Systematic Review and Meta-Analysis

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Efficacy of infliximab, cyclosporine and tacrolimus on ulcerative colitis

A meta-analysis

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Abstract

Background: Positioning infliximab (IFX), cyclosporine and tacrolimus (TAC) for treating ulcerative colitis (UC) is in great debate.

Methods: A literature search identified studies that investigated IFX vs. cyclosporine or IFX vs TAC in UC patients. Short-term remission, short-term, 1-year and 3-year colectomy rate were employed as primary end-points to assess efficacy. Odds ratios (ORs) with 95% confidence intervals (CIs) were analyzed.

Results: Overall, 15 studies comprised 596 patients in IFX group and 866 in calcineurin inhibitors group (644 received cyclosporine and 222 received TAC). No significant difference was seen between IFX and calcineurin inhibitors with regard to short-term remission. IFX led to a lower short-term (OR: 0.59, 95% CI: 0.43–0.82, *P*:.001), 1-year (OR: 0.53, 95% CI: 0.38–0.73, $P < .001$), 3-year colectomy (OR: 0.41, 95% CI: 0.20–0.84, *P*:.02) than calcineurin inhibitors. IFX led to a lower short-term (OR: 0.51, 95% CI: 0.36–0.71, $P < .001$), 1-year (OR: 0.53, 95% CI: 0.37–0.74, *P*:.003) colectomy and a trend of lower 3-year colectomy (OR: 0.49, 95% CI: 0.22–1.06, *P*:.07) than cyclosporine while no significant difference was seen between IFX and TAC. Results of network meta-analysis showed that the order was cyclosporine, TAC and IFX from high rate to low with regard to short-term and 1-year colectomy.

Conclusion: IFX treatment leads to a lower short-term, 1-year colectomy rate and a trend of lower 3-year colectomy rate in UC patients than cyclosporine while no significant difference is seen between IFX and TAC. TAC may be superior than cyclosporine with regard to efficacy based on indirect comparisons. Randomized trials with fixed protocol are warranted to identify the optimal medical strategy in patients with UC.

Abbreviations: CI = confidence interval, CsA = cyclosporine, IFX = infliximab, ORs = odds ratio, TAC = tacrolimus, UC = ulcerative colitis.

Keywords: calcineurin inhibitors, cyclosporine, infliximab, tacrolimus, ulcerative colitis

1. Introduction

Incidence and prevalence of ulcerative colitis (UC), an idiopathic chronic immune-mediated inflammatory condition of the large intestine, has stabilized in high-incidence areas such as Western Europe and North America and is increasing in low-incidence areas, such as the developing world.[1–3] That may partly attribute to environment, diet, exercise, depression and anxiety.[4,5] Nearly 1 million individuals each are affected by this disease in the United States and Europe.[4] The hallmark

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XJ and RG authors contributed equally to this study.

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All data generated or analyzed during this study are included in this published article [and its supplementary information files].

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symptoms of UC are intermittent bloody diarrhea, rectal urgency, and tenesmus. As many as 25 percent of patients with UC have extraintestinal manifestations, including osteoporosis, oral ulcerations, arthritis, and et al.[6] Patients with active disease are more likely to have comorbid psychological conditions of anxiety and depression. Though UC does not significantly increase mortality, it seriously menaces quality of life and work ability, increases risk of colorectal cancer, increases mortality from liver diseases.[1,4,7,8]

Its treatment is far from satisfaction. Five-year cumulative risk of colectomy is 10% to 15%.[1] T cell modulators/suppressors are applied to treat UC because T cells are proven to play a pivotal role.[9,10] Calcineurin inhibitors suppress T cells functions by blocking transcription of genes involved in T cells activation.[11–13] Antitumor necrosis factor α (Anti-TNF-α) antibodies interfere with endogenous TNF-α activity via binding to human TNF-α what plays a decisive role in activation, expansion, and phenotypical stability of T cells.[10,14,15] Thus, both calcineurin inhibitors and anti-TNF-α antibodies have been considered for UC therapy.[4]

Cyclosporine (CsA) and tacrolimus (TAC) are 2 calcineurin inhibitors recommended to treat UC.[4,16–19] Infliximab (IFX) has conventionally been 1 of the mainstays of anti-TNF-α therapy for UC.[4,16–19] But, positioning IFX, CsA and TAC for treating UC is in great debate because efficacy varied greatly among different reports. Croft et al reported that IFX was superior than CsA while the study of Sjoberg et al indicated that CsA was superior than IFX.[19,20] Endo et al reported that IFX treatment yielded better short-term remission than TAC while the study of Yamamoto et al suggested that TAC treatment yielded better than IFX.[18,21] Here, we conducted a systematic review and network meta-analysis to compare relative efficacy of IFX, TAC and CsA. Efficacy of IFX vs. calcineurin inhibitors, IFX vs. CsA, IFX vs. TAC and TAC vs. CsA were also meta-analyzed.

2. Methods

2.1. Literature search

We performed a systematic literature review after the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) Statement and the Cochrane Handbook for Systematic Reviews of Interventions.[22] We systematically searched PubMed, MEDLINE, Cochrane Library to identify published studies what examined the efficacy of IFX vs calcineurin inhibitors (TAC and/or CsA). The bibliographic search was performed by two reviewers in May 6, 2019. The following search terms were used: "colitis" and "infliximab or remicade or anti-TNF" and "tacrolimus or fujimycin or FK506 or cyclosporine or cyclosporin or ciclosporin" in any field. Articles written in English were included.

Studies were selected by two reviewers. All studies were selected if they met the following criteria: the efficacy of IFX vs calcineurin inhibitors (TAC and/or CsA) was included in the study. Studies without enough data were excluded from analysis.

All analyses were based on previous published studies, thus no ethical approval and patient consent are required in this study.

2.2. Data extraction

Each included study was reviewed in full by 2 investigators. The 2 investigators confirmed eligibility for inclusion in the meta-analysis based on the following criteria:

(1) published as an abstract, conference paper or full text;
(2) include patients with UC;
(3) present the efficacy of IFX vs calcineurin inhibitors (TAC and/or CsA); and
(4) provide sufficient information to calculate odds ratio (OR) and 95% confidence interval (CI).

Following information was extracted: number of enrolled patients, gender, age, duration of disease prior to intervention, C-reactive protein (CRP), albumin level, short-term (about 2 to 3 months) clinical response, short-term clinical remission, short-term colectomy, 1-year colectomy, 3-year colectomy. Data were independently cross-checked.

2.3. Statistical analysis

Meta-analysis of aggregate patient data was conducted by combining ORs of individual studies into a pooled OR using a random-effects model. Statistical pooling of effect measures was based on the level of heterogeneity among studies, which was assessed with the Cochrane Q test and the I^2 statistic. No significant heterogeneity was indicated by $P > .1$ in Cochrane Q tests and a ratio less than 50% in I^2 statistics. OR was calculated using a fixed-effects model the Mantel-Haenszel method. Publication bias that included a small-study effect was evaluated by visual inspection of funnel plots for all assessed comparisons. Statistical analyses were performed using Review Manager, version 5.3 (The Nordic Cochrane Center, Copenhagen, Denmark). $P < .05$ was considered significant.

We conducted network meta-analysis using a multivariate, consistency model, random-effects meta-regression using STATA v.13.0 (College Station, TX). This frequentist approach provides a point estimate from the network along with 95% CI from the frequency distribution of the estimate.[16]

3. Results

3.1. Search results

As shown in Figure 1, a total of 390 articles were identified initially using the above search strategy employing Endnote. Three hundred and sixty-two articles were excluded on review of the title and abstract. After further careful review of 28 articles of the full text, a further 13 studies were excluded. One was a protocol; 1 was a comment; 1 focused on side effects; 1 was original article that was later released in full publication; 3 did not provide sufficient information; 6 reported outcomes in patients who did not meet enrollment criteria. Finally, 15 studies were eligible for meta-analysis.[12,13,15,17–21,23–29]

3.2. Study characteristics

Of included 15 studies, 2 were prospective studies and 13 were retrospective. Both prospective studies were multicenter, unblinded and 1 of them was RCT. Only 2 of 13 retrospective studies were multicenter. Overall, the meta-analysis comprised 596 patients in IFX group and 866 patients in calcineurin inhibitors group. The detailed information was summarized in Tables 1–4 and supplementary Table 1, http://links.lww.com/MD/F100.

Nine studies were selected to meta-analyze efficacy of IFX vs CsA.[12,13,17,19,20,24,25,27,28] Two were prospective, multicenter studies and 7 were retrospective cohort studies. The meta-

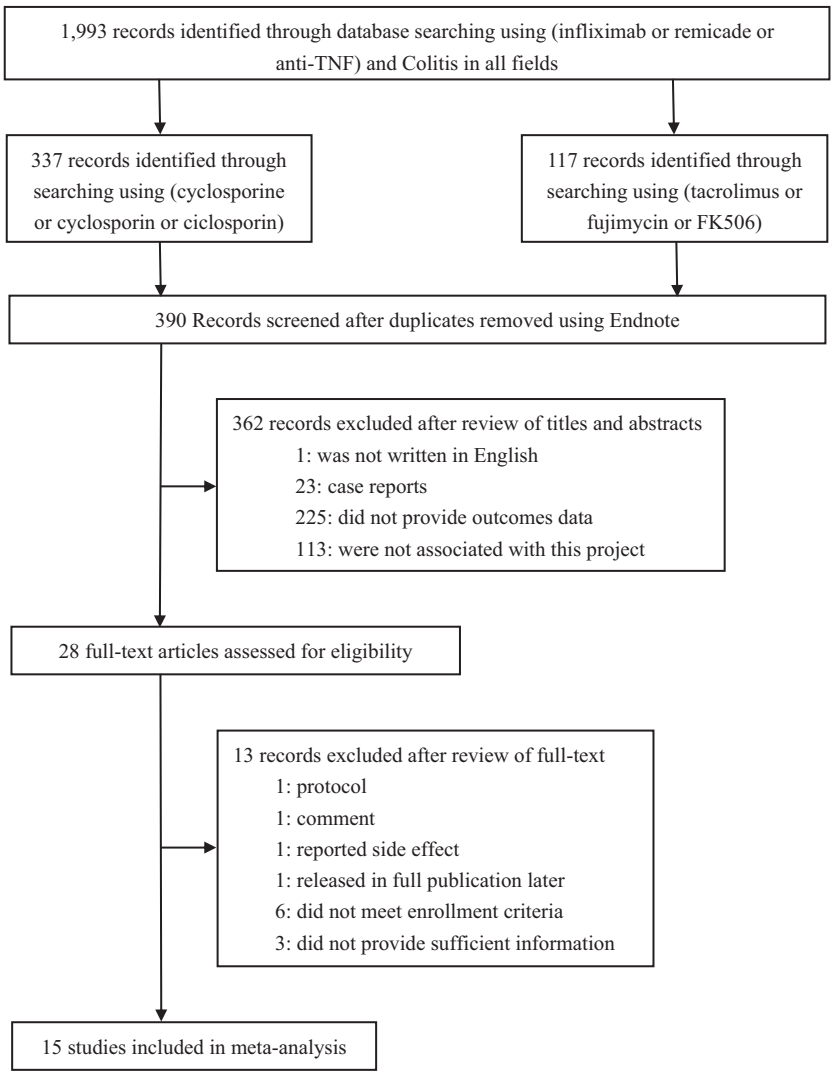

Figure 1. Preferred reporting items for meta-analyses flow chart.

