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Network meta-analysis and cost-effectiveness analysis of infliximab, cyclosporine and tacrolimus for ulcerative colitis

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Abstract

Background: Assess the efficiency and cost-effectiveness of infliximab, cyclosporine and tacrolimus for the treatment of ulcerative colitis (UC).

Methods: A literature search identified studies that investigated infliximab, cyclosporine or tacrolimus compared with placebo in UC patients. Short-term, long-term remission rates and response rates were employed to assess efficacy. Odds ratios with 95% confidence intervals were analyzed. A Markov model was constructed to simulate the progression in a cohort of patients with UC, with an over 10 years of time horizon, with a discount rate of 3%, and established threshold of €30,000/quality-adjusted life-year (QALY) or ¥82442/QALY.

Results: Results of network meta-analysis showed that the order was cyclosporine, tacrolimus, infliximab and placebo from high rate to low with regard to short-term clinical response. The comparison between infliximab versus cyclosporine achieved an incremental cost effectiveness ratio (ICER) of €184435/QALY and ¥531607/QALY, with a 0.34893 QALYs difference of efficacy, and an incremental cost of €64355 and ¥185494. Tacrolimus versus cyclosporine reached an ICER of €44236/QALY and ¥57494/QALY, with a difference of 0.40963 QALYs in efficacy, and a raising cost to €18120 and ¥23551. The probabilistic sensitivity analysis shows that cyclosporine would be cost-effective in the 75.8% of the simulations, tacrolimus in the 24.2%, and infliximab for the 0%.

Conclusion: Infliximab, cyclosporine and tacrolimus as salvage therapies are efficacious. For long-term of clinical remission, the order of pharmacological agents was tacrolimus, infliximab and cyclosporine from high efficacy to low while no significant difference is seen. In cost-effectiveness analysis, the cyclosporine versus infliximab or tacrolimus is expected to be at best.

Abbreviations: CSA = cyclosporine, ICER = incremental cost effectiveness ratio, IFX = infliximab, QALY = quality-adjusted life-year, UC = ulcerative colitis, TAC = tacrolimus.

Keywords: ulcerative colitis, infliximab, cyclosporine, tacrolimus, cost effectiveness analysis, markov model

1. Introduction

Ulcerative colitis (UC) is an idiopathic immune-mediated chronic inflammatory disease that primarily involves the colon and rectum.[1,2] In most of high-incidence areas, such as Western Europe and North America, incidence of UC has stabilized. In some low-incidence areas, such as the developing world, its incidence is increasing and that may partly attribute to psychological burden or changes in lifestyle.[3,4] Initial symptoms usually are typical manifestations of rectal inflammation: mixed blood and mucus diarrhea, abdominal pain and rectal urgency. Other clinical symptoms include weight loss, anemia, fever, and other extraintestinal manifestations. Long-term uncontrolled inflammation also associated with atypical hyperplasia or colorectal cancer.[1,5–7] Although UC does not significantly increase mortality, it seriously menaces quality of life and work ability.[8]

XW QL and SS contributed equally to this work.

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Besides, medical costs of long-term treatment and loss of work ability increase economic pressure for patients.[9]

In patients with mildly to moderately active UC, not severely active UC, 5-aminosalicylate therapies have been shown to be effective and safe. Corticosteroids have been widely used to treat moderate to severe active UC, but approximately 30% to 40% are steroids resistance and part of patients who are responsive to corticosteroid therapy will become steroid-dependent.[2,10] Anti-tumor necrosis factor-α biologics and calcineurin inhibitors has emerged as effective options for patients with moderate to severe UC, particularly for steroids resistant UC. Infliximab, a recombinant tumor necrosis factor-α monoclonal antibody, binds to and neutralizes tumor necrosis factor-α which plays a decisive role in activation, amplification and phenotypic stability of *T* cells. Cyclosporine and tacrolimus are 2 calcineurin inhibitors and inhibit the function of *T* cells by blocking transcription of *T* cell activating related genes.[2,11] Infliximab, cyclosporine and tacrolimus were reported to be effective to treat moderate to severe UC. However, there is no head-to-head trials to compare efficacies of the 3.[2] We previously conducted a meta-analysis to compare efficacies of infliximab, cyclosporine and tacrolimus using infliximab as a control and 13 of the 15 included trials were retrospective.[2] Here, we meta-analyzed efficacies of the 3 medications using placebo as a control and all included trials are prospective. Cost-effective analysis was also conducted here because difference in medical costs among them are huge.

2. Materials and methods

2.1. Meta-analysis and network meta-analysis

2.1.1. Search strategy and eligible criteria. 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.[2] We systematically searched PubMed, MEDLINE and Cochrane Library to identify published studies what examined the efficacy of infliximab and/or calcineurin inhibitors (tacrolimus [TAC] and/or cyclosporine [CSA]) compared with placebo.

The following search terms were used: ("colitis" or IBD or "inflammatory bowel disease") and ("infliximab" or remicade or anti-TNF or "tacrolimus" or fujimycin or FK506 or cyclosporine or cyclosporin or ciclosporinin) in any field. Articles written in English were included.

All studies were selected under the criteria: published in summary or in full text; included activity UC patients; clinical trials showing infliximab (IFX) and/or calcineurin inhibitors (TAC and/or CSA) versus placebo.; all included trials are prospective study. Studies without enough data were excluded from analysis.

All analyses were based on previously published studies, so the study did not require ethical approval and patient consent.

2.1.2. Study selection, data extraction and quality assessment. Each included study was thoroughly reviewed by 2 investigators. Two investigators confirmed the study included in the meta-analysis according to the review criteria and the following data were extracted from each included study: the first author, year of publication, country, design type, number of enrolled patients, gender, age, evaluation time, clinical response rate, clinical remission rate. Data were independently cross-checked.

2.1.3. Statistical analysis. Meta-analysis of aggregate patient data was conducted by combining Odds ratios 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 I2 statistic. No significant heterogeneity was indicated by $P > .1$ in Cochrane Q tests and a ratio less than 50% in I2 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.[2]

We performed network meta-analysis using a multivariate, consistency model, random-effects meta regression using STATA v.13.0. This frequentist approach provides a point estimate from the network along with 95% CI from the frequency distribution of the estimate.[2]

2.2. Cost-effectiveness analysis

2.2.1. Model structure. A Markov model was constructed to estimate the cost and clinical effect with IFX, CSA and TAC in the treatment of active UC (the model structure is shown in Fig. 1). The Markov model was given a time horizon of 10 years. The model simulates the development of the disease and identify 6 health states based on the severity of the disease: active colitis, clinical response, surgical (transition state), postsurgery remission, postsurgery complications and death.

The target population was a hypothetical group who consisted of steroid-refractory active UC adult patients with an average weight of 70 kg who should be contraindicated, unresponsive, or intolerance treatment of corticosteroids, 5-aminosalicylates (5-ASA) or azathioprine. These patients were assigned to therapeutic options of IFX, TAC and CSA, respectively, and monitored to treatment reactions. During the treatment period, patients with clinical response continued to receive treatment and maintained the response status, otherwise they eventually lost their response. During the treatment stage, patients without response changed to surgical treatment. Once patients changed to surgical treatment, they would stop the medication and would change to the surgical section of Markov model. This was reflected in the surgical part by 3 additional health states of surgery, postsurgery remission and postsurgery complications. In the model, the patient might change from any health state to death.

In this model, patients were treated with one of the following methods:

IFX: 5 mg/kg intravenous in 0, 2 and 6 weeks and every 8 weeks thereafter.

TAC: 4mg/d oral therapy.

CSA: 2mg/kg/d intravenous injection within the first 2 weeks and 5 mg/kg/d oral treatment after 2 weeks.

The patients who underwent surgical intervention could not concurrently receive any medication mentioned above.

2.2.2. Base-case analysis. The incremental cost-effectiveness ratio (ICER) based on the number of quality-adjusted life-years (QALYs) were calculated. The calculation was conducted using Tree-Age Pro 2014 software (Tree-Age Software, Inc., Boston, Massachusetts).[12] Each cycle length was 8 weeks. Estimate of

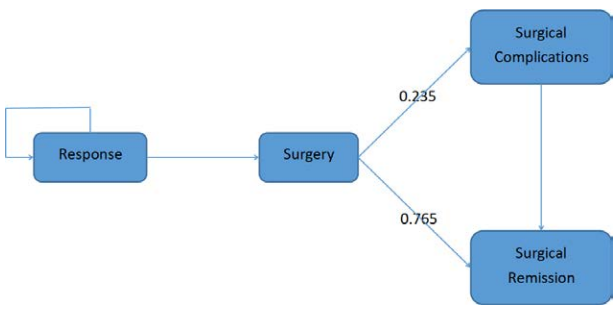

Figure 1. Markov diagram.

the cost was obtained from Dutch payment and Hebei Province Hospital System, China. A threshold limit of €30,000/QALY and ¥82,442/QALY was adopted according to the literature[13] and the average annual salary of local employees in China.

2.2.3. Sensitivity analysis. This study uses a single-factor sensitivity analysis, by changing the parameters in model to observe the results. Single-factor sensitivity setting variable range of ± 20%, showing the results using a tornado diagram to identify the parameters that affect the most on the results.

We also analyzed the consequences of modifying by 20%, in the lowest and the upper limit.[12] The following parameters included: weight, discount rate, cost of each drug, the surgical cost, the utility of each state and clinical response rates of CSA, TAC and IFX.

Monte Carlo simulations were performed with 1000 iterations, to make the probabilistic sensitivity analysis (PSA) for the options considered cost-effective in the base-case scenario via the cost-effectiveness scatterplot and the cost-effectiveness acceptability curves.[12]

3. Results

3.1. Studies included and the risk of bias

3.1.1. Literature search. A total of 3144 articles were identified using the above search strategy and 3113 were excluded on review of the title and abstract. A further 21 studies were excluded after careful review of the full text. Sixteen were not relevant, 2 did not have placebo control group, 3 did not provide sufficient data. Finally, 10 clinical trials were included. Details were shown in Figure 2.

