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Efficacy and Safety of Tacrolimus Therapy for Active Ulcerative Colitis; A Systematic Review and Meta-analysis

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Abstract

Background: Approximately 25% of patients with ulcerative colitis [UC] experience a severe flare requiring steroid therapy to avoid colectomy. We performed a systematic review and meta-analysis to assess the efficacy of tacrolimus as a rescue therapy for active UC.

Methods: Electronic databases were searched for relevant studies assessing the efficacy of tacrolimus for active UC. Outcomes included short- and long-term clinical response, colectomy free rates, and rate of adverse events in randomised controlled trials [RCTs] and observational studies.

Results: Two RCTs comparing high trough concentration [10–15 ng/ml] versus placebo [$n = 103$] and 23 observational studies [$n = 831$] were identified. Clinical response at 2 weeks was significantly higher with tacrolimus compared with placebo (risk ratio [RR] = 4.61, 95% confidence interval [CI] = 2.09–10.17, $p = 0.15 \times 10^{-3}$] among RCTs. Rates of clinical response at 1 and 3 months were 0.73 [95% CI = 0.64–0.81] and 0.76 [95% CI = 0.59–0.87], and colectomy-free rates remained high at 1, 3, 6, and 12 months [0.86, 0.84, 0.78, and 0.69, respectively] among observational studies. Among RCTs, adverse events were more frequent compared with placebo [RR = 2.01, 95% CI = 1.20–3.37, $p = 0.83 \times 10^{-2}$], but there was no difference in severe adverse events [RR = 3.15, 95% CI = 0.14–72.9, $p = 0.47$]. Severe adverse events were rare among observational studies [0.11, 95% CI = 0.06–0.20].

Conclusions: In the present meta-analysis, tacrolimus was associated with high clinical response and colectomy-free rates without increased risk of severe adverse events for active UC.

Keywords: Ulcerative colitis; tacrolimus; immunosuppressant; systematic review; meta-analysis

1. Introduction

Ulcerative colitis [UC] is a type of inflammatory bowel disease that affects the colorectum.[1] Traditional therapies for UC include 5-aminosalicylates, corticosteroids, and immunosuppressants. Advances in understanding the immunological pathways have led to the development of biologicals, which are now widely used for induction and maintenance of remission.[2,3] Approximately 25% of patients with

UC experience a severe flare during their disease course, requiring hospitalisation and high-dose corticosteroid therapy.[4] Furthermore, 30% of UC patients with a severe attack may undergo colectomy due to steroid-refractory disease.[5] In patients with severe steroid-refractory UC, intravenous ciclosporine, infliximab, or colectomy are potential therapeutic options.[6,7] Tacrolimus, a calcinurin inhibitor with a more potent inhibitory effect on activated T cells compared

with ciclosporine, has been increasingly used for the treatment of severe and steroid-refractory UC.[8,9]

Despite the undoubted efficacy of tacrolimus in inducing remission in UC, the number of studies assessing its efficacy and safety in UC are still limited. Randomised controlled trials [RCTs] performed by Ogata *et al*. have reported the efficacy of tacrolimus in inducing remission in steroid-refractory UC patients.[10,11] Several guidelines now recommend the use of tacrolimus in steroid-refractory active UC.[12,13]

Ciclosporine has shown beneficial short-term response in severe steroid-refractory UC patients in small RCTs[14]; however, nearly half of the patients underwent colectomy after a year despite the addition of thiopurines as a maintenance therapy.[6,15] The long-term outcome of UC patients treated with tacrolimus remains largely unknown. Treatment with tacrolimus in transplant patients is associated with risks of kidney injury and infections,[16] and whether the same applies to patients with UC who are commonly treated for a limited duration also remains unknown.

In the present systematic review and meta-analysis, we aimed to assess the short- and long-term effect as well as the safety of tacrolimus as a rescue therapy in patients with acute UC.

2. Materials and Methods

2.1. Data sources
We searched MEDLINE [1993–May 2015], Google scholar [1993–2015], and the Cochrane Central Register of Controlled Trials [May 2015] for studies assessing the efficacy of tacrolimus in severe and steroid-refractory UC. We also searched abstracts from bibliographies of identified articles for additional references.

2.2. Search strategy and study selection
To be eligible for inclusion, we considered RCTs and observational studies evaluating the efficacy of tacrolimus for UC that assessed clinical remission and/or response. There were no restrictions regarding age, sex, and duration of the study. We imposed no geographical or language restrictions and articles in languages other than English, Japanese or German were translated if necessary. Two authors [YK and FK] independently screened each of the potential titles, abstracts, and/or full-manuscripts to determine whether they were eligible for inclusion. Areas of disagreement or uncertainty were resolved by consensus between the authors. The corresponding authors of studies were contacted to provide additional information on trials if required. The following terms were used in the search procedure: 'tacrolimus', 'ulcerative colitis', 'therapy', 'treatment', 'randomized control trial', 'prospective study', 'retrospective study', [both as medical subject headings and free-text terms]. These were combined by using the set operator. Search strategy is described in Figure 1.