Table 1

Characteristics of studies included in the systematic review and meta-analysis of infliximab vs cyclosporine.

First author	Publication year	Location	Type of study	patients	Regimen	No. of patients	Gender Male/ Female	Mean age (years)	Duration of disease prior to intervention (yr)	CRP (mg/L)
Dean, K. E.[13]	2012	New Zealand	Retrospective, single-center	SR UC	IFX	19	11/8	25	1.0	32 (1–259)
					CsA	19	12/7	31	3.0	56 (9–236)
Laharie, D.[24]	2012	Europe	Multicenter, unblinded, RCT	SR severe UC	IFX	57	30/27	36	1.0	46 (28–73)
					CsA	58	30/28	39	2.4	30 (16–67)
Mocciaro, F.[27]	2012	Italy	Retrospective, single-center	SR severe UC	IFX	30	15/15	37	4.0	NA
					CsA	35	15/20	34.9	3.0	NA
Sjoberg, M.[19]	2012	Australia& Sweden	Retrospective, Multicenter,	SR MtoS UC	IFX	49	30/19	38	3	NA
					CsA	43	21/22	32	5	NA
Croft, A.[20]	2013	Australia	Prospective, multicenter, unblinded	SR severe UC	IFX	38	15/23	26	0.34	72 (31–213)
					CsA	43	26/17	28	3.57	53 (29–113)
Lowenberg, M.[28]	2014	Holland	Retrospective, single-center	SR-ASUC	IFX	16	9/7	34	4	NA
					CsA	26	15/11	37	2	NA
Kim, E. H.[12]	2015	Korea	Retrospective, single-center	SR UC	IFX	33	25/8	44	6.4	30 (28–489)
					CsA	10	3/7	56	10.1	11 (2–48)
Duijvis, N. W.[17]	2016	USA	Retrospective, single-center	MtoS UC	IFX	22	14/8	35.5	4.0	NA
					CsA	33	17/16	37.7	2.9	NA
Ordas, I.[25]	2017	Spain	Retrospective, Multicenter,	SR-ASUC	IFX	131	76/55	40.9	3.1	NA
					CsA	377	217/160	36.0	1.7	NA

ASUC = acute severe ulcerative colitis, CsA = cyclosporine, IFX = infliximab, MtoS = moderate-to-severe, NA = not applicable, SR = steroid-refractory, UC = ulcerative colitis.

Table 2

Characteristics of studies included in the systematic review and meta-analysis of infliximab vs tacrolimus.

First author	Publication year	Location	Type of study	patients	Regimen	No. of patients	Gender Male/ Female	Mean age (yr)	Duration of disease prior to intervention (yr)	CRP (mg/L)
Endo, K.[18]	2016	Japan	Retrospective, single-center	SR UC	IFX	48	31/17	24	4	100 (1–750)
					TAC	47	30/17	30	3.8	40 (10–2310)
Nuki, Y.[26]	2016	Japan	Retrospective, single-center	MtoS UC	IFX	25	10/15	39	6	75 (24–171)
					TAC	21	7/14	37	7	48 (15–278)
Yamamoto, T.[21]	2016	Japan	Retrospective, single-center	SR/D MtoS UC	IFX	40	NA	NA	NA	18 (14–21)
					TAC	50	29/21	43	4.5	21 (18–25)
Matsumoto, S.[15]	2017	Japan	Retrospective, single-center	SR/D MtoS UC	IFX	14	NA	NA	NA	NA
					TAC	29	18/11	39	3.8	NA
Yamagami, H.[23]	2017	Japan	Retrospective, single-center	SR MtoS UC	IFX	58	25/33	42.2	NA	30 (10–80)
					TAC	64	36/28	37.9	NA	260 (55–722)
Otsuka, T.[29]	2018	Japan	Retrospective, single-center	SR MtoS UC	IFX	18	9/9	47	4.2	200 (0–1812)
					TAC	11	6/5	51	1.0	130 (0–767)

ASUC = acute severe ulcerative colitis, IFX = infliximab, MtoS = moderate-to-severe, NA = not applicable, SR = steroid-refractory, TAC = tacrolimus, UC = ulcerative colitis.

Table 3

Data extracted for measured outcomes of infliximab vs cyclosporine.

First author	Publication year	patients	Regimen	No. of patients	Short-term efficacy			1-yr Colectomy %	3-yr Colectomy %
					Time	Remission %	Colectomy %		
Dean, K. E.[13]	2012	SR UC	IFX	19	3M	NA	21	37	NA
			CsA	19		NA	63	68	NA
Laharie, D.[24]	2012	SR severe UC	IFX	57	14W	46	21	NA	NA
			CsA	58		40	17	NA	NA
Mocciaro, F.[27]	2012	SR severe UC	IFX	30	3M	83	17	17	27
			CsA	35		71	28.5	48	57
Sjoberg, M.[19]	2012	SR MtoS UC	IFX	49	3M	NA	33	43	NA
			CsA	43		NA	7	23	NA
Croft, A.[20]	2013	SR severe UC	IFX	38	3M	NA	24	35	NA
			CsA	43		NA	47	58	NA
Lowenberg, M.[28]	2014	SR UC	IFX	16	3M	NA	25	NA	NA
			CsA	26		NA	19.2	NA	NA
Kim, E. H.[12]	2015	SR UC	IFX	33	3M	45.5	0	3.0	3.0
			CsA	10		30.0	10.0	30.0	60.0
Duijvis, N. W.[17]	2016	MtoS UC	IFX	22	3M	52.4	29	48	67
			CsA	33		64.9	36	58	64
Ordas, I.[25]	2017	SR-ASUC	IFX	131	3M	NA	14.5	23.6	NA
			CsA	377		NA	24.1	29.7	NA

ASUC = acute severe ulcerative colitis, CsA = cyclosporine, IFX = infliximab, MtoS = moderate-to-severe, NA = not applicable, SR = steroid-refractory, UC = ulcerative colitis.

Table 4

Data extracted for measured outcomes of infliximab vs tacrolimus.

First author	Publication year	patients	Regimen	No. of patients	Short-term efficacy				1-yr Colectomy %	3-yr Colectomy %
					Time	Reponse %	Remission %	Colectomy %		
Endo, K.[18]	2016	SR UC	IFX	48	2M	81.3	68.8	3	3	3
			TAC	47		68.1	55.3	4	8	18
Nuki, Y.[26]	2016	MtoS UC	IFX	25	10W	92	76.0	0	NA	NA
			TAC	21		85	66.7	0	NA	NA
Yamamoto, T.[21]	2016	SR/D MtoS UC	IFX	40	12W	65	30	15	20	NA
			TAC	50		62	40	10	24	NA
Matsumoto, S.[15]	2017	SR/D MtoS UC	IFX	14	12W	NA	57	NA	NA	NA
			TAC	29		NA	55	38	38	NA
Yamagami, H.[23]	2017	SR MtoS UC	IFX	58	14W	NA	37.9	NA	NA	NA
			TAC	64		NA	50	NA	NA	NA
Otsuka, T.[29]	2018	SR MtoS UC	IFX	18	12W	94.4	77.8	0	0	NA
			TAC	11		72.7	72.7	0	25	NA

ASUC = acute severe ulcerative colitis, IFX = infliximab, MtoS = moderate-to-severe, NA = not applicable, SR = steroid-refractory, TAC = tacrolimus, UC = ulcerative colitis.