3.1.2. Study characteristics. Of included 10 studies, all were prospective and 8 were multicenter. Six studies were selected to meta-analyze efficacy of IFX versus placebo,[14–19] 2 were selected to meta-analyze efficacy of CSA versus placebo,[20,21] 2 were selected to meta-analyze efficacy of TAC versus placebo.[22,23] The meta-analysis comprised 1017 patients, 437 treated with IFX, 27 treated with CSA, 51 treated with TAC, and 502 treated

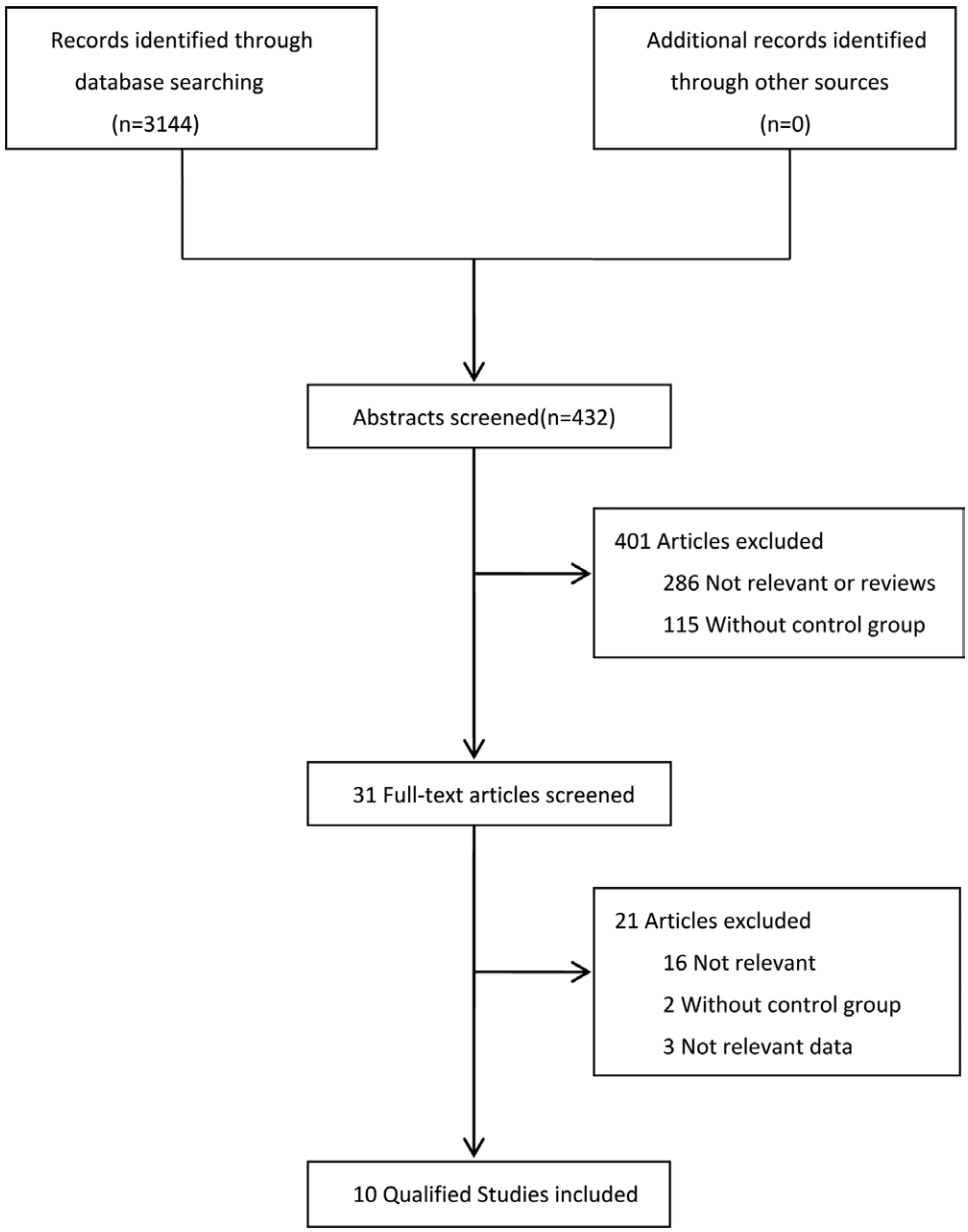

Figure 2. Preferred reporting items for meta-analyses flow chart.

with placebo. The detailed information was summarized in Table 1.

3.1.3. Quality assessment. In all included studies, their baselines are comparable. Quality assessment was performed for each study in accordance with the Cochrane Deviation Risk Assessment tool and shown in Figure 3.

3.1.4. Markov model inputs. A transition probability represents the probability of a cohort of patients moving from 1 health state to another at the end of each treatment cycle. Due to lack of data from head-to-head clinical trials comparing treatments 1 with each other, the probabilities of achieving response were estimated via comprehensive cumulative probability of 6 placebo-controlled trials of the 3 drugs (see Table 2).[15,16,18,20,22,23] In the surgical model cycle, patients undergoing surgery could move to one of the postsurgery health states (postsurgery remission or postsurgery complications). Patients in postsurgery remission could continue in the same health state. Patients experiencing postsurgery complications could respond to the treatment for their complications and enter postsurgery remission. The likelihood of surgical complications was calculated based on the study by Chaudhary MA.[13] There is no evidence that the lives of patients with ulcerative colitis are shorter, thus the probability of death was based on general population death rates.

Utilities: Utilities are ratios reflecting patient preferences for particular health states, ranging from 0 (death) to 1 (perfect health). Utilities of the 5 Markov health states (surgery only was a temporary transition state) were obtained from the study by Xie, F. Arseneau, K.O. et al.[24,25] The utilities are shown in Table 3.

Costs: The perspective was that of the Dutch payment and the Chinese payment; Modeled costs included direct healthcare costs (drug costs, consultant visits, hospital stay, surgery, endoscopy, therapeutic drug monitoring, and daycare), but not indirect healthcare costs (such as lost productivity costs for patients and their families), or direct non-healthcare costs (such as patient transportation costs).

Drug Acquisition and Administration Costs: Because IFX is administered IV in the hospital, the total cost associated with IFX was broken down into its acquisition cost and the cost of administering an IV infusion. The cost associated with CSA, IFX and healthcare resource use were drawn from a previous modeling study reported by Chaudhary, M.A. et al[13]; the drug cost of TAC was obtained from Muduma, G. et al,[26] then converted into Euro.

Surgical Procedures: Surgery consisting of a proctocolectomy with an ileoanal pouch, is standard treatment for patients not responding to therapy, usually performed in 2 separate operations. Therefore, costs are comprised of 2 surgical interventions, ileostomy (€1320.38) and colectomy with ileorectal anastomosis (€2728.64).[13] Patients successfully treated with surgery is discharged from the hospital after 10 days. In case of surgical complications (e.g., postsurgery wound infection, small bowel obstruction), an additional 10 days in the general

Table 1

Study characteristics.

First author	Publication year	Location	Type of study	Patients	Regimen	No.of patients	Gender Male/Female	Mean age (years)	Course	Response %	Remission %
Sands, B. E.	2001	USA	Multicenter; prospective	Severe,Steroid-Refractory UC	5mg/kg IFX	3	2/1	43.7	2W		66.7
					Placebo	3	2/1	40.3			0.0
Probert, C. S.	2003	UK	Multicenter; prospective	Moderately severe Steroid-Refractory UC	5mg/kg IFX	23	—	41	6W		39.0
					Placebo	20	—	40			30.0
Rutgeerts, P.	2005	USA	Multicenter, prospective	Moderate to Severe,Steroid-Refractory UC	5mg/kg IFX (RCT1)	121	78/43	42.4	54W	45.5	34.7
					Placebo (RCT1)	121	72/49	41.4		19.8	16.5
					5mg/kg IFX (RCT2)	121	76/45	40.5	30W	47.1	25.6
					Placebo (RCT2)	123	71/52	39.3		26.0	10.6
Jarnerot, G.	2005	Sweden	Multicenter; prospective	Severe to Moderately Severe,Steroid-Refractory UC	5mg/kg IFX	24	16/8	37.5	3M		40.0
					Placebo	21	8/13	36.2			33.0
Jiang, X. L.	2015	China	Single-cente, prospective	Moderate to Severe,Steroid-Refractory UC	5mg/kg IFX	41	26/15	34.3	30W	65.8	51.2
					Placebo	41	25/16	34.5		26.8	24.4
Kobayashi ,T.	2016	Japan	Multicenter, prospective	Steroid-Refractory UC	5mg/kg IFX	104	66/38	40	30W	46.2	21.2
					Placebo	104	67/37	37.8		31.7	16.3
Lichtiger S	1994	USA	Multicenter, prospective	Severe,Steroid-Refractory UC	CSA	11	4/7	34	2W	82.0	
					Placebo	9	5/4	43		0.0	
Sandborn WJ	1993	USA	Single-cente, prospective	Primary sclerosing cholangitis who have coexisting ulcerative colitis	CSA	16	10/6	36	1Y		93.8
					Placebo	10	6/4	45			60.0
H Ogata	2012	Japan	Multicenter, prospective	Moderate to Severe,Steroid-Refractory UC	TAC (10–15 ng/ml)	32	—	—	2W	59.3	11.1
					Placebo	30	—	—		13.3	0.0
H Ogata	2006	Japan	Multicenter, prospective	Moderate to Severe,Steroid-Refractory UC	TAC (10-15ng/ ml)	19	9/10	33.3	12W	68.4	20.0
					Placebo	20	9/11	30		10.0	5.9

CSA = cyclosporine, TAC = tacrolimus.

Table 2

Transition probabilities imputed in the models.

Probability	Estimate	SE	Source
FIX	0.67	0.007	Rutgeerts, P. et al[18]and Jiang, X.L. et al[15] And Kobayashi, T. et al[16]
CSA	0.82	0.001	Lichtiger, S. et al[20]
TAC	0.64	0.002	H Ogata et al[22,23]

CSA = cyclosporine, SE = standard error, TAC = tacrolimus.