2.3. Data extraction and quality assessment
All data were independently abstracted in duplicate by two authors [YK and FK] by using a data abstraction form. Data on the study characteristics, such as author name, year of publication, country, sample size, age of patients, type of medication used, outcome, and incidence of adverse effects, were collected. Studies that reported events on neither treated nor control groups were excluded from analysis. The Jadad score, a scale that assesses the methodological quality of a clinical trial, was used to assess the quality of RCTs.[17]

2.4. Outcome assessment
The primary outcome measure of interest was the number of patients achieving clinical response [CR]. Additionally, colectomy-free survival rates at different time points and the rate of adverse reactions were assessed. Analyses were done separately for RCTs and observational studies. Data of intention-to-treat analysis were used except where indicated.

The secondary outcomes were the incidence of overall adverse events in RCTs and the incidence of severe adverse events in both RCTs and observational studies during the treatment of tacrolimus. Analyses were done separately for RCTs and observational studies. Overall adverse event incidence was calculated based on the adverse events reported in each RCT. In regard to severe adverse events, we defined them as those which were specified as such in the study or adverse events which led to discontinuation or reduction of tacrolimus therapy.

Subgroup analysis was performed among the studies that reported the trough concentration of tacrolimus. High trough was defined as > 10 ng/ml and low trough was defined as < 10 ng/ml.

2.5. Statistical analysis
Random-effects meta-analysis was performed to compare the efficacy between the pair of therapies, where applicable. We also evaluated the presence of heterogeneity across trials by using the I^2 statistic, which quantifies the percentage of variability that can be attributed to between-study differences. To assess the potential for publication bias, we performed Begg's and Egger's tests and constructed funnel plots to visualise possible asymmetry when three or more studies were available.[18,19] For observational studies, data were pooled and shown as forest plots. All statistical analyses were performed with Comprehensive Meta Analysis V2 [Biostat, Englewood, NJ, USA]. We followed the Cochrane Handbook for Systematic Reviews of Interventions in the report of this meta-analysis.[20]

3. Results

3.1. Study characteristics
We identified 9518 citations through literature search, excluded 9494 titles and abstracts after initial screening, and assessed 25 full-text articles for eligibility [Figure 1]. We ultimately included two RCTs which assessed the efficacy of tacrolimus compared with placebo in steroid-refractory UC. We identified 23 observational studies reporting the effect of tacrolimus; of these, 21 studies were retrospective cohort studies and 2 were prospective cohorts. A total of 103 patients were included in the analysis of RCTs and 831 patients for the observational studies.

The characteristics and outcomes of the included studies[8,10,11,21,22,23,24,25,26,27,28,29,30,31,32,33,34,35,36,37,38,39,40,41,42] are summarised in Tables 1 and 2. The two RCTs were conducted among adult patients with moderately-severely active steroid-refractory or steroid-dependent UC. In both studies, the study duration was 2 weeks followed by an open-label 10-week extension in which all patients received tacrolimus. The quality of the studies assessed by the Jadad score showed a median of 4.5 [range 4–5], and both trials were rated to be of good methodological quality.

In all, 23 observational studies reported the efficacy of tacrolimus in steroid-refractory UC patients: eight studies were performed in adult patients; two studies in paediatric patients [less than 18 years old]; and seven studies were performed in both adult and paediatric patients. There was no description about age of patients in six
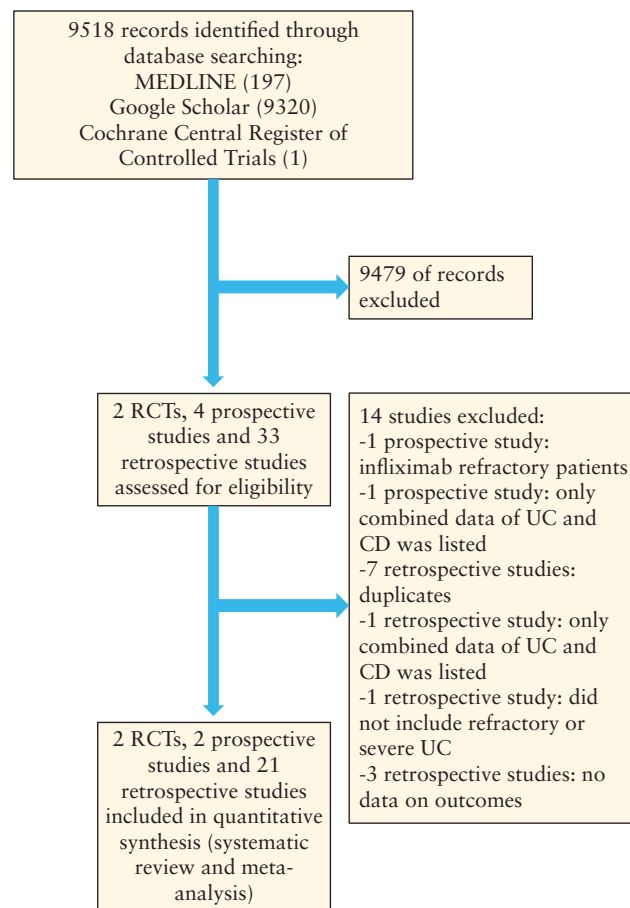
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┌─────────────────────────────┐
│  9518 records identified     │
│  through database searching: │
│  MEDLINE (197)               │
│  Google Scholar (9320)       │
│  Cochrane Central Register   │
│  of Controlled Trials (1)    │
└─────────────────────────────┘
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9479 of records excluded