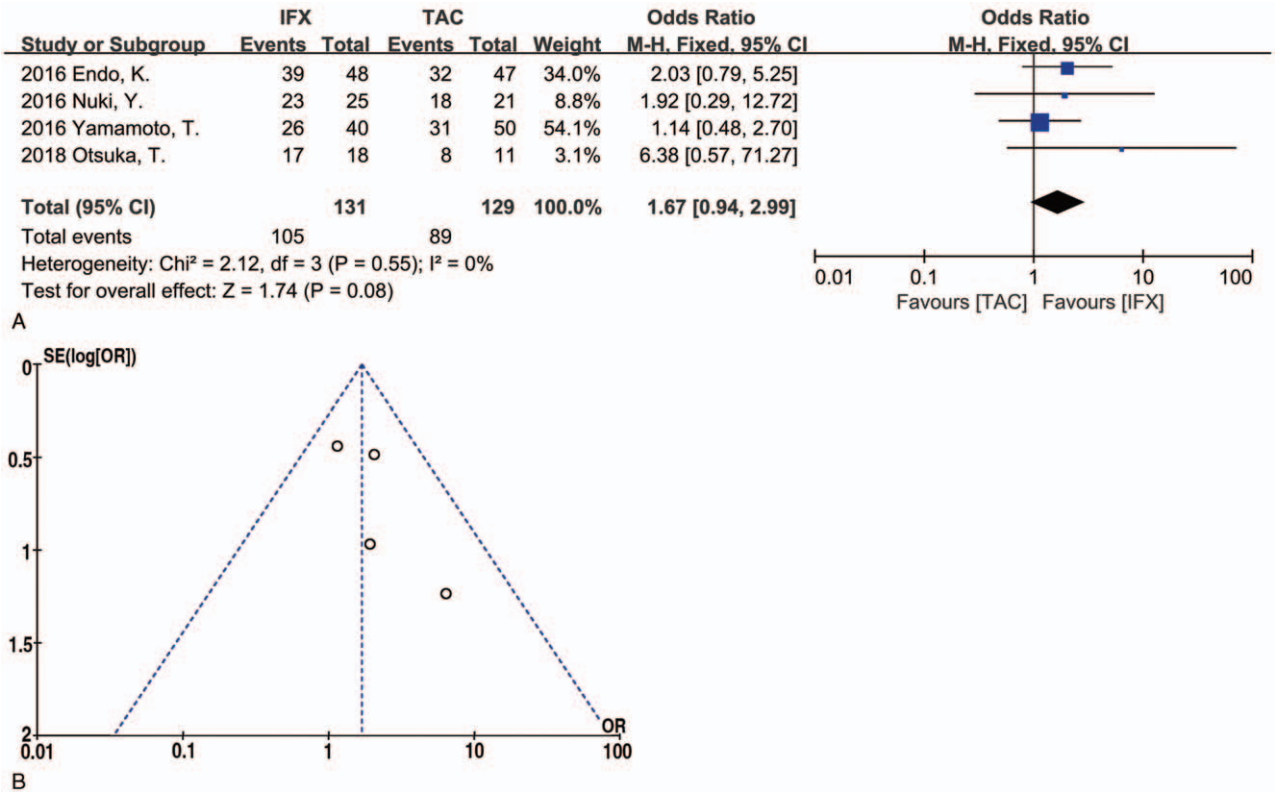

Figure 2. Short-term response of IFX and TAC. A: Forest plot. B: Funnel plot.

analysis comprised 393 patients in IFX group and 644 patients in CsA group. Eight studies were carried out in the Western and only 1 was carried out in the Eastern, Korea. Tables 1 and 3 and supplementary Table 1, http://links.lww.com/MD/F100 list the identified studies and their main characteristics.

Six studies were selected to meta-analyze efficacy of IFX vs. TAC.[15,18,21,23,26,29] Overall, the meta-analysis comprised 203 patients in IFX group and 222 patients in TAC group. All 6 studies were carried out in Japan and all were retrospective cohort studies. Tables 2 and 4 and supplementary Table 1, http://links.lww.com/MD/F100 list the identified studies and their main characteristics.

3.3. Induction of short-term clinical response

Four studies reported short-term clinical response and all focused on IFX vs TAC.[18,21,26,29] Two hundred and sixty subjects were included; 131 received IFX and 129 received TAC. Efficacy was assessed between 2 months and 14 weeks. The pooled OR was 1.67 [95% CI: 0.94–2.99, *P*:.08]. Those indicate that IFX might induce higher short-term clinical response rate than TAC (Fig. 2A).

Visual inspection of the corresponding funnel plot revealed no publication bias (Figure 2B).

3.4. Induction of short-term clinical remission

Ten studies reported short-term clinical remission (Figs. 3 and 4).[12,15,17,18,21,23,24,26,27,29] Three hundred and forty-four patients received IFX and 362 received calcineurin inhibitors. Efficacy was assessed between 2 months and 14 weeks. The pooled OR was 1.05 [95% CI: 0.77–1.44, *P*:.75] (Fig. 3A). Four studies comprised 331 patients focused on steroid-refractory moderate-to-severe UC.[23,24,27,29] The pooled OR was 1.02 [95% CI: 0.65–1.60, *P*:.94] (Fig. 4A). Those suggest that there is no significant difference between IFX and calcineurin inhibitors in UC or in steroid-refractory moderate-to-severe UC.

Four studies, 1 prospective and 3 retrospective, focused on IFX vs CsA.[12,17,24,27] One hundred and forty-one patients received IFX and 140 received CsA. Efficacy was assessed between 3 months and 14 weeks. The pooled OR was 1.23 [95% CI: 0.74–2.05, *P*:.42] (Fig. 3A). Two studies comprised 180 patients focused on steroid-refractory severe UC. The pooled OR was 1.45 [95% CI: 0.77–2.71, *P*:.25] (Fig. 4A). Those suggest that there is no significant difference in short-term clinical remission between IFX and CsA in UC or steroid-refractory severe UC.

Six studies, all retrospective, focused on IFX vs. TAC and included 203 patients who received IFX and 222 patients who received TAC (Figs. 3 and 4).[15,18,21,23,26,29] Efficacy was assessed between 2 months and 14 weeks. The pooled OR was 0.96 [95% CI: 0.64–1.42, *P*:.82] (Fig. 3A). Two studies comprised 151 patients focused on steroid-refractory moderate-to-severe UC. The OR was 0.68 [95% CI: 0.35–1.33, *P*:.26] (Fig. 4A). Those suggest that there is no difference in short-term clinical remission between IFX and TAC in UC or steroid-refractory moderate-to-severe UC.

Visual inspection of the corresponding funnel plot revealed no publication bias (Fig. 3B and 4B).

3.5. Short-term colectomy

It is well accepted that colectomy rate is the primary end-point to assess efficacy in UC treatment.[12,13,17,18,20,21,24,25,27,28] Short-

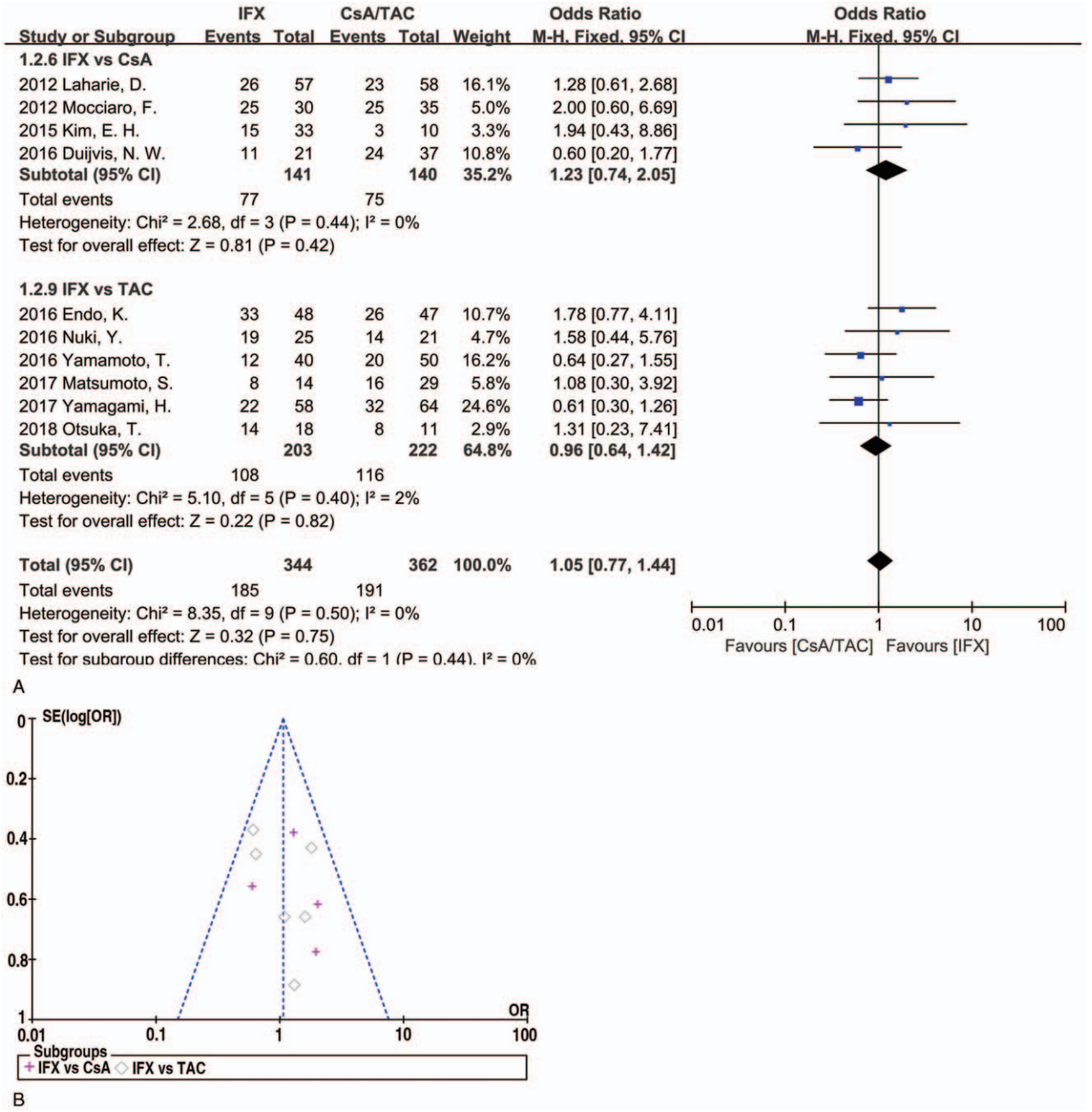

Figure 3. Short-term remission of IFX and calcineurin inhibitors. A: Forest plot. B: Funnel plot.

term colectomy was reported in 13 studies. Two studies were excluded because no patient received colectomy in neither IFX group nor calcineurin inhibitors group[26,29] and 1 was excluded because of heterogeneity.[19] Ten studies were included.[12,13,17,18,20,21,24,25,27,28] Efficacy was assessed between two months and 14 weeks. One thousand one hundred and thirty patients were included, 432 in IFX group and 698 in calcineurin inhibitors group (Figs. 5 and 6). The pooled OR was 0.59 [95% CI: 0.43–0.82, *P*:.001] (Fig. 5). If heterogeneity was not taken in account, the pooled OR was 0.66 [95% CI: 0.49–0.89, *P*:.007] (supplementary Figure 1, http://links.lww.com/MD/F101). Those results suggest that IFX leads to a lower colectomy rate at short-term than calcineurin inhibitors.