Table 3

Utilities probabilities imputed in the models.

Point estimate	Utilities:	SE
0.79	Response	0.035
0.32	Active UC	0.045
0.68	Postsurgery remission	0.042
0.49	Postsurgery complications	0.046

SE = standard error.

ward are assumed to reflect the cost for the treatment of these complications.

Healthcare Resource Use: All patients are assumed to have an endoscopy when they are admitted into the hospital to evaluate the severity of UC and after achieving (surgical) remission in the first 8 weeks. After that, endoscopy would take place once in 8 weeks. Costs for a diagnostic endoscopy were calculated by taking the average of a colonoscopy (€307.78) and a sigmoidoscopy (€180.58), since both techniques are used for diagnosis of the exacerbation.[13] The frequency of consultant visit is assumed to synchronized with the endoscopy. Immunomodulators are also known for a significant side-effect profile and require careful monitoring.[27] When patients receive IV cyclosporine, their cyclosporine levels are measured every 2 days. While on oral cyclosporine, patients' cyclosporine levels should be tested biweekly for the first month, and then every 3 to 4 weeks. The cost of drug monitoring of tacrolimus is assumed consistent with cyclosporine cost. The discount rate is used to reflect time preferences. The cost and utility values both calculated at a 3% discount rate for the model.

Assuming the average weight is 70 kg for the patients, the unit and total costs are detailed in Table 4, 5.

3.2. Meta-analysis

Short-term clinical remission/response and long-term clinical remission/response were meta-analyzed, respectively. Six studies were selected for the meta-analysis of short-term clinical remission of IFX versus placebo.[14–19] The meta-analysis comprised 846 subjects, 428 in IFX group and 418 in placebo group. Efficacy was assessed between 2 weeks and 3 months. The pooled OR was 3.65 [95%CI: 2.56~5.20, $P < .00001$] (Fig. 4). Three studies were selected for the meta-analysis of short-term clinical response of IFX versus placebo.[15,16,18] The meta-analysis comprised 776 subjects, 387 in IFX group and 389 in placebo group. Efficacy was assessed at 8 weeks. The pooled OR was 3.56 [95%CI: 2.65~4.79, $P < .00001$] (Fig. 5). Visual inspection of the corresponding funnel plot revealed no publication bias (Fig. 4, 5). Those indicate that IFX might induce higher short-term clinical remission rate and response rate than placebo.

Three studies were selected for the meta-analysis of long-term clinical remission of IFX versus placebo.[15,16,18] The meta-analysis comprised 776 subjects, 387 in IFX group and 389 in placebo group. Efficacy was assessed between 3 months and 1 year. The pooled OR was 2.39 [95%CI: 1.68~3.42, $P < .00001$] (Fig. 6). Three studies were selected for the meta-analysis of long-term clinical response.[15,16,18] The meta-analysis comprised 774 subjects, 385 in IFX group and 389 in placebo group. Efficacy was assessed between 3 months and 1 year. The pooled OR was 2.53 [95%CI: 1.88~3.41, $P < .00001$] (Fig. 7). Visual inspection of the corresponding funnel plot revealed no publication bias (Fig. 6, 7). Those suggest that IFX can effectively induce long-term clinical remission and clinical response.

Two prospective trials focusing on efficacy of TAC versus placebo were conducted and reported.[22,23] Short-term clinical remission and clinical response were assessed at 2 weeks. The meta-analysis of short-term clinical remission comprised 94 patients, 47 in TAC group and 47 in placebo group, and the pooled OR was 5.53 [95%CI: 0.91~33.74, $P = .06$] (Fig. 8). The meta-analysis of short-term clinical response comprised 96 patients, 46 in TAC group and 50 in placebo group, and the pooled OR was 12.32 [95%CI: 4.36~34.81, $P < .00001$] (Fig. 9). Visual inspection of the corresponding funnel plot revealed no publication bias (Figure 8, 9). Those indicate that TAC can effectively induce short-term clinical remission and clinical response.

Two prospective trials focusing on efficacy of CSA versus placebo were reported.[20,21] Short-term clinical response was assessed at 2 weeks and long-term clinical remission was assessed at 1 year. The meta-analysis of short-term clinical response comprised 20 patients, 11 in CSA group and 9 in placebo group, and the pooled OR was 72.20 [95%CI: 3.04~1713.30, $P = .008$] (Fig. 10). The meta-analysis of long-term clinical remission comprised 26 patients, 16 in CSA group and 10 in placebo group, and the pooled OR was 10.00 [95%CI: 0.92~108.82, $P = .06$] (Fig. 11). Visual inspection of the corresponding funnel plot revealed no publication bias (Fig. 10, 11). Those suggest that CSA might induce higher short-term clinical response rate and long-term clinical remission rate than placebo.

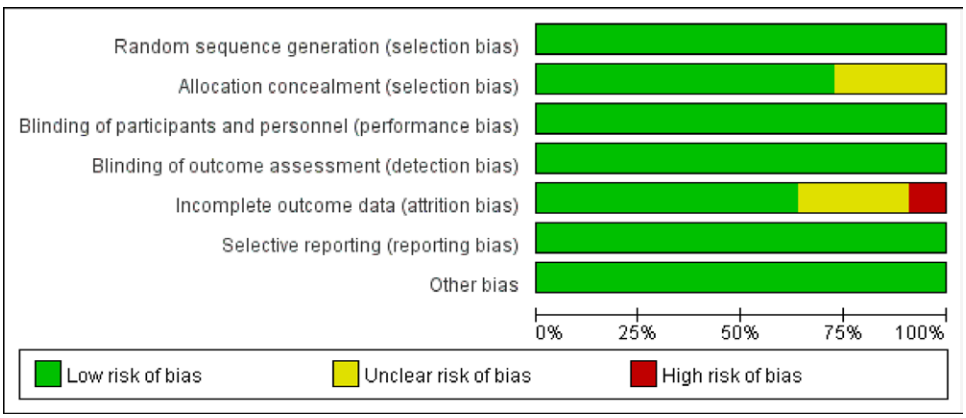

Figure 3. Bias Assessment risk.

Table 4

Total drug treatment cost estimates based on a typical 70 kg patient.

Healthcare use	Costs/unit (€)	Induction therapy (0–8 weeks)			Maintenance treatment (8 weeks cycle)			Surgery	Surgery Complication
		Infliximab	Tacrolimus	Cyclosporine	Infliximab	Tacrolimus	Cyclosporine		
Consult visit	70.65	2	2	2	1	1	1	1	0
Hospital day	402.62	0	0	0	0	0	0	10	10
Surgery	4049.02	0	0	0	0	0	0	1	0
Daycare infliximab	256.66	3	0	0	1	0	0	0	0
Therapeutic drug monitoring	104.65	0	9	9	0	2	2	0	0
Diagnostic endoscopy	244.18	2	2	2	1	1	1	1	0
Subtotal for resource use		€ 1399.64	€ 1571.51	€ 1571.51	€ 571.49	€ 524.13	€ 524.13	€ 8390.05	€ 4026.20
Infliximab	2264.78	3	0	0	1	0	0	0	0
Cyclosporine (intravenous)	9.28	0	0	14	0	0	0	0	0
Cyclosporine (oral)	11.16	0	0	42	0	0	56	0	0
Tacrolimus	6.57	0	56	0	0	56	0	0	0
Subtotal for medication costs		€ 6794.34	€ 367.92	€ 598.64	€ 2264.78	€ 367.92	€ 624.96	€ 0.00	€ 0.00
Total cost		€ 8193.98	€ 1939.43	€2170.15	€2836.27	€ 892.05	€ 1149.09	€ 8390.05	€ 4026.20

Table 5

Total drug treatment cost estimates based on a typical 70 kg patient in China.

Healthcare use	Costs/unit (¥)	Induction therapy (0–8 weeks)			Maintenance treatment (8 weeks cycle)			Surgery	Surgery complication
		Infliximab	Tacrolimus	Cyclosporine	Infliximab	Tacrolimus	Cyclosporine		
Consult visit	25	2	2	2	1	1	1	1	0
Hospital day	124	0	0	0	0	0	0	10	10
Surgery	6951	0	0	0	0	0	0	1	0
Therapeutic drug monitoring	170	0	9	9	0	2	2	0	0
Diagnostic endoscopy	391.24	2	2	2	1	1	1	1	0
Subtotal for resource use		¥ 832.48	¥ 2362.48	¥ 2362.48	¥ 416.24	¥ 756.24	¥ 756.24	¥ 8607.24	¥ 1240.00
Infliximab	7023.8	3	0	0	1	0	0	0	0
Cyclosporine (intravenous)	7.5	0	0	14	0	0	0	0	0
Cyclosporine (oral)	2.5	0	0	42	0	0	56	0	0
Tacrolimus	2.99	0	56	0	0	56	0	0	0
Subtotal for medication costs		¥ 21,071.40	¥ 167.44	¥ 210.00	¥ 7023.80	¥ 167.44	¥ 140.00	¥ 0.00	¥ 0.00
Total cost		¥ 21,903.88	¥ 2529.92	¥ 2572.48	¥ 7440.04	¥ 923.68	¥ 896.24	¥ 8607.24	¥ 1240.00

3.3. Network meta-analysis

Network meta-analysis was performed to compare the relative efficacy of IFX, TAC, CSA and placebo (Fig. 12, Table 6).

For short-term of clinical response, the order of pharmacological agents was CSA, TAC, IFX and placebo from high efficacy to low. There was a significant difference between CSA/TAC/IFX and placebo. There was no significant difference among CSA, TAC and IFX.

For short-term of clinical remission, the order was TAC, IFX and placebo from high efficacy to low. There was a significant difference between IFX and placebo. There was no significant difference between TAC and IFX or between TAC and placebo.

For long-term of clinical remission, the order was CSA, IFX and placebo from high to low. There was a significant difference between IFX and placebo. There was no significant difference between CSA and IFX or between CSA and placebo.

