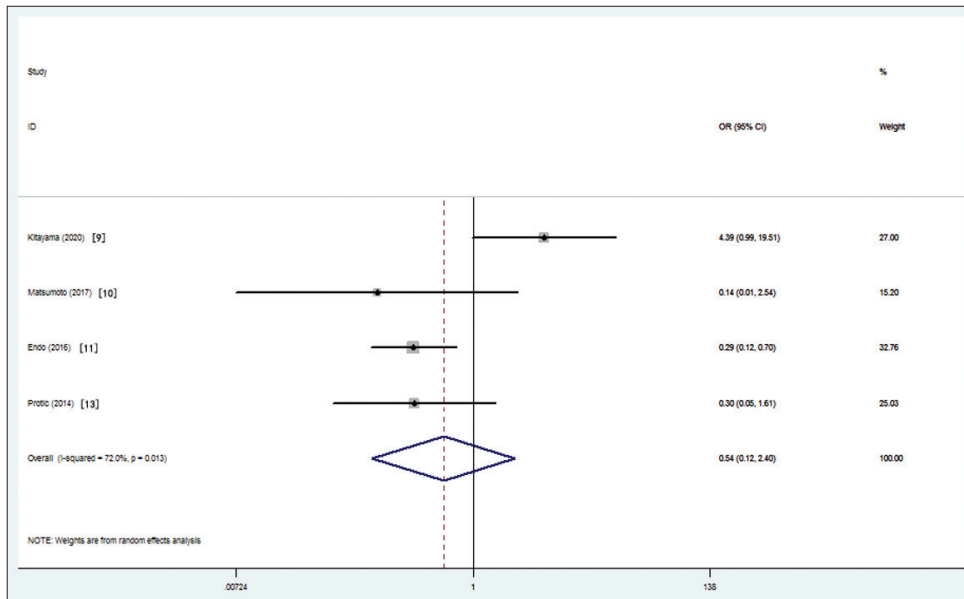
Supplemental Figure 2: Forest plot of non-randomized studies reporting colectomy rates of IFX vs. CYS at 3 months and 1st year



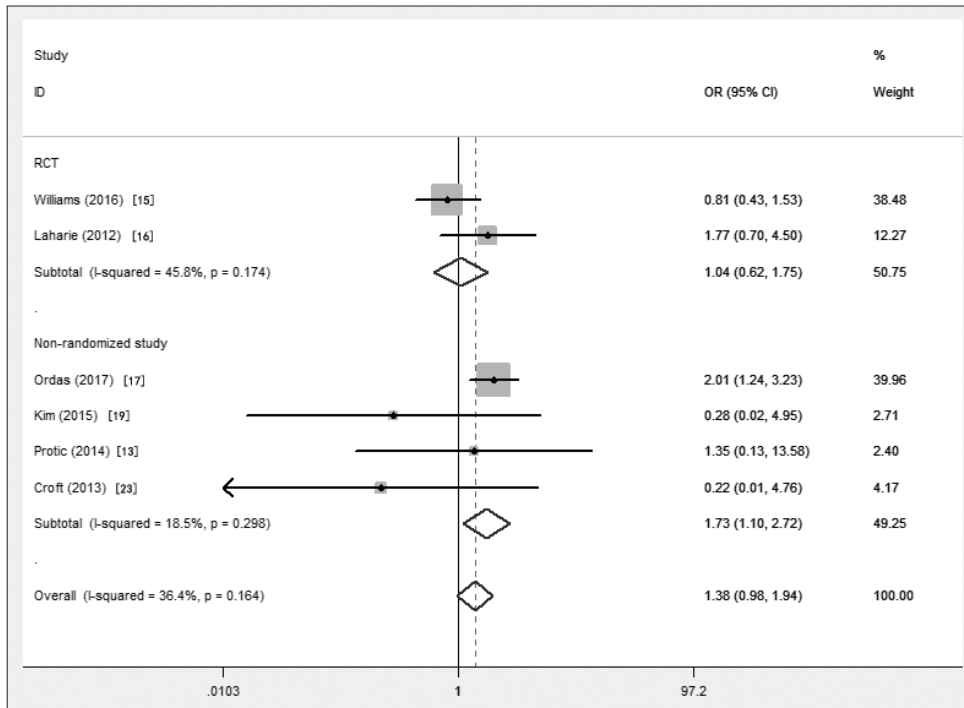
Supplemental Figure 3: Forest plot of non-randomized studies reporting colectomy rates of IFX vs. CYS from 2nd to 8th year



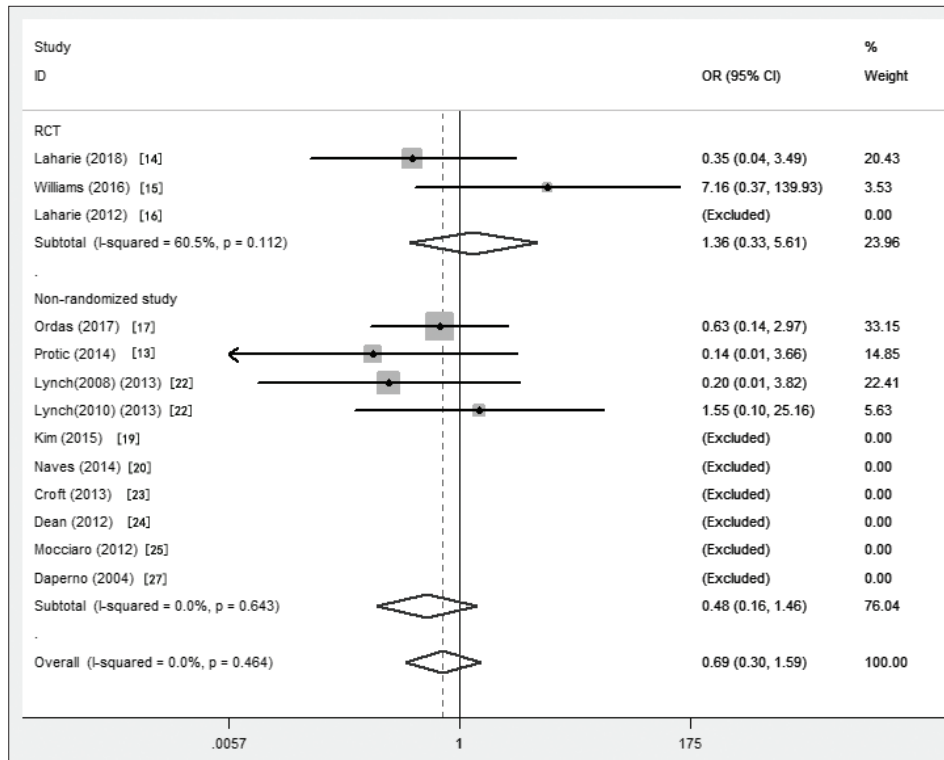
Supplemental Figure 4: Forest plot of all studies reporting the rates of AE of IFX vs. CYS



Supplemental Figure 5: Forest plot of all studies reporting the rates of AE of IFX vs. TAC



Supplemental Figure 6: Forest plot of all studies reporting the rates of SAE of IFX vs. CYS



Supplemental Figure 7: Forest plot of all studies reporting the rates of mortality of IFX vs. CYS