Eight studies, 2 prospective and 6 retrospective, focused on IFX vs CsA.[12,13,17,20,24,25,27,28] One hundred and ninety-five subjects were included in 2 prospective studies; 94 received IFX and 101 received CsA.[20,24] The OR of prospective studies was 0.70 [95% CI: 0.36–1.33, *P*:.37] (supplementary Figure 2, http://links.lww.com/MD/F102). Seven hundred and fifty subjects were included in 6 retrospective studies; 250 received IFX and 500 received CsA.[12,13,17,25,27,28] The OR of retrospective studies was 0.52 [95% CI: 0.34–0.78, *P*:.002] (supplementary Figure 2, http://links.lww.com/MD/F102). The pooled OR of all 8 studies was 0.51 [95% CI: 0.36–0.71, $P < .001$] (Fig. 5, supplementary Figure 2, http://links.lww.com/MD/F102). If heterogeneity was not taken in account and 9 studies reported

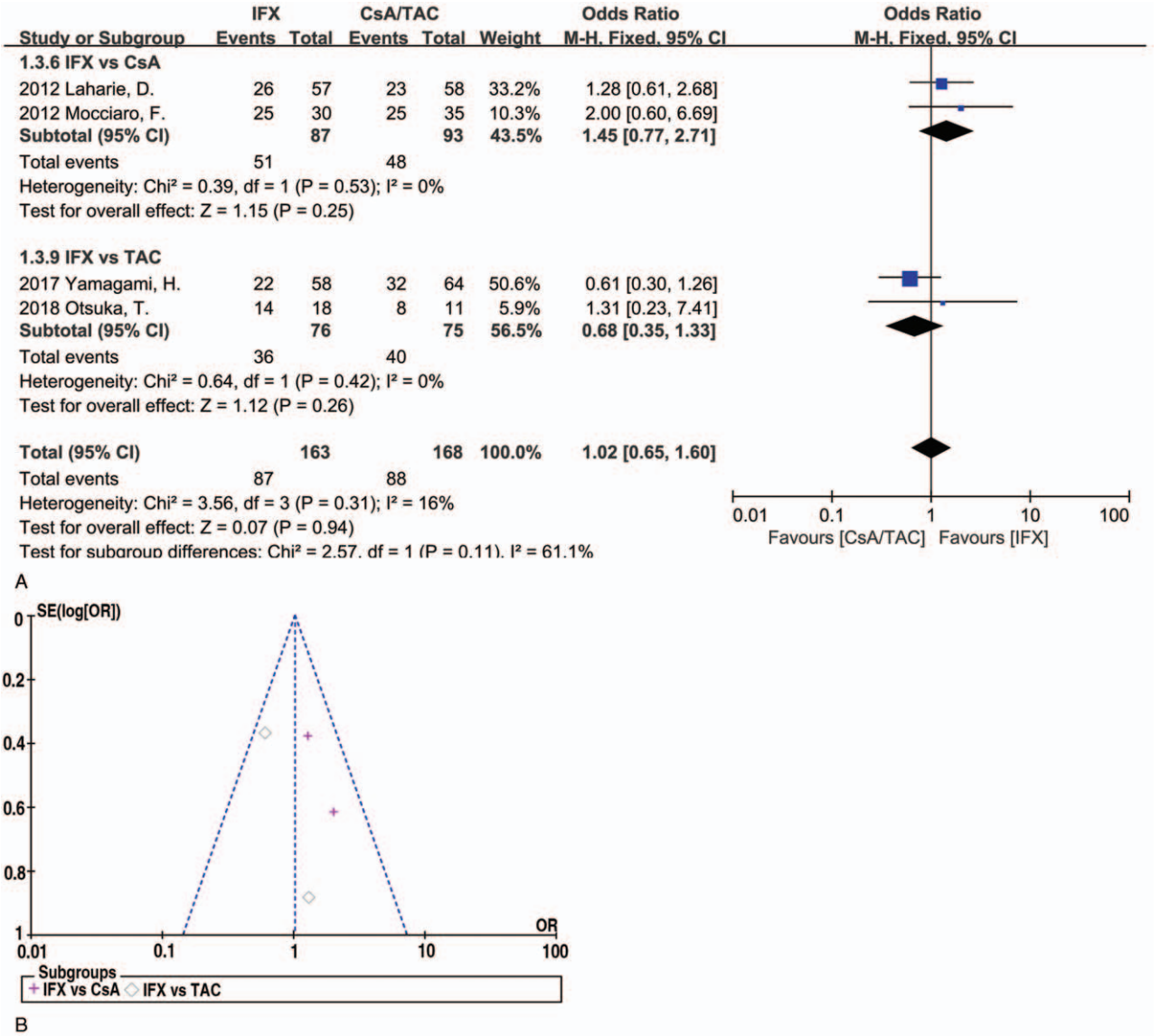

Figure 4. Short-term remission on steroid-refractory moderate-to-severe UC of IFX and calcineurin inhibitors. A: Forest plot. B: Funnel plot.

short-term colectomy were included, the pooled OR was 0.56 [95% CI: 0.40–0.79, *P*:.001] (supplementary Figure 1, http://links.lww.com/MD/F101). Those results suggest that IFX leads to a lower colectomy rate at short-term than CsA. Two prospective studies and 3 retrospective studies focused on steroid-refractory severe UC.[20,24,25,27,28] The OR of prospective studies was 0.70 [95% CI: 0.36–1.33, *P*:.27] and the OR of retrospective studies was 0.58 [95% CI: 0.36–0.92, *P*:.02]. The pooled OR of the five studies was 0.61 [95% CI: 0.42–0.89, *P*:.01] (Fig. 6). Together with the resulted mentioned before, those unanimously indicate that IFX was superior than CsA to avoid short-term colectomy in UC and steroid-refractory severe UC.

Results of meta-analysis of IFX vs TAC were not concordant with those of IFX vs CsA. Short-term colectomy was reported in 4 studies focused on IFX vs. TAC.[18,21,26,29] Two studies were excluded because no patient received colectomy in neither IFX group nor TAC group.[26,29] Two studies, all retrospective, were included.[18,21] Eighty-eight patients received IFX and 97 patients received TAC. Efficacy was assessed between two months and 12 weeks. The OR was 0.91 [95% CI: 0.38–2.21, *P*:.84] (Fig. 5). That suggests that there is no difference in short-term colectomy rate between IFX and TAC in UC.

Visual inspection of the corresponding funnel plot revealed no publication bias.

3.6. One-year colectomy

One-year colectomy was reported in 10 studies. One study was excluded because of heterogeneity.[19] Nine hundred and seventy-one patients were included, 360 in IFX group and 611 in calcineurin inhibitors group.[12,13,17,18,20,21,25,27,29] The pooled OR was 0.53 [95% CI: 0.38–0.73, $P < .001$] (Fig. 7). If heterogeneity was not taken in account and all studies reported 1-year colectomy were included, the pooled OR was 0.63 [95% CI: 0.47–0.85, *P*:.003] (supplementary Fig. 3, http://links.lww.

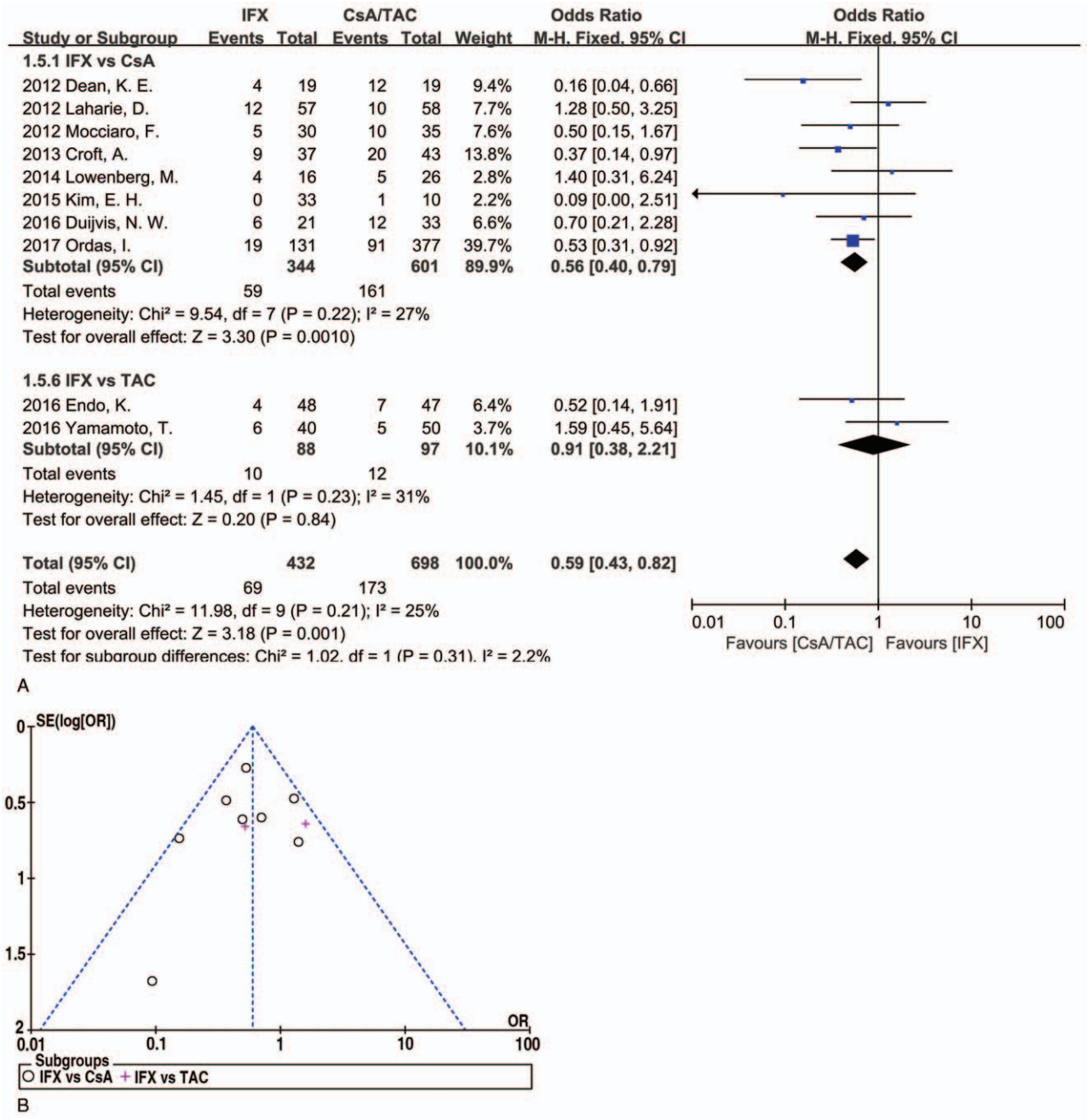

Figure 5. Short-term colectomy of IFX and calcineurin inhibitors. A: Forest plot. B: Funnel plot.

com/MD/F103). Those results suggest that IFX leads to a lower colectomy rate at 1 year than calcineurin inhibitors.