We included the studies of each drug versus placebo, along with the head-to-head trials of IFX versus CSA and IFX versus TAC. The network meta-analysis was performed again to compare the relative efficacy of IFX, TAC, CSA and placebo (Fig. 13, Table 7).

For short-term of clinical response, the order of pharmacological agents was CSA, IFX, TAC and placebo from high efficacy to low. There was a significant difference between CSA/TAC/IFX versus placebo. No significant difference was observed between the CSA, TAC and the IFX.

For short-term of clinical remission, the order of pharmacological agents was IFX, CSA, TAC and placebo from high efficacy to low. There was a significant difference between CSA/TAC/IFX versus placebo. No significant difference was observed between the CSA, TAC and the IFX.

For long-term of clinical response, the order of pharmacological agents was IFX, TAC and placebo from high efficacy to low. There was a significant difference between IFX and placebo. No significant difference was observed between TAC and IFX or between TAC and placebo.

For long-term of clinical remission, the order of pharmacological agents was TAC, IFX, CSA and placebo from high efficacy to low. There was a significant difference between TAC/IFX and placebo. No significant difference was observed between the CSA, TAC and the IFX, or between CSA and placebo.

3.4. Cost-effectiveness analysis

3.4.1. Base-case analysis. The results in the basic case have been given in Tables 8, 9and Figure 14, 15. The model runs for

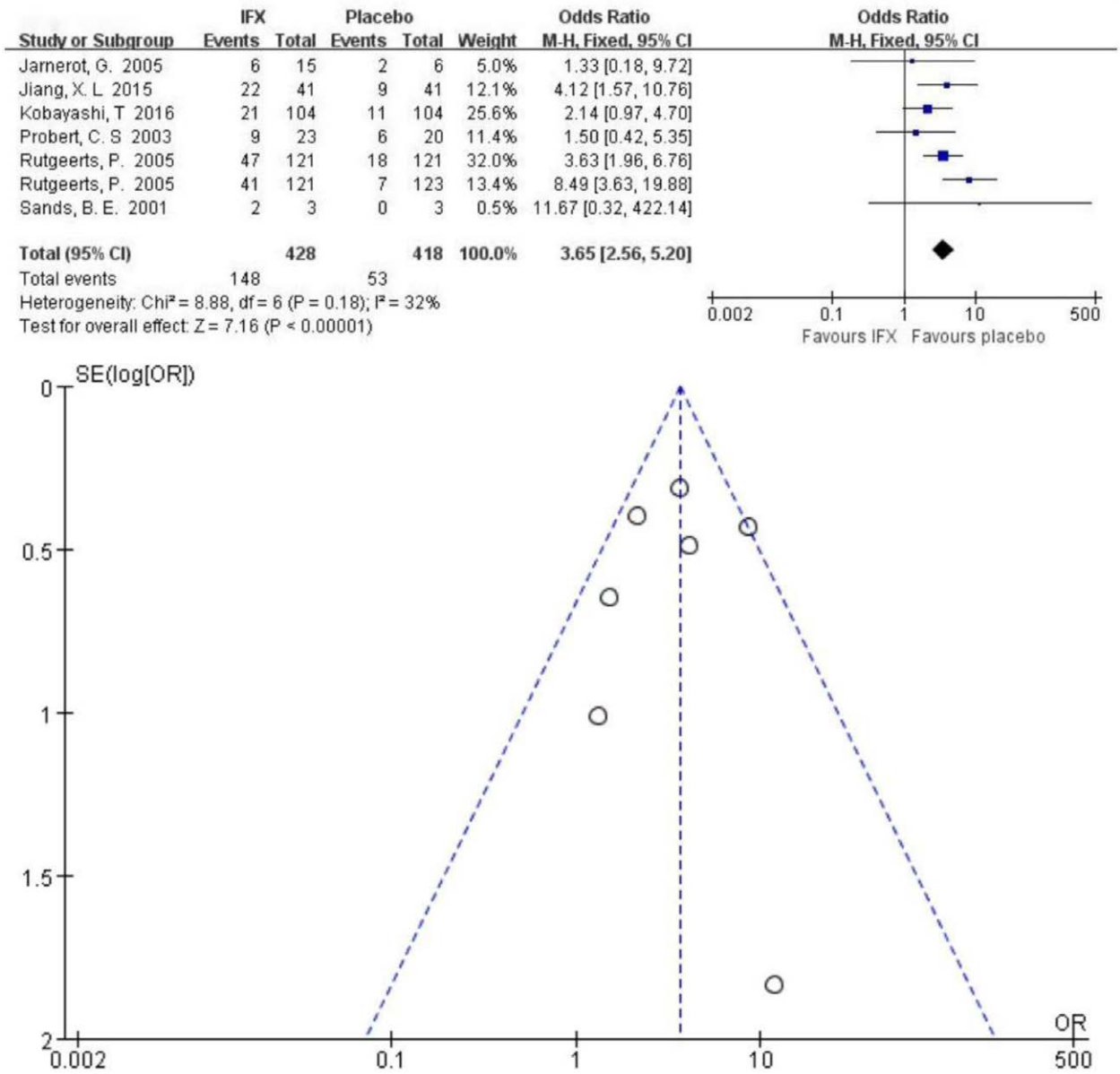

Figure 4. Short-term clinical remission of IFX and placebo. (Above: Forest plot. Below: Funnel plot), IFX = infliximab.

10 years and the results show that the CSA cost €58,191.35 and yielded 19.00128 QALYs, the corresponding numbers is €76,311.67 and 19.41091 QALYs for the TAC, and €1,22,546.34 and 19.35021 QALYs for the IFX. The ICER is €44,235.81/QALY for TAC versus CSA, and €1,84,435.24/QALY for IFX versus CSA. Under the willingness to pay threshold of €30,000 per QALY, neither TAC nor IFX is cost-effective, but TAC is closer to the threshold.

Based on the Chinese payment, the results show that the CSA cost ¥51,510.40 and yielded 19.00128 QALYs, the corresponding numbers is ¥75,061.60 and 19.41091 QALYs for the TAC, and ¥2,37,003.92 and 19.35021 QALYs for the IFX. The ICER is ¥57,493.8277/QALY for TAC versus CSA, and ¥5,31,606.7007/QALY for IFX versus CSA. Under the threshold of willingness to pay ¥82,442 per QALY, The TAC is cost-effective.

3.4.2. The results of sensitivity analysis. One-Way Sensitivity Analysis: 1-way sensitivity analyses show that the result of Cost-effective analysis is most sensitive to the changes in clinical response rate of CSA and drug cost of CSA, and discount rate. The surgical cost and the cost of postsurgery complications also have certain extent of impact for the result (Fig. 16).

When the CSA response rate is 0.656, TAC is more cost-effective than CSA, and both is more cost-effective than IFX. In addition to this, the changes of other parameters have no influence for the stability of the results. For the defined threshold of €30,000/QALY, neither TAC nor IFX is cost-effective for the patients who weight is in the range of 56 to 84 kg. But with the weight growth, TAC approaches the threshold. About the drug response rates, TAC is cost-effective when CSA response rate is 0.7216 or TAC response rate is 0.768. Concerning the utility values, TAC is cost-effective when the utility value of remission state is from 0.632 to 0.6952 or the utility value of postsurgery remission state is 0.816 (See Table S1, Supplemental Digital Content, http://links.lww.com/MD/H953).

The cost-effectiveness scatterplot shows that TAC and IFX are located above for CSA. It indicates that the difference of 3

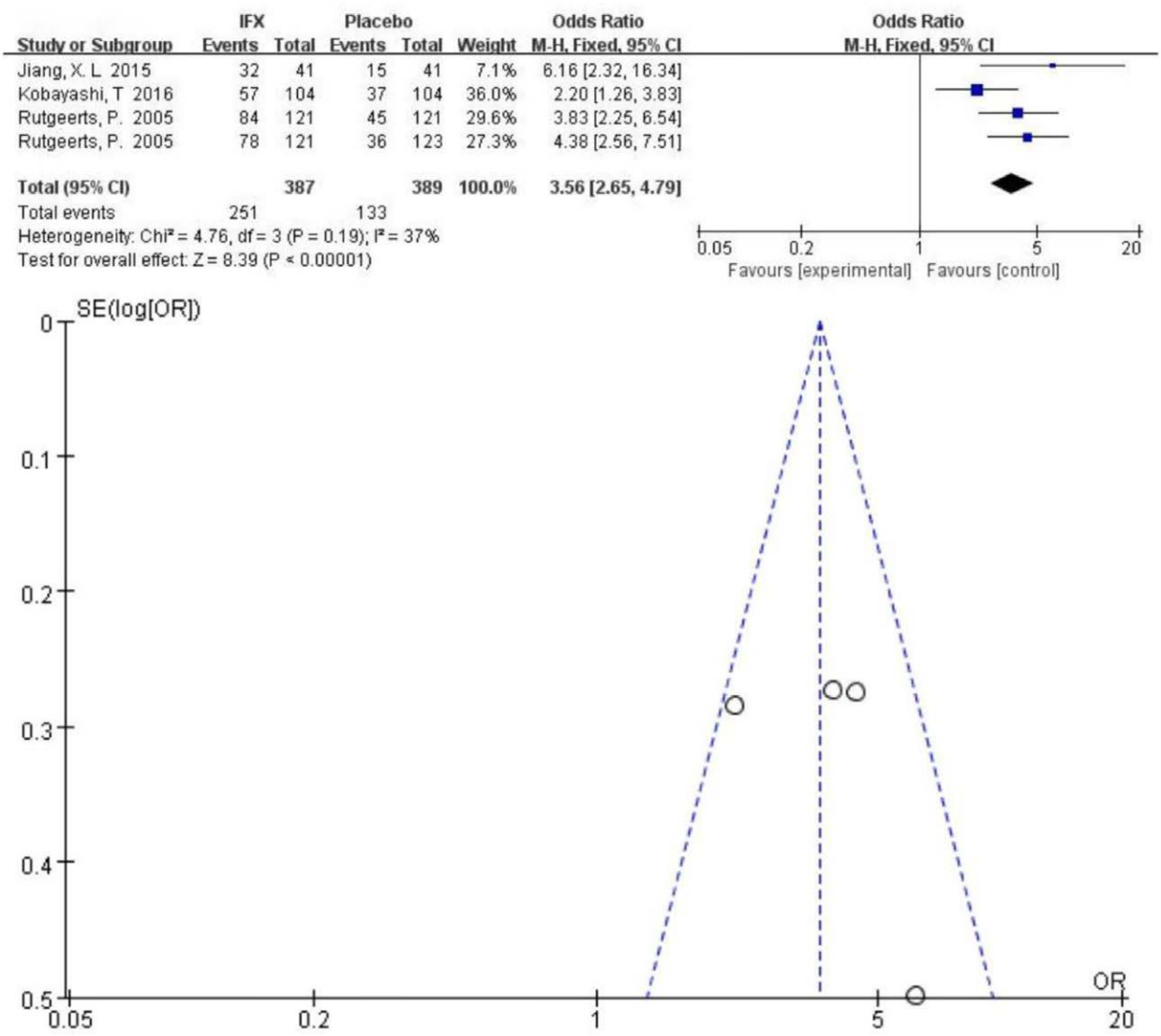

Figure 5. Short-term clinical response of IFX and placebo. (Above: Forest plot. Below: Funnel plot).

drugs is small in the effectiveness, but the cost is IFX, TAC, CSA from high to low (Fig. 17).