2 RCTs, 4 prospective studies and 33 retrospective studies assessed for eligibility

14 studies excluded:
-1 prospective study: infliximab refractory patients
-1 prospective study: only combined data of UC and CD was listed
-7 retrospective studies: duplicates
-1 retrospective study: only combined data of UC and CD was listed
-1 retrospective study: did not include refractory or severe UC
-3 retrospective studies: no data on outcomes

2 RCTs, 2 prospective studies and 21 retrospective studies included in quantitative synthesis (systematic review and meta-analysis)

Figure 1. Flow chart of assessment of studies identified in the meta-analysis.

studies. There were 13 studies that described the mean duration of tacrolimus therapy [3.75–25.2 months] and 14 studies that described the follow-up period [0.5–118 months].

3.2. Meta-analysis of RCTs

Two RCTs comparing high target serum trough concentration [10–15 ng/ml] versus placebo were included in our meta-analysis [Table 1]. Both were multicentre placebo controlled RCTs with high quality [Jadad score 4–5] and together comprised 103 patients with active steroid-refractory or steroid-dependent UC.

Tacrolimus induced a significantly higher rate of clinical response at 2 weeks compared with placebo (risk ratio [RR] = 4.61, 95% confidence interval [CI] = 2.09–10.17, $p = 0.15 \times 10^{-3}$) [Figure 2A]. Number needed to treat was 2.23 [95% CI = 1.64–3.50]. Rates of remission or mucosal healing could not be combined due to lack of data in either of the studies. There were no patients that underwent colectomy during the study period in either of the RCTs. Tacrolimus caused significantly higher drug-related adverse events compared with placebo [RR = 2.01, 95% CI = 1.20–3.37, $p = 0.83 \times 10^{-2}$], but there was no difference in severe adverse events [RR = 3.15, 95% CI = 0.14–72.9, $p = 0.47$] [Figure 2B, C].

3.3. Meta-analysis of observational studies

There were 23 prospective and retrospective observational studies with a total of 831 patients included in our analysis [Table 2]. More than 80% of the patients included in the study were steroid-refractory

UC patients, with the remainder being steroid-dependent cases. Most of the studies were among adult patients, but some were performed among the paediatric population. More than 92% of the patients received tacrolimus per os [by mouth; PO] and only a small proportion received it intravenously.

As shown in Figure 3A, tacrolimus demonstrated high rates of clinical response at 1 [0.73, 95% CI = 0.64–0.81] and 3 months [0.76, 95% CI = 0.59–0.87] among the observational studies. At 1 month, the clinical response rate was numerically, but not significantly, higher among the studies that administered tacrolimus at a high trough concentration [> 10 ng/ml] as compared with those that administered it at a low trough concentration [< 10 ng/ml]. There was moderate to high heterogeneity in these analyses [$I^2 = 44.69$ at 1 month and $I^2 = 65.29$ at 3 months].

Colectomy-free rates remained high at 1 [0.86, 95% CI = 0.64–0.95], 3 [0.84, 95% CI = 0.76–0.90], 6 [0.78, 95% CI = 0.51–0.92], and 12 months [0.69, 95% CI = 0.50–0.83] [Figure 3B]. The rates were numerically higher among the studies that administered tacrolimus at a high trough concentration [> 10 ng/ml] as compared with those that administered it at a low trough concentration [< 10 ng/ml] at the induction phase. There was moderate to high heterogeneity in each of the analyses at 1, 6, and 12 months [$I^2 = 31.22$ at 1 month, $I^2 < 0.10 \times 10^{-7}$ at 3 months, $I^2 = 46.76$ at 6 months, and $I^2 = 65.08$ at 12 months]. The relatively high heterogeneity was thought to be due to differences in the backgrounds of the studies. No publication bias was noted in these analyses as assessed by Begg's and Egger's tests.