Six studies, 1 prospective and 5 retrospective, focused on IFX vs. CsA.[12,13,17,20,25,27] The OR of the prospective study was 0.39 [95% CI: 0.16–0.97, *P*:.04] and that of retrospective studies was 0.55 [95% CI: 0.38–0.80, *P*:.002] (supplementary Figure 4, http://links.lww.com/MD/F104). The pooled of all 6 studies was 0.53 [95% CI: 0.37–0.74, $P < .001$] (Fig. 7, supplementary Figure 4, http://links.lww.com/MD/F104). If heterogeneity was not taken in account and 7 studies reported 1-year colectomy were included, the pooled OR was 0.65 [95% CI: 0.47–0.89, *P*:.007] (supplementary Figure 3, http://links.lww.com/MD/F103). Those results suggest that IFX leads to a lower colectomy rate at 1 year than CsA. One prospective study and 2 retrospective studies focused on steroid-refractory severe UC.[20,25,27] The pooled OR of the 3 studies was 0.57 [95% CI: 0.39–0.83, *P*:.004] (Fig. 8). Together with the results mentioned before, those unanimously indicate that IFX is superior than CsA to avoid 1-year colectomy in UC and steroid-refractory severe UC.

Results of meta-analysis of IFX vs TAC were not concordant with that of IFX vs CsA. Three studies focused on IFX vs TAC.[18,21,29] Eighty-nine patients received IFX and 94 patients received TAC. The OR was 0.55 [95% CI: 0.23–1.30, *P*:.17]

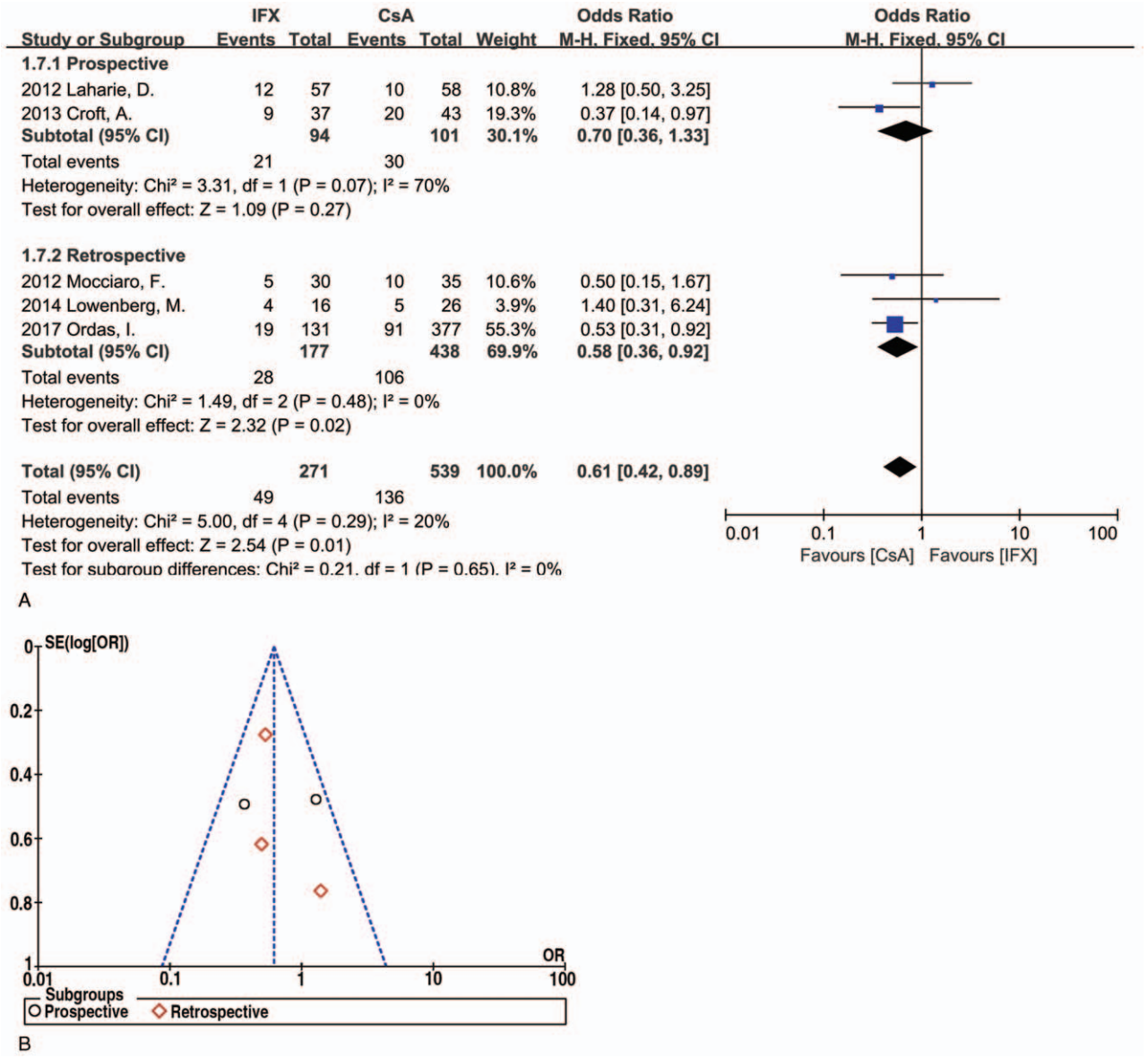

Figure 6. Short-term colectomy on steroid-refractory severe UC of IFX and CsA. A: Forest plot. B: Funnel plot.

(Fig. 7). Those suggest that there is no significant difference in 1-year colectomy rate between IFX and TAC in UC.

Visual inspection of the corresponding funnel plot revealed no publication bias.

3.7. Three-year colectomy

Three-year colectomy was the primary end-point in 4 studies and all were retrospective studies.[12,17,18,27] Because of heterogeneity, 1 study was excluded.[12] Seventy-seven patients received IFX and 104 patients received calcineurin inhibitors. The pooled OR was 0.41 [95% CI: 0.20–0.84, *P*:.02] (Fig. 9). If heterogeneity was not taken in account and all studies reported 3-year colectomy were included, the pooled OR was 0.30 [95% CI: 0.16–0.59, $P < .001$] (supplementary Figure 5, http://links.lww.com/MD/F105). Those results suggest IFX treatment leads to a lower 3-year colectomy rate than calcineurin inhibitors in UC.

Two study focused on IFX vs CsA and the OR was 0.49 [95% CI: 0.22–1.06, *P*:.07] (Fig. 9). Those results suggest IFX treatment might lead to a lower 3-year colectomy rate than CsA. One study focused on IFX vs TAC and the OR was 0.16 [95% CI: 0.02–1.42, *P*:.10] (Fig. 9).

Visual inspection of the corresponding funnel plot revealed no publication bias.

3.8. Network meta-analysis among IFX, TAC and CsA

Network meta-analysis to compare the relative efficacy of IFX, TAC, and CsA was done (Fig. 10, Table 5).

For induction of clinical remission, the order of pharmacological agents was TAC, IFX and CsA from high efficacy to low. But there was no significant difference. (Table 5)

For short-term colectomy, the order of pharmacological agents was CsA, TAC, and IFX from high colectomy rate to low. There