3.4.3. Probabilistic Sensitivity Analysis The result of probabilistic sensitivity analysis is displayed in a cost-effective acceptability curve (Fig. 18). The acceptability curve shows that the CSA has higher probability, account for 75.8% of the simulation results, TAC is 24.2% and IFX is 0%, at the willingness to pay threshold of €30,000 per QALY. As the threshold of the willingness to pay increases, the probability of TAC having cost-effective advantage gradually increases. When the payment willingness threshold reaches €44,200 to €44,400/QALY, TAC reaches 50%, and CSA is 50%, IFX remains 0%. If the payment willingness threshold continues to rise, the probability of cost-effective advantage of TAC will higher than CSA (Fig. 18).

4. Discussion

UC generally runs a chronic course and is characterized by alternating periods of exacerbation and remission.[1,2] Corticosteroids are first-line therapy. However, approximately 30% of patients do not respond to corticosteroid therapy and about 20% patients who are responsive to corticosteroid therapy will become steroid dependent after 1 year of treatment.[2,28–31] Infliximab, cyclosporine and tacrolimus are salvage therapies.[14–23,32,33] Here, we meta-analyzed efficacies of the 3 medications. Infliximab significantly induced short-term clinical remission (OR:3.65; 95%CI:2.56–5.20; $P < .00001$)/response (OR:3.56; 95%CI:2.65–4.79; $P < .00001$) and long-term clinical remission (OR:2.39; 95%CI:1.68–3.42; $P < .00001$)/response (OR:2.53; 95%CI:1.88–3.14; $P < .00001$) in steroid-refractory active UC patients (Fig. 4–7). And in the induction phase, cyclosporine and tacrolimus are associated with statistically significant beneficial effects relative to placebo (Fig. 8–11). These indicate that infliximab, cyclosporine and tacrolimus are efficacious salvage therapies. This is consistent with our previous work[2] and the study by Narula et al.[34]

Nonetheless, positioning infliximab, cyclosporine and tacrolimus for treating UC is in great debate. We previously conducted a network meta-analysis to compare relative efficacies of IFX, TAC and CSA.[2] In that work, 13 of 15 included studies were retrospective and IFX was employed as the comparator because no head to head trial to compare efficacies of cyclosporine and

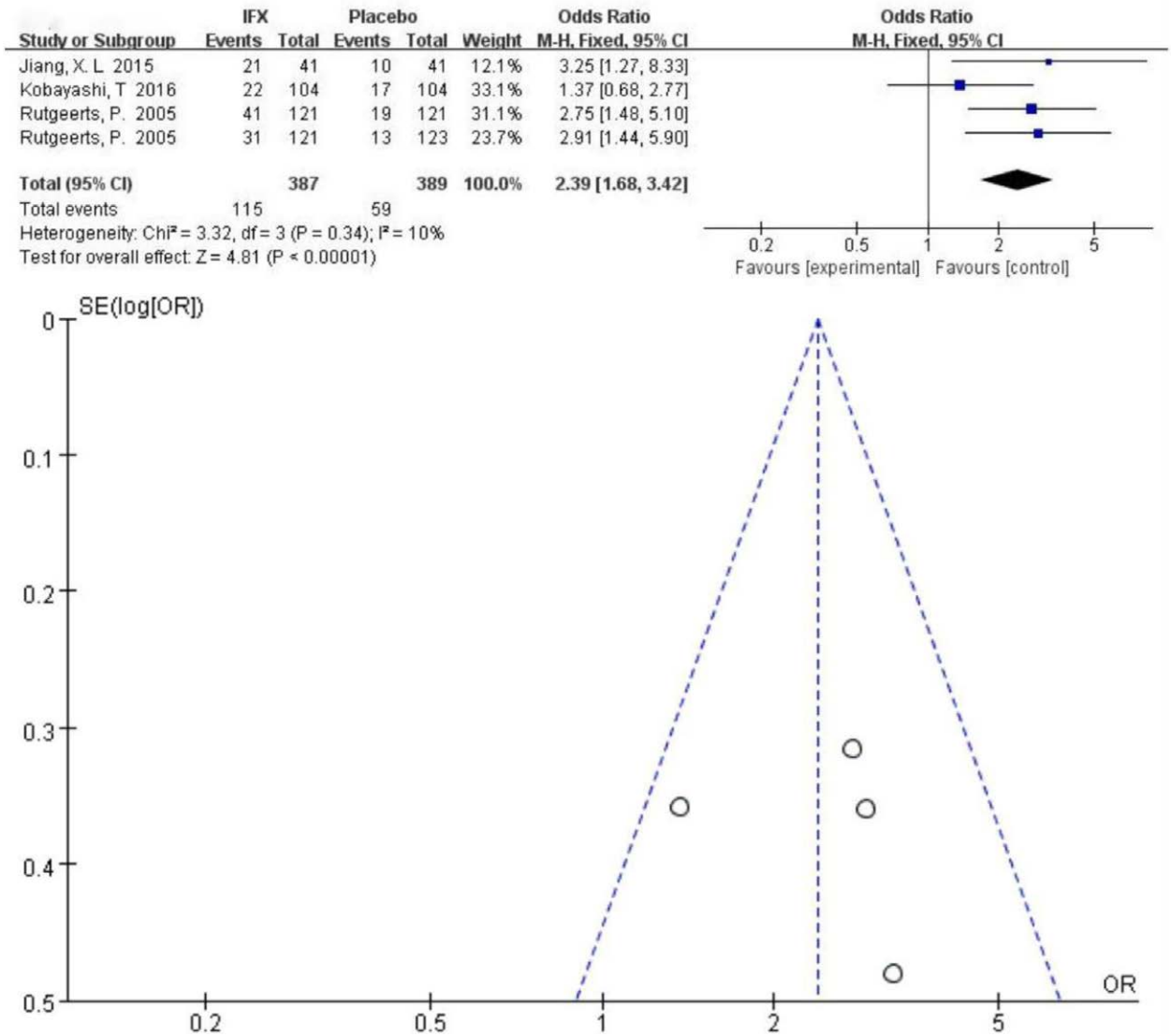

Figure 6. Long-term clinical remission of IFX and placebo. (Above: Forest plot. Below: Funnel plot), IFX = infliximab.

tacrolimus was reported. Here, we included prospective studies on the 3 medications versus placebo. The result was that cyclosporine was superior than infliximab (long-term of clinical remission) (Table 2), and that was different to the previous work. This difference maybe is a small number of CSA trials with small sample sizes introducing significant uncertainty in results. Therefore, we combined previous and this work, and performed data updates. The order of pharmacological agents was tacrolimus, infliximab, cyclosporine and placebo from high efficacy to low (long-term of clinical remission) (Table 3), and that was similar to the previous work. These indicate that infliximab is superior than cyclosporine in the treatment of UC.

UC generally begins in young adulthood and lasts throughout life.[2] Because of the chronic and recurrent nature of the disease, patients with UC often require either continuous or intermittent treatment throughout the course of their disease.[35] Cyclosporine and tacrolimus are 2 calcineurin inhibitors recommended to treat UC as salvage therapy.[1] Infliximab has conventionally been one of the mainstays of anti-TNF-α therapy for UC.[1] Due to the differences in drug prices, the cost of the treatment varies greatly. So we performed cost-effective analysis of infliximab, cyclosporine and tacrolimus. And the cost-effective analysis included both the Dutch and China perspectives (represents the high-income and middle-income countries, respectively). According to the Dutch payment perspective, the order of cost-effectiveness agents was cyclosporine, tacrolimus and infliximab from high to low. This result is similar to the China payment perspective. At the same time, our results suggest that the cost of treating UC in China is higher than in Dutch, more especially for the treatment of infliximab. This may be because the 2 countries are at different levels of development. Based on our analysis, cyclosporine would be the most cost-effective alternative for the target population. Because costs were estimated from previous modeling studies, the productivity costs were excluded even though they are significant in UC. Therefore, the results were exploratory in nature and should be interpreted with caution.