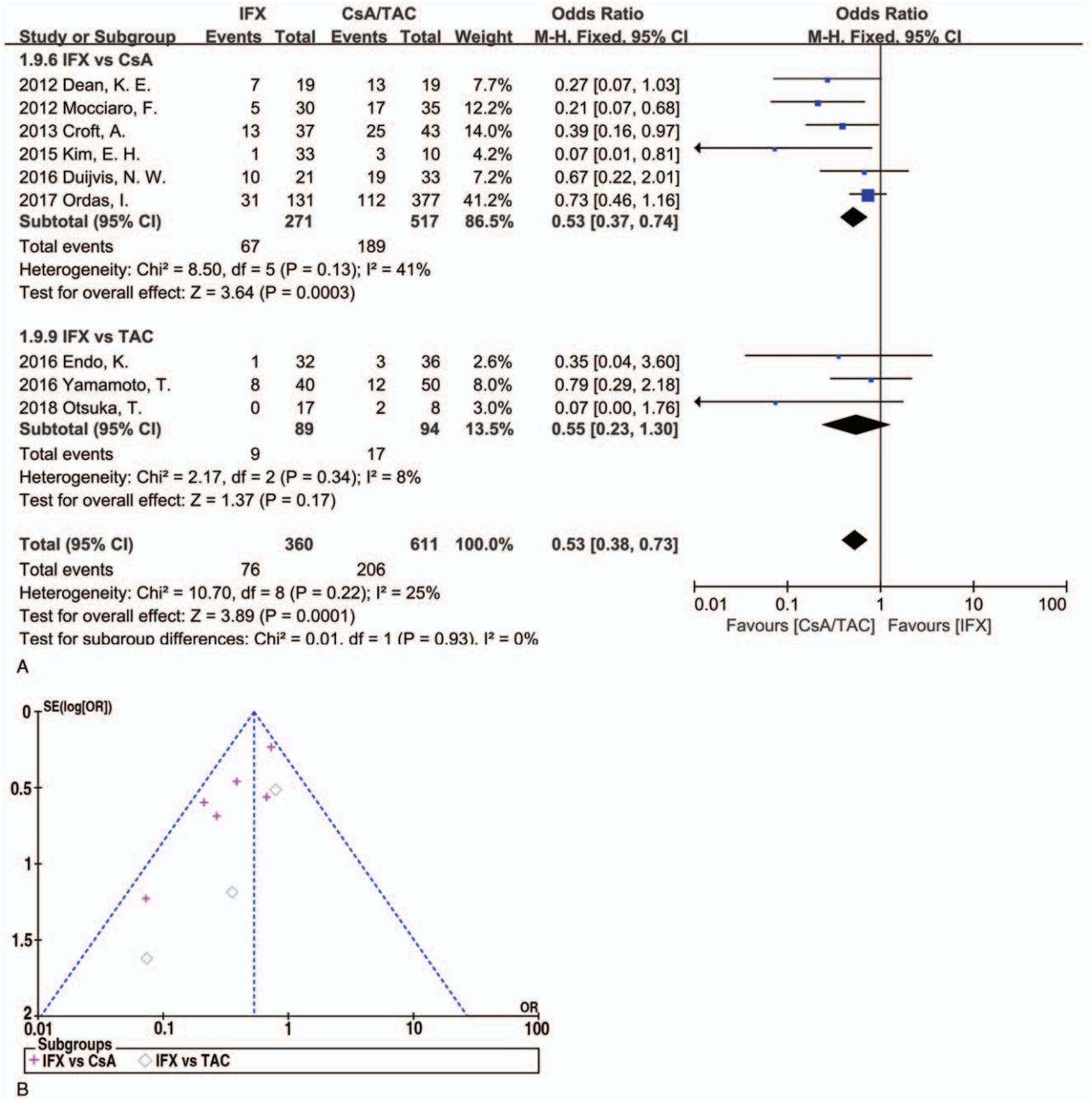

Figure 7. One-year colectomy of IFX and calcineurin inhibitors. A: Forest plot. B: Funnel plot.

was a significant difference between CsA and IFX. No significance was observed between TAC and IFX, or between TAC and CsA. (Table 5)

For 1-Year colectomy, the order of pharmacological agents was CsA, TAC and IFX from high colectomy rate to low. There was a significant difference between CsA and IFX. No significance was observed between TAC and IFX, or between TAC and CsA. (Table 5)

4. Discussion

UC generally begins in young adulthood and lasts throughout life. The efficacy and safety of treatment is far from satisfaction. Five-year cumulative risk of colectomy is 10% to 15%.[1] Immunosuppression with high-dose corticosteroids is first-line therapy.[4,16] Regretfully, up to 30% of the patients are unresponsive to corticosteroid therapy and part of the patients who are responsive to corticosteroid therapy will become steroid-dependent.[15,21] Those require salvage therapy. Studies on efficacy of anti-TNF-α antibodies or calcineurin inhibitors to treat UC as salvage therapies are accumulating. IFX has conventionally been 1 of the mainstays of anti-TNF-α therapy for UC.[4,16] CsA and TAC are 2 calcineurin inhibitors recommended to treat UC as salvage therapy.[4] Almost all these studies indicated that both calcineurin inhibitors and anti-TNF-α antibodies were efficacious. IFX treatment induced the short-term

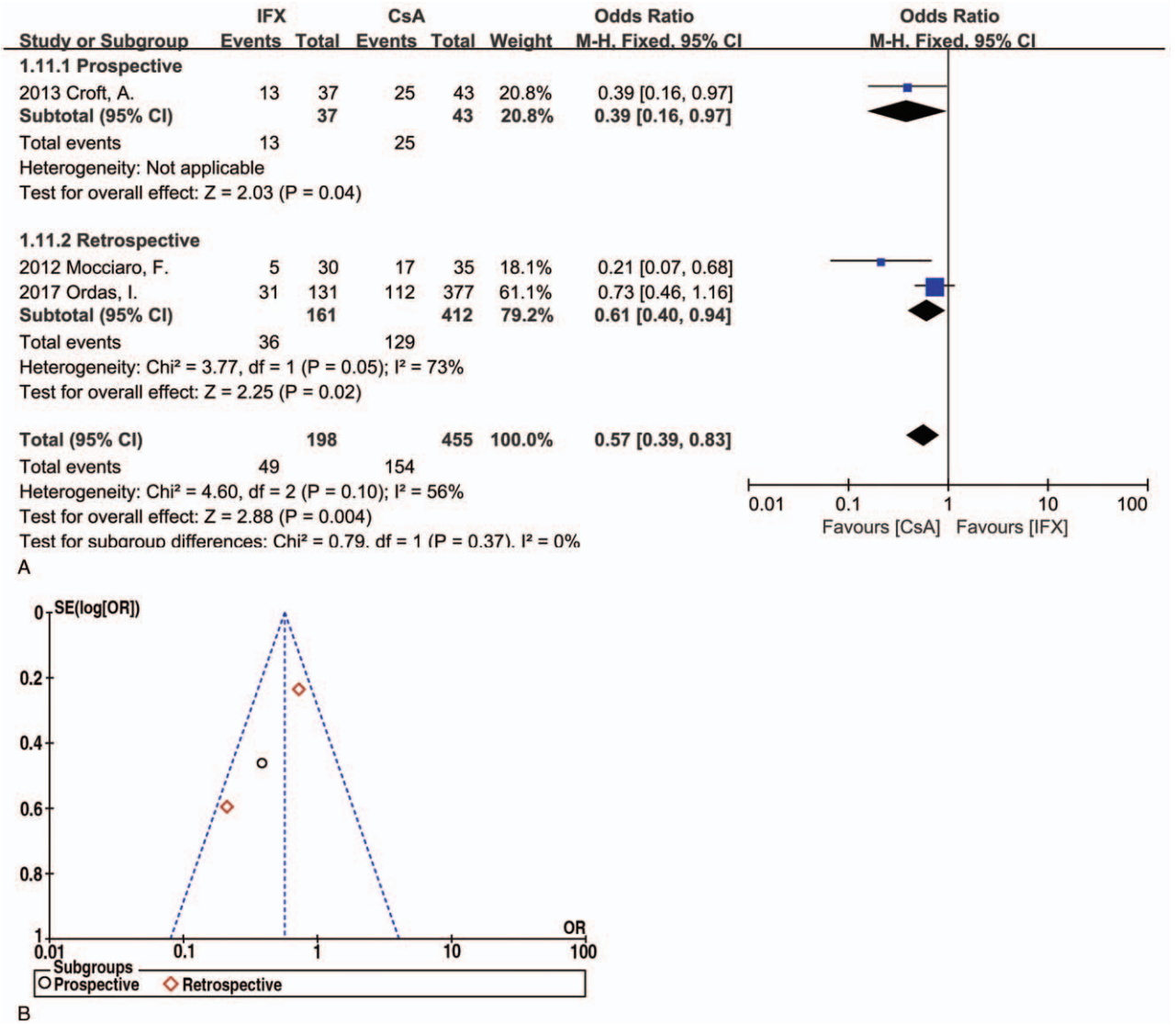

Figure 8. One-year colectomy on steroid-refractory severe UC of IFX and CsA. A: Forest plot. B: Funnel plot.

remission rate ranging from 30% (12/40) to 83% (25/30) and calcineurin inhibitors induced remission rate ranging from 30% (3/10) to 73% (8/11).[21,27] IFX treatment decreased 1-Year colectomy rate ranging from 3% (1/33) to 48% (10/21) and calcineurin inhibitors decreased 1-Year colectomy rate ranging from 8% (3/36) to 68% (13/19).[12,13,17,18]

Efficacy of IFX and calcineurin inhibitors on UC were compared here. IFX induced similar short-term remission rate as calcineurin inhibitors (OR: 1.05; 95% CI: 0.77–1.44; *P*:.75) (Fig. 3). Colectomy is generally the last choice of salvage therapy and it seriously causes morbidity.[4,25] Therefore, risk of colectomy has been extensively studied and the colectomy rate are the primary end-point to access the efficacy of medications in most of studies. IFX treatment significantly decreased colectomy rate in UC patients than calcineurin inhibitors did. With increased time post-treatment, results favored IFX more. ORs of colectomy were 0.59 [95% CI: 0.43–0.82, *P*:.001], 0.53 [95% CI: 0.38–0.73, $P < .001$], 0.41 [95% CI: 0.20–0.84, *P*:.02] at the end of short-term, 1 year and 3 years, respectively (Figures 5, 7, 9). These indicate that IFX is superior than calcineurin inhibitors in the treatment of UC.

However, these could not lead to the conclusion that IFX is superior than each of calcineurin inhibitors in the treatment of UC. IFX significantly decreased colectomy rate in UC patients than CsA did while it did not significantly decrease colectomy rate than TAC did. IFX vs CsA ORs of colectomy were 0.51 [95% CI: 0.36–0.71, $P < .001$], 0.53 [95% CI: 0.37–0.74, $P: < .001$], 0.49 [95% CI: 0.22–1.06, *P*:.07], at the end of short-term, 1 year and 3 years, respectively (Figures 5, 7, 9). But, IFX vs. TAC ORs of colectomy were 0.91 [95% CI: 0.38–2.21, *P*:.84], 0.55 [95% CI: 0.23–1.30, *P*:.17], 0.16 [95% CI: 0.02–1.42 *P*:.10], at the end of short-term, 1 year and 3 years, respectively (Figures 5, 7, 9). Therefore, IFX is superior than CsA while there is no significant difference between IFX and TAC.