Besides inherent limitations of individual trials, there are some limitations to our analysis. First, different types of studies were included. This analysis included 2 single-center prospective studies and 8 multicenter prospective studies. Second, colectomy is generally the last choice of salvage therapy. Therefore, the colectomy rate is the primary end-point

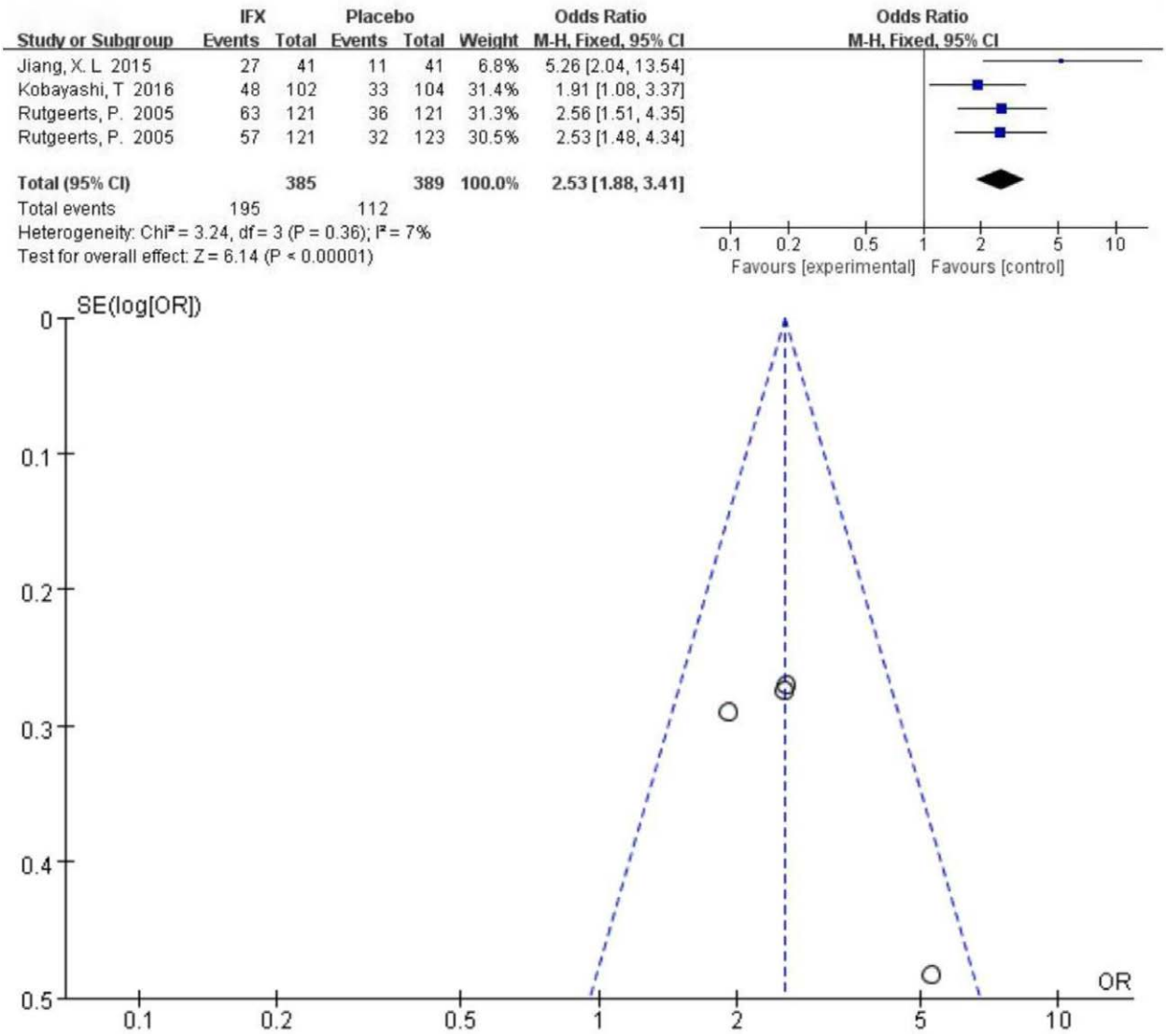

Figure 7. Long-term clinical response of IFX and placebo. (Above: Forest plot. Below: Funnel plot), IFX = infliximab.

to access the efficacy of medications in most of studies. IFX treatment significantly decreased colectomy rate in UC patients than cyclosporine and tacrolimus did (OR:0.63; 95%CI:0.47–0.85; P:0.003).[2] With increased time of post-treatment, results favored IFX more (OR:0.30; 95%CI:0.16–0.59; $P < .001$).[2] It suggests that infliximab treatment can decrease in the associated costs of complications from hospitalization and surgery, and can improve the health-related quality of life (HRQL) of these patients in the long term. Given the short duration of the RCTs of therapies, the data about colectomy rate is lacking, so that no correlation analysis performed. This is a serious deficiency for our study, maybe will reverses the results. Third, only a few trials were included and sample size is small in some trials. This problem is more serious in the trials of CSA versus placebo. Consequently, confidence levels were wide and there was a great deal of variability. Fourth, the induction strategy used in clinical trials is different, and maintenance therapy all is diverse between each study, and even in the same study. For example, at induction course, the CSA was administered in different methods, intravenous injection at 2 to 4 mg/kg or oral drug at 5 to 10 mg/kg, while IFX was given 5 mg/kg as a single induction dose, injection respectively at weeks 0, 2 and 6. The different strategies may have some impact on the therapeutic results. Fifth, the transfer probabilities in the model is based on the data of published trial, while the evaluation time of the 2 clinical trials of TAC is short (2 weeks), and the trial about clinical response of CSA included only 1 and the sample size is relatively small. Thus, we performed 1-way sensitivity analysis and probabilistic sensitivity analysis to mitigated this deviation. Sixth, the associated cost of treatment also extracted from the literature. And the weight in the model is the weight of our hypothetical population. They may have some influence on the results of cost-effectiveness analysis. But, the sensitivity analysis that we performed has mitigated these deviations. Seventh, the indirect cost is not included in our model, such as loss of labor production, need the care of others. We observed that the age of patients is between 30 and 50 years old, which means they are at the stage of career development. In Van der Valk et al's study, loss of labor productivity rose to 39% of total UC costs.[36] Therefore, it is necessary to carry out a cost-effectiveness analysis that includes the indirect costs. Eighth, the regimen of maintenance therapy is various between clinical trials. Usually, the patients with UC who through induction therapy with calcineurin inhibitors were recommended with thiopurines

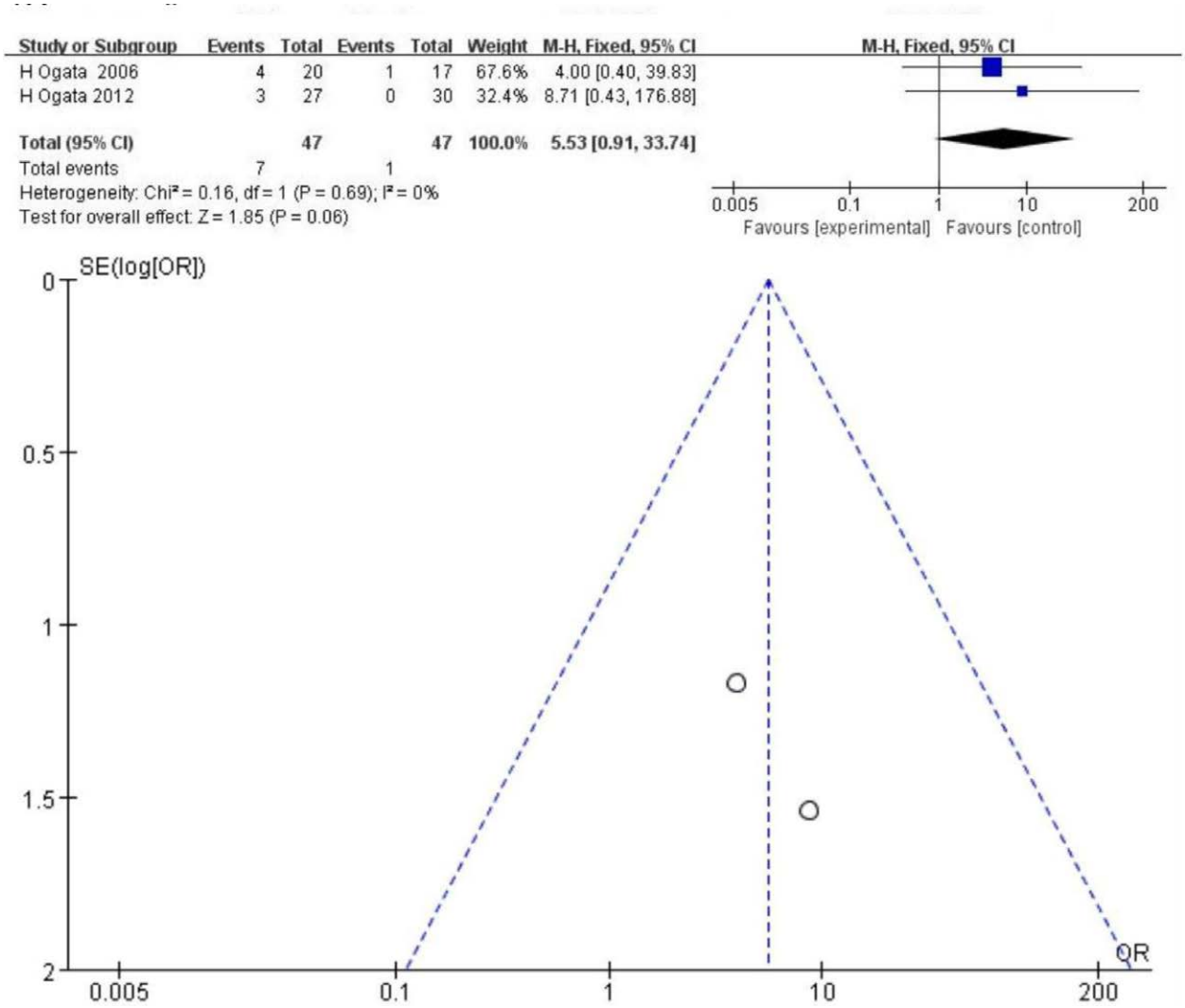

Figure 8. Short-term clinical remission of TAC and placebo. (Above: Forest plot. Below: Funnel plot), TAC = tacrolimus.

and vedolizumab (the anti-integrin drug) to maintain remission. While the patients who through induction therapy with IFX were treated with IFX to maintain remission. But recent research has showed that calcineurin inhibitors in combination with vedolizumab can saved more than 2 thirds of the patients from colectomy.[37] This research suggests that different treatment strategies during the maintenance phase of remission may be influence the ultimate outcome of treatment. If so, induction therapy with calcineurin inhibitors, followed by biological agents to maintain remission, such as infliximab, adalimumab, golimumab, and vedolizumab may become potential choices for higher efficacy or more cost-effectiveness. Of course, the efficacy of these treatment regimens needs further research to assess.

In conclusion, for the patients with UC, the CSA appears more cost-effective than TAC and IFX. The analysis provides a reference for physicians and patients when choosing treatment options.

Acknowledgments

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All authors have read and agreed to the published version of the manuscript.

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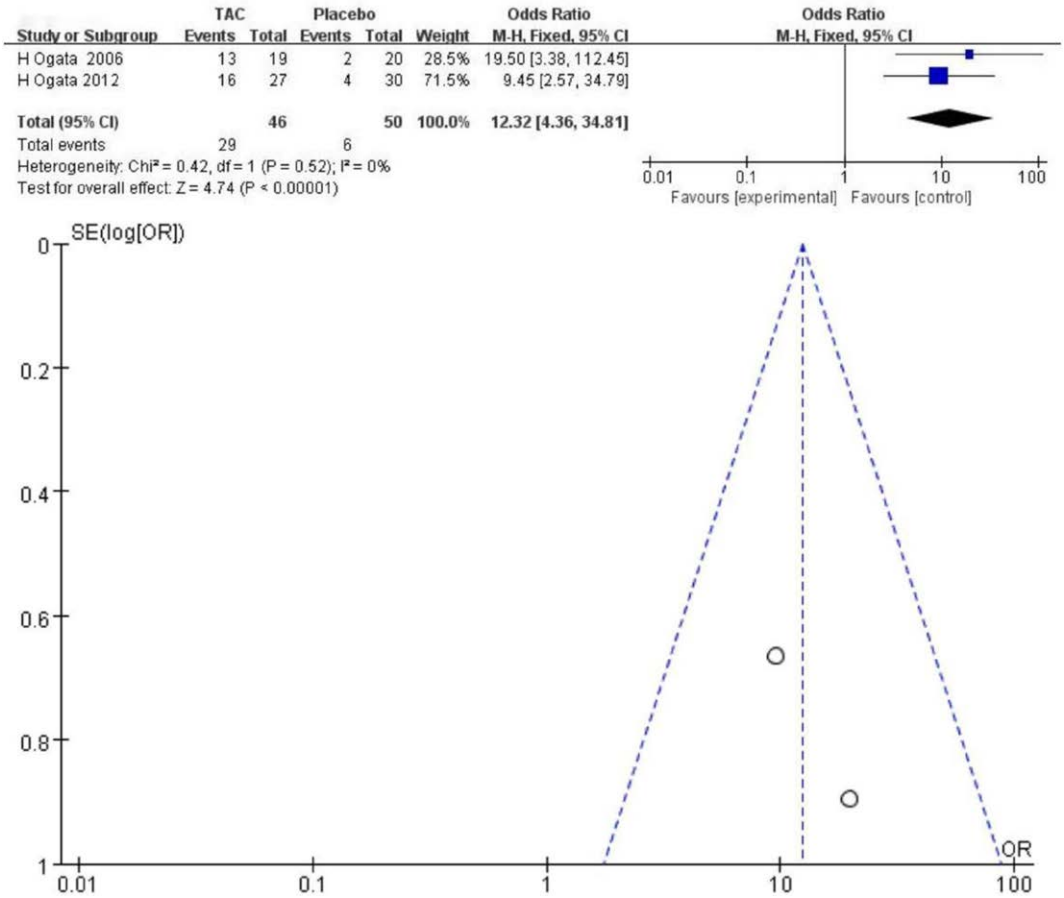

Figure 9. Short-term clinical response of TAC and placebo. (Above: Forest plot. Below: Funnel plot), TAC = tacrolimus.

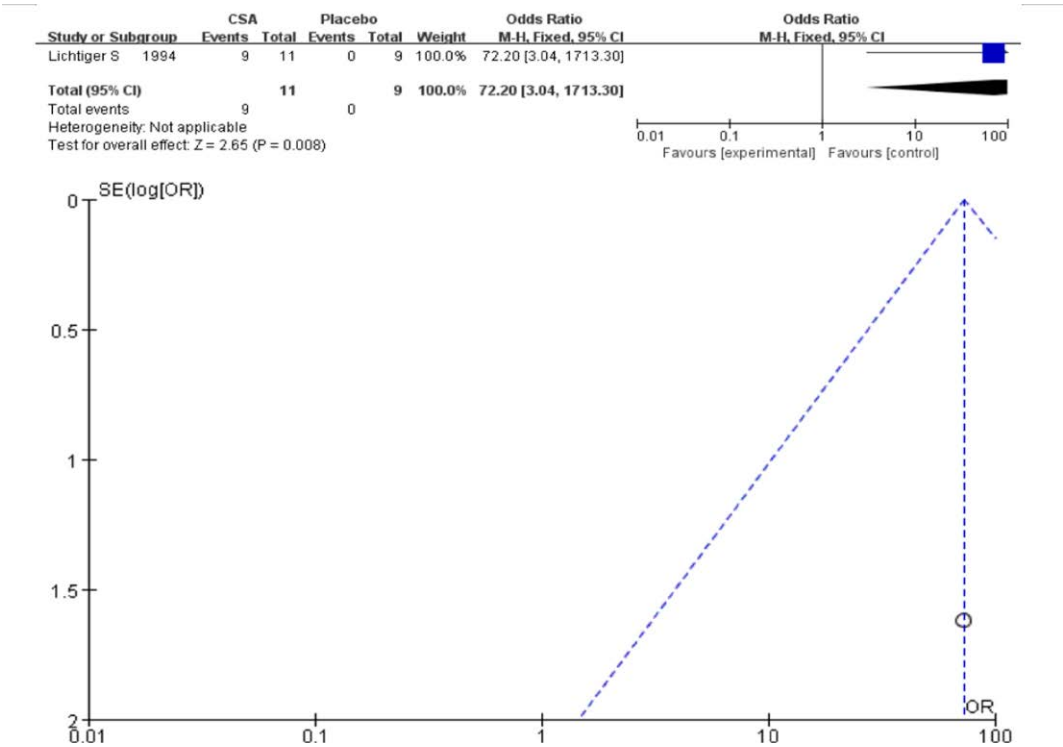

Figure 10. Short-term clinical response of CSA and placebo. (Above: Forest plot. Below: Funnel plot), CSA = cyclosporine.

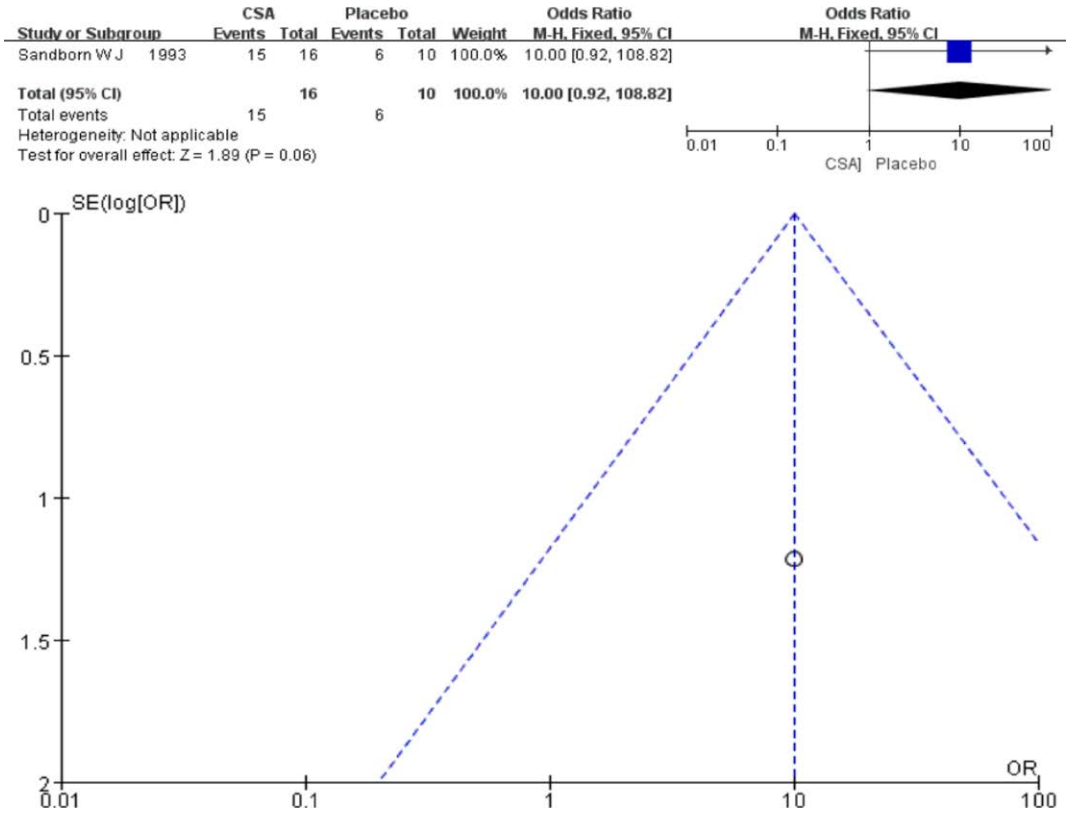

Figure 11. Long-term clinical remission of CSA and placebo. (Above: Forest plot. Below: Funnel plot), CSA = cyclosporine.

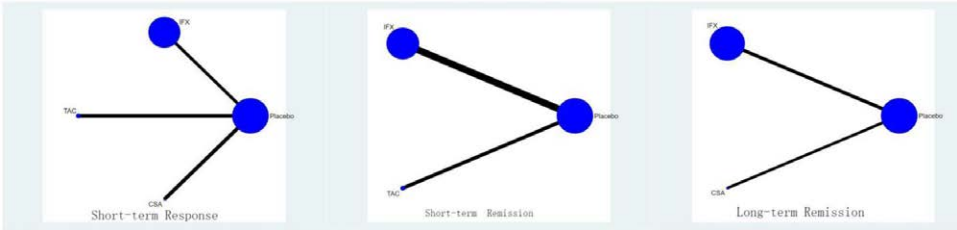

Figure 12. Network of included studies with the available direct comparisons for induction of short-term response, short-term remission and long-term remission. The size of nodes and the thickness of edges are weighted according to the number of studies evaluating each treatment and direct comparison respectively.