Then, the above data lead to the hypothesis that TAC might be superior than CsA. Network meta-analysis was done to test this hypothesis because there is no head-to-head trial. Results supported that TAC treatment induced higher short-term

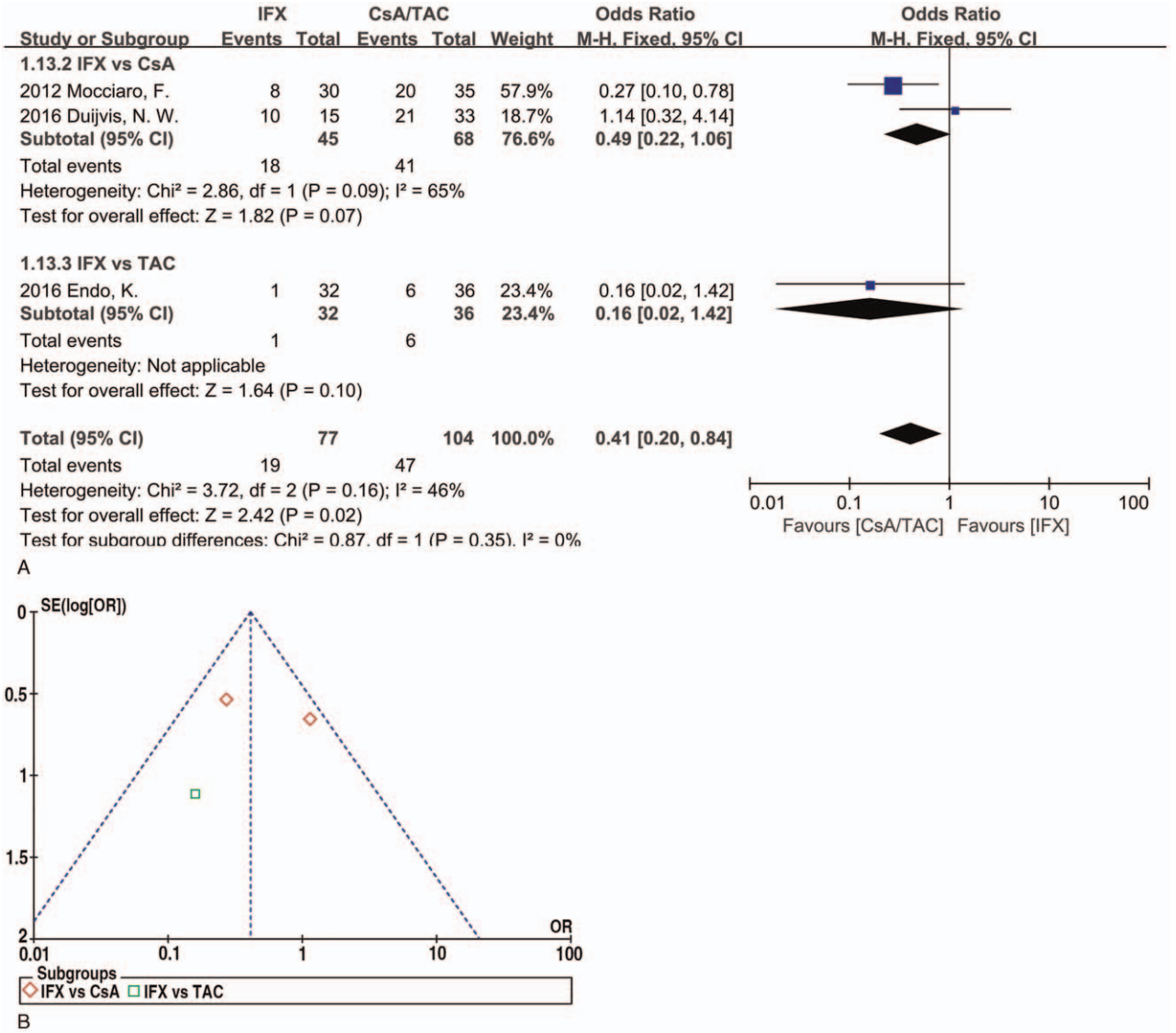

Figure 9. Three-year colectomy of IFX and calcineurin inhibitors. A: Forest plot. B: Funnel plot.

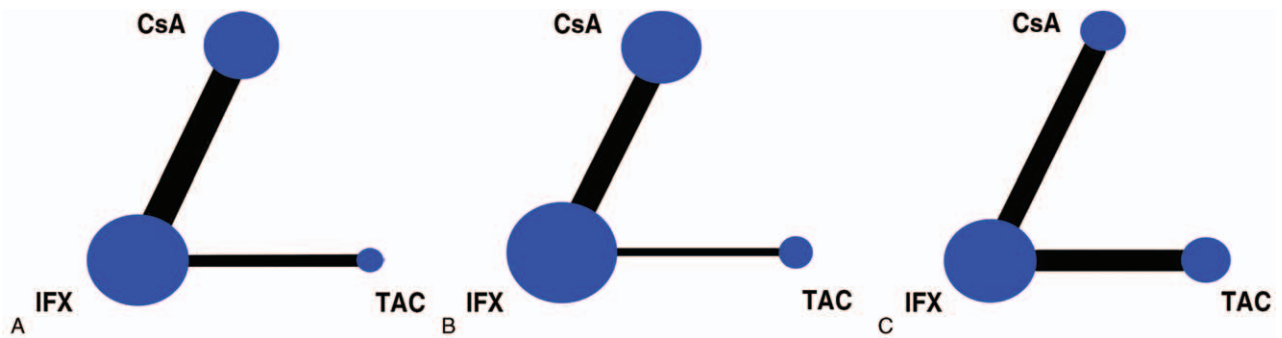

Figure 10. Network of included studies with the available direct comparisons for induction of short-term remission (A), short-term colectomy(B) and 1-year colectomy (C). The size of nodes and the thickness of edges are weighted according to the number of studies evaluating each treatment and direct comparison respectively.

Table 5

Network meta-analysis. Comparisons should be read from left to right.

Short-term Remission	TAC	1.186 (0.665, 2.119)	1.047 (0.700, 1.566)
		CsA	0.883 (0.580, 1.345)
			IFX
Short-term colectomy	TAC	0.626 (0.239, 1.640)	1.085 (0.438, 2.690)
		CsA	1.732 (1.257, 2.385)
			IFX
1-yr colectomy	TAC	0.729 (0.273, 1.946)	1.436 (0.569, 3.627)
		CsA	1.969 (1.423, 2.726)
			IFX

OR for comparisons are in the cell in common between the column-defining and row-defining treatment. OR > 1 favours row-defining treatment. Numbers in parentheses indicate 95% confidence interval. CsA = cyclosporine, IFX = infliximab, TAC = tacrolimus.

remission (OR: 1.186, 95% CI: 0.665, 2.119), lower short-term colectomy (OR: 0.626, 95% CI: 0.239, 1.640) and lower 1-Year colectomy (OR: 0.729, 95% CI: 0.273, 1.946) than CsA (Table 5). These support that TAC might be superior than CsA.

While the majority of patients have a mild to moderate course, up to 30% patients experience a severe disease course.[2,5,30] Lok et al reported that according to medical records in his hospital, 39.7% presented with mild disease, 30.2% with moderate disease and 27.4% with severe disease.[2] Nearly 30% to 40% of severe UC patients fail steroids treatment and may require colectomy in the short term.[27] Even those who avoid colectomy in the short term face a significant long-term risk of colectomy.[30] CsA was first shown to be effective in acute steroid-refractory severe UC more than 2 decades ago.[30,31] Five studies compared efficacy of CsA and IFX in steroid-refractory severe UC. ORs of colectomy were 0.61 [95% CI: 0.42–0.89, *P*:.01], 0.57 [95% CI: 0.39–0.83, *P*:.004] at the end of short-term and 1 year, respectively (Figs. 6 and 8). These results indicate that IFX is superior than CsA in the treatment of steroid-refractory severe UC. Regretfully, no studies compared efficacy of IFX and TAC in steroid-refractory severe UC.

At the same time, it seems that the IFX vs CsA OR of short-term remission favours IFX while the IFX vs TAC OR favours TAC, particularly in steroid-refractory moderate-to-severe UC (*P*:.25∼.26) (Figs. 3 and 4). Restults of Network meta-analysis also suggests that the order of pharmacological agents was TAC, IFX and CsA from high efficacy to low (Table 5). Even so, there is no significant difference between calcineurin inhibitors and IFX in UC, steroid-refractory moderate-to-severe UC or steroid-refractory severe UC (*P*:.25∼.94) (Figs. 3 and 4 and Table 5). Futher studies should be carried out to make a convincing conclusion.

Thiopurines and vedolizumab (the anti-integrin drug) are recommended in UC patients, especially acute severe UC patients, who achieve remission with calcineurin inhibitors treatment. In this study, almost all patients who achieved remission with calcineurin inhibitors were treated with thiopurines to maintenance remission. All patients who achieved remission with IFX were treated with IFX to maintenance remission. Recent research showed that calcineurin inhibitors in combination with vedolizumab allowed more than two thirds of patients to avoid colectomy.[32] This highlights difference in long-term efficacy between IFX and calcineurin inhibitors might be caused by difference in treatment to maintenance remission. If so, treatment with calcineurin inhibitors followed by biological agents, such as IFX, might be a potential choice for higher efficacy, more economical cost. Further studies are needed to assess this strategy.