Table 6

Network meta-analysis. Comparisons should be read from left to right. OR for comparisons are in the cell in common between the column-defining and row-defining treatment, OR < 1 favor row-defining treatment. Numbers in parentheses indicate 95% confidence interval.

	Short-term Response		
IFX			
0.50 (0.16,1.59)	**TAC**		
0.05 (0.00,1.25)	0.10 (0.00,2.89)	**CSA**	
3.61 (2.48,5.25)	7.16 (2.42,21.14)	72.20(2.96,1760.64)	**Placebo**
Short-term remission			
IFX			
0.69 (0.10,4.88)	**TAC**		
3.43 (2.10,5.59)	5.00 (0.75,33.45)	**Placebo**	
Long-term remission			
IFX			
0.24 (0.02,2.72)	**CSA**		
2.39 (1.63,3.50)	10.00 (0.91,110.38)	**Placebo**	

CSA = cyclosporine, IFX = infliximab, TAC = tacrolimus.

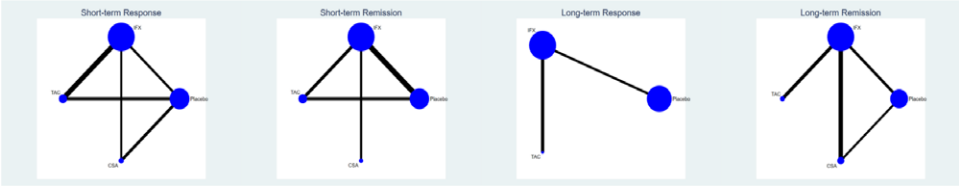

Figure 13. Network of included studies with the available direct comparisons for induction of short-term response, short-term remission and long-term response, long-term remission. The size of nodes and the thickness of edges are weighted according to the number of studies evaluating each treatment and direct comparison respectively.

Table 7

Network meta-analysis. Comparisons should be read from left to right. OR for comparisons are in the cell in common between the column-defining and row-defining treatment, OR < 1 favor row-defining treatment. Numbers in parentheses indicate 95% confidence interval.

Short-term response			
IFX			
1.16 (0.65,2.05)	**TAC**		
1.00 (0.42,2.38)	0.86 (0.31,2.43)	**CSA**	
4.36 (2.71,7.02)	3.77 (1.91,7.42)	4.37 (1.62,11.80)	**Placebo**
Short-term remission			
IFX			
1.13 (0.67,1.93)	**TAC**		
1.08 (0.46,2.54)	0.96 (0.35,2.61)	**CSA**	
3.56 (2.31,5.48)	3.14 (1.62,6.10)	3.28 (1.26,8.53)	**Placebo**
Long-term response			
IFX			
2.54 (0.69,9.28)	**TAC**		
2.53 (1.88,3.41)	1.00 (0.26,3.78)	**Placebo**	
Long-term remission			
IFX			
0.99 (0.44,2.25)	**TAC**		
1.32 (0.69,2.53)	1.33 (0.47,3.75)	**CSA**	
2.58 (1.54,4.34)	2.59 (1.02,6.63)	1.95 (0.87,4.38)	**Placebo**

CSA = cyclosporine, IFX = infliximab, TAC = tacrolimus.

Table 8

Results of CEA in Dutch.

Strategy	QALY	Incremental efficacy (QALY)	Cost (€)	Incremental cost (€)	ICER (€/QALY)	Avg CE (€/QALY)
CSA	19.00128	0	58,191.3527	0	0	3062.4967
TAC	19.41091	0.40963	76,311.6688	18,120.3161	44,235.81	3931.3798
IFX	19.35021	0.34893	1,22,546.3421	64,354.9894	1,84,435.24	6333.07546

CSA = cyclosporine, CEA = cost-effective analysis, IFX = infliximab, QALY = quality-adjusted life-year, TAC = tacrolimus.

Table 9

Results of CEA in China.

Strategy	QALY	Incremental efficacy (QALY)	Cost (¥)	Incremental cost (¥)	ICER (¥/QALY)	Avg CE (¥/QALY)
CSA	19.00128	0	51,510.40069	0	0	2710.891
TAC	19.41091	0.40963	75,061.59735	23,551.19666	57,493.8277	3866.9798
IFX	19.35021	0.34893	2,37,003.9268	1,85,493.5261	5,31,606.7007	12,248.132

CSA = cyclosporine, CEA = cost-effective analysis, IFX = infliximab, QALY = quality-adjusted life-year, TAC = tacrolimus.

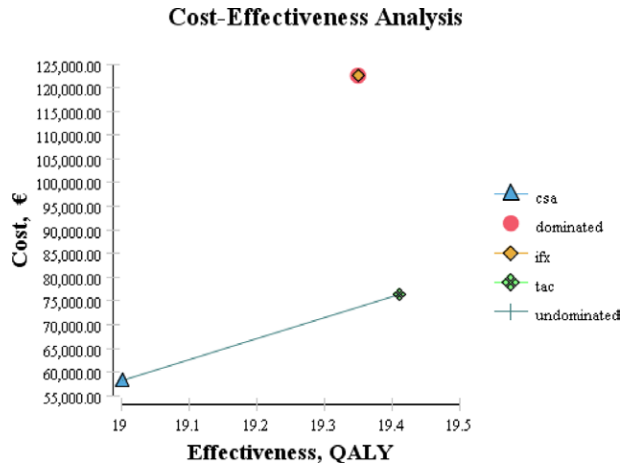

Figure 14. Cost-effectiveness analysis in Dutch.

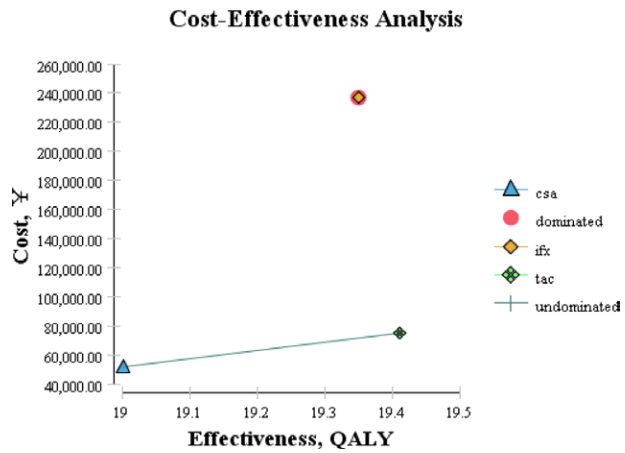

Figure 15. Cost-effectiveness analysis in China.

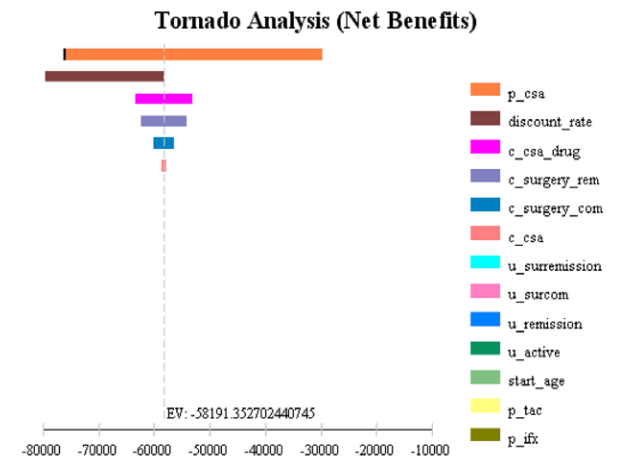

Figure 16. One-way sensitivity analysis results: infliximab, cyclosporine and tacrolimus.

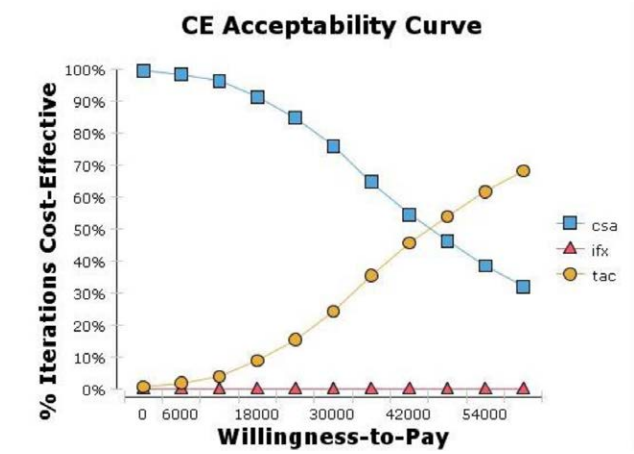

Figure 17. Cost-effectiveness Scatterplot.

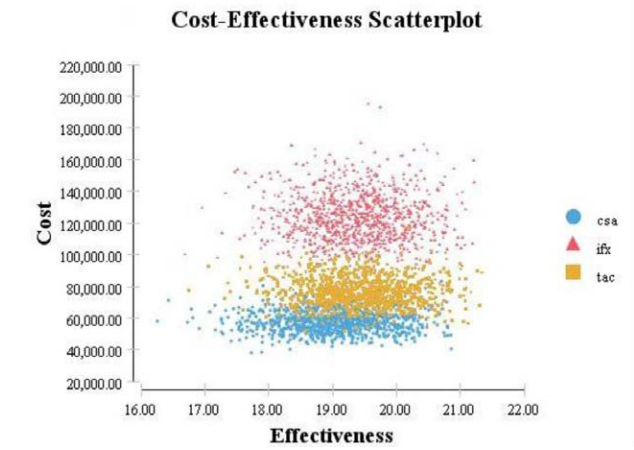

Figure 18. Cost-effectiveness acceptability curves.

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