Besides inherent limitations of individual trials, there are limitations to our analyses. First, different types of studies were included. This meta-analysis study included 2 prospective studies and 12 retrospective studies. 1 parallel, open-label, randomised controlled trial assayed efficacy of IFX vs CsA.[24] No difference was found in the short-term colectomy rate and colectomy rates at longer intervals were not provided.[24] One prospective study showed colectomy rate was significantly lower in IFX group than in CsA at 3-month and 12-month ($P = .04$). Second, the sample size in each trial is small and only a few trials were included. Consequently, confidence levels were very wide and there was a great deal of variability. That is more serious in meta-analysis of IFX vs TAC. All those made it hard to draw conclusions and weakened the reliability. Third, clinical indices to assess clinical response/remission differed among studies. The partial Mayo score (pMS),[29] the full Mayo score,[23] Lichtiger index,[24] Rachmilewitz Clinical Activity Index,[18] fulminant colitis index[19] and others were employed in studies. Though those correlate with each other and should be equally useful to assess short-term efficacy in UC, little variability among studies might be unavoidable. Fourth, disease associated confounders, particularly CRP, duration of disease prior to intervention and albumin level among studies varied enormously (Tables 1 and 2). CRP is commonly used as an inflammatory marker and correlates with the severity of disease.[4,23] CRP levels and/or durations of disease prior to intervention at baseline were statistically different between groups in several studies but both of them are significantly influenced the clinical outcomes.[4,23,30,33] Fifth, induction strategy differed a lot and maintenance therapy differed more among studies, sometimes even in 1 study. For example, at induction course, CsA was initially administered in different method, intravenously at 2 to 4 mg/kg or orally at 5 to 10 mg/kg. IFX was given as a single induction dose of 5 mg/kg, 3 induction infusions at weeks 0, 2, and 6. Different strategies may affect the results.[34] Sixth, there were no head-to-head trials to compare efficacy of CsA and TAC. The comparative efficacy analyses were based on indirect comparisons.

In summary, IFX treatment led to a lower short-term, 1-year colectomy rate and a trend of lower 3-year colectomy rate in UC patients and a lower short-term, 1-year colectomy rate in steroid-refractory severe UC patients than CsA. These indicate that IFX is superior than CsA. No significant differences in short-term, 1-year and 3-year colectomy rate were found between IFX and TAC. Results of network meta-analysis hint that TAC may be superior than CsA. Conclusion is significantly limited. Pragmatic head-to-head trials comparing TAC and CsA would significantly enhance clinical practice. Randomized trials with fixed protocol

are warranted to identify the optimal medical strategy in patients with UC or severe UC.

Author contributions

Jianming He conceived and designed the project. Qian Yang, Xuemei Jia, Ruitong Guo, Jianping Liu and Bolin Li did the literature search and data extraction. Zhenbiao Hu, Jianxin Liu and Jianming He did the statistical analysis. Jianming He, Xuemei Jia and Ruitong Guo prepared the figures. Jianming He and Qian Yang discussed the data. Jianming He wrote the manuscript. All authors reviewed the manuscript.

References

[1] Fumery M, Singh S, Dulai PS, et al. Natural history of adult ulcerative colitis in population-based cohorts: a systematic review. Clin Gastroenterol Hepatol 2018;16:343–56. e343.

[2] Lok KH, Hung HG, Ng CH, et al. Epidemiology and clinical characteristics of ulcerative colitis in Chinese population: experience from a single center in Hong Kong. J Gastroenterol Hepatol 2008; 23:406–10.

[3] Sharara AI, Al Awadhi S, Alharbi O, et al. Epidemiology, disease burden, and treatment challenges of ulcerative colitis in Africa and the Middle East. Expert Rev Gastroenterol Hepatol 2018;12:883–97.

[4] Rubin DT, Ananthakrishnan AN, Siegel CA, et al. ACG clinical guideline: ulcerative colitis in adults. Am J Gastroenterol 2019;114:384–413.

[5] Ng SC, Kaplan GG, Tang W, et al. Population density and risk of inflammatory bowel disease: a prospective population-based study in 13 countries or regions in Asia-Pacific. Am J Gastroenterol 2019;114: 107–15.

[6] Langan RC, Gotsch PB, Krafczyk MA, et al. Ulcerative colitis: diagnosis and treatment. Am Fam Physician 2007;76:1323–30.

[7] He J, Shin H, Wei X, et al. NPC1L1 knockout protects against colitis-associated tumorigenesis in mice. BMC Cancer 2015;15:189.

[8] Liang X, Hu J, He J. An optimized protocol of azoxymethane-dextran sodium sulfate induced colorectal tumor model in mice. Chin Med Sci J 2019;34:270–7.

[9] Fukaura K, Iboshi Y, Ogino H, et al. Mucosal profiles of immune molecules related to t helper and regulatory T cells predict future relapse in patients with quiescent ulcerative colitis. Inflamm Bowel Dis 2019; 25:1019–27.

[10] Lai LJ, Shen J, Ran ZH. Natural killer T cells and ulcerative colitis. Cell Immunol 2019;335:1–5.

[11] Williams CR, Gooch JL. Calcineurin inhibitors and immunosuppression - a tale of two isoforms. Expert Rev Mol Med 2012;14:e14.

[12] Kim EH, Kim DH, Park SJ, et al. Infliximab versus cyclosporine treatment for severe corticosteroid-refractory ulcerative colitis: a Korean, retrospective, single center study. Gut Liver 2015;9:601–6.

[13] Dean KE, Hikaka J, Huakau JT, et al. Infliximab or cyclosporine for acute severe ulcerative colitis: a retrospective analysis. J Gastroenterol Hepatol 2012;27:487–92.

[14] Zou H, Li R, Hu H, et al. Modulation of regulatory T cell activity by TNF receptor type II-targeting pharmacological agents. Front Immunol 2018;9:594.

[15] Matsumoto S, Kawamura H, Nishikawa T, et al. Tacrolimus versus anti-tumor necrosis factor agents for steroid-refractory active ulcerative colitis based on the severity of endoscopic findings: a single-center, open-label cohort study. Clin Exp Gastroenterol 2017;10:249–58.

[16] Singh S, Fumery M, Sandborn WJ, et al. Systematic review with network meta-analysis: first- and second-line pharmacotherapy for moderate-severe ulcerative colitis. Aliment Pharmacol Ther 2018; 47:162–75.

[17] Duijvis NW, Ten Hove AS, Ponsioen CI, et al. Similar short- and long-term colectomy rates with ciclosporin and infliximab treatment in hospitalised ulcerative colitis patients. J Crohns Colitis 2016;10:821–7.

[18] Endo K, Onodera M, Shiga H, et al. A comparison of short- and long-term therapeutic outcomes of infliximab- versus tacrolimus-based strategies for steroid-refractory ulcerative colitis. Gastroenterol Res Pract 2016;2016:3162595.

[19] Sjoberg M, Walch A, Meshkat M, et al. Infliximab or cyclosporine as rescue therapy in hospitalized patients with steroid-refractory ulcerative colitis: a retrospective observational study. Inflamm Bowel Dis 2012;18:212–8.

[20] Croft A, Walsh A, Doecke J, et al. Outcomes of salvage therapy for steroid-refractory acute severe ulcerative colitis: ciclosporin vs infliximab. Aliment Pharmacol Ther 2013;38:294–302.

[21] Yamamoto T, Shimoyama T, Umegae S, et al. Tacrolimus vs. anti-tumour necrosis factor agents for moderately to severely active ulcerative colitis: a retrospective observational study. Aliment Pharmacol Ther 2016;43:705–16.

[22] Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (editors). Cochrane Handbook for Systematic Reviews of Interventions version 6.1 (updated September 2020). Cochrane, 2020. Available from https://training.cochrane.org/cochrane-handbook-systematic-reviews-nterventions.

[23] Yamagami H, Nishida Y, Nagami Y, et al. A comparison of short-term therapeutic efficacy between infliximab and tacrolimus for moderate to severe ulcerative colitis. Rom J Intern Med 2017;55:151–7.

[24] Laharie D, Bourreille A, Branche J, et al. Ciclosporin versus infliximab in patients with severe ulcerative colitis refractory to intravenous steroids: a parallel, open-label randomised controlled trial. Lancet 2012;380: 1909–15.

[25] Ordas I, Domenech E, Manosa M, et al. Long-term efficacy and safety of cyclosporine in a cohort of steroid-refractory acute severe ulcerative colitis patients from the ENEIDA Registry (1989-2013): a nationwide multicenter study. Am J Gastroenterol 2017;112:1709–18.

[26] Nuki Y, Esaki M, Asano K, et al. Comparison of the therapeutic efficacy and safety between tacrolimus and infliximab for moderate-to-severe ulcerative colitis: a single center experience. Scand J Gastroenterol 2016;51:700–5.

[27] Mocciaro F, Renna S, Orlando A, et al. Cyclosporine or infliximab as rescue therapy in severe refractory ulcerative colitis: early and long-term data from a retrospective observational study. J Crohns Colitis 2012;6:681–6.

[28] Lowenberg M, Duijvis NW, Ponsioen C, et al. Length of hospital stay and associated hospital costs with infliximab versus cyclosporine in severe ulcerative colitis. Eur J Gastroenterol Hepatol 2014;26:1240–6.

[29] Otsuka T, Ooi M, Tobimatsu K, et al. Short-term and long-term outcomes of infliximab and tacrolimus treatment for moderate to severe ulcerative colitis: retrospective observational study. Kobe J Med Sci 2018;64:E140–8.

[30] Narula N, Marshall JK, Colombel JF, et al. Systematic review and meta-analysis: infliximab or cyclosporine as rescue therapy in patients with severe ulcerative colitis refractory to steroids. Am J Gastroenterol 2016;111:477–91.

[31] Lichtiger S, Present DH, Kornbluth A, et al. Cyclosporine in severe ulcerative colitis refractory to steroid therapy. N Engl J Med 1994; 330:1841–5.

[32] Pellet G, Stefanescu C, Carbonnel F, et al. Efficacy and safety of induction therapy with calcineurin inhibitors in combination with vedolizumab in patients with refractory ulcerative colitis. Clin Gastroenterol Hepatol 2019;17:494–501.

[33] Macaluso FS, Maida M, Ventimiglia M, et al. Factors affecting clinical and endoscopic outcomes of Placebo arm in trials of biologics and small molecule drugs in ulcerative colitis: a meta-analysis. Inflamm Bowel Dis 2019;25:987–97.

[34] Shah SC, Naymagon S, Panchal HJ, et al. Accelerated infliximab dosing increases 30-day colectomy in hospitalized ulcerative colitis patients: a propensity score analysis. Inflamm Bowel Dis 2018;24:651–9.