Incidents of severe adverse events were rare among the observational studies [0.11, 95% CI = 0.06–0.20] [Figure 3C]. There was

high heterogeneity [I^2 = 59.80] and some publication bias was noted in this analysis [Begg: p = 0.043, Egger: p = 9.34 x 10⁻³]. This heterogeneity and publication bias were thought to be due to differences in the background of the observational studies, and the possibility of the presence of unreported studies, respectively. Subgroup analysis among different trough concentrations at the induction phase demonstrated similar results.

4. Discussion

In the present study, we performed a systematic review and meta-analysis to assess the efficacy of tacrolimus in active UC. Meta-analysis of RCTs showed superiority of tacrolimus over placebo in inducing short-term clinical response. Meta-analysis of observational studies showed high rates of short-term clinical response as well as high colectomy-free rates that persisted over a period of 1 year.

Approximately 25% of patients with UC experience a severe flare during their disease course, requiring hospitalisation and high-dose corticosteroid therapy,[4] which puts them at risk for colectomy.[5] Intravenous ciclosporine has shown excellent short-term outcome as a salvage therapy in patients with severe steroid-refractory UC,[14] but its use is limited to tertiary centres due to the difficulty of management and high risk for adverse effects. More recently, infliximab has shown comparable effect to ciclosporine in this setting.[43] Tacrolimus has a similar mechanism of action to ciclosporine, and has been more commonly used than ciclosporine in organ transplants.[44] The aim of our systematic review and meta-analysis was to combine data and to assess the efficacy of tacrolimus in severe and steroid-refractory UC.

We identified two RCTs that compared tacrolimus with placebo therapy in moderate-severe steroid-refractory or steroid-dependent UC. Our meta-analysis demonstrated that tacrolimus was significantly more effective than placebo in inducing short-term clinical response at 2 weeks. This result was supported by the meta-analysis of 23 observational studies, which showed similarly high clinical response rates at 1 and 3 months. One major issue in the setting of treating severe UC is the poor long-term outcome including the risk of colectomy. Indeed, the majority of the observational studies associated with ciclosporine have shown that approximately 50% of patients will undergo colectomy in 1–2 years.[6] We showed that colectomy-free rates remained high at 70–90% during a follow-up of up to 12 months among the observational studies.

The use of calcineurin inhibitors is associated with various side effects including kidney injury, tremor, and infections.[16,45,46] This is one of the reasons why its use is limited to tertiary centres with more experience in patient care. Among the RCTs and observational studies included in our meta-analysis, there were 38 patients among 11 studies who experienced severe adverse events.[8,10,21,22,23,24,26,30,37,38,39] All of them improved with discontinuation or reduction of tacrolimus and some of the patients were treated medically according to their symptoms. Whereas the rate of overall adverse effects was more common with tacrolimus compared with placebo therapy in RCTs, the risk of serious adverse effects was not increased with tacrolimus. Among the 14 observational studies which reported the incidence of severe adverse effects, the duration of tacrolimus therapy was specified in 9 studies,[8,21,22,23,24,26,29,39,41] which ranged from 3.75 to 11 months. The combined risk of adverse effects with tacrolimus among observational studies was low, supporting its long-term safety.

The shortcoming of our study is the small number of RCTs directly comparing tacrolimus with placebo. However, both studies were of good quality as shown by a median Jadad score of 4.5. Furthermore,

Table 1. Characteristics of randomised controlled trials of tacrolimus in active UC.

Study, year, [reference]	Age	Dosage and schedule of therapy	Control group	Study duration	ITT/PP	Jadad score	Definition of clinical response	Definition of clinical remission	Patients [n] Tacro	Cont	Steroid-resist-ant/dependent Tacro	Cont	Clinical response at 2 weeks [n] Tacro	Cont	Clinical remission at 2 weeks [n] Tacro	Cont
Ogata *et al.* 2006[10]	Adult	0.05 mg/kg/day PO, trough level of 10–15 ng/ml [high trough group[a]] and 5–10 ng/ml [low trough group] kept for 2 weeks	Placebo	2 weeks of RCT and 10 weeks of open-label extension	PP	4	Reduction in DAI ≥ 4 with improvement of all categories	DAI score ≤2, with no individual subscore > 1	19[b]	20	5/14	5/15	13	2	0	0
Ogata *et al.* 2012[11]	Adult	1–2.5 mg PO twice daily, trough level of 115 ng/ml kept for 2 weeks	Placebo	2 weeks of RCT and 10 weeks of open-label extension	PP	5	Reduction in DAI ≥ 4 with improvement of all categories	DAI score ≤ 2 with individual subscore of 0 or 1	32	30	NA [all were resistant or dependent]		16	4	3	0

UC, ulcerative colitis; tacro, tacrolimus, cont, controls; ITT, intention to treat; PP, per protocol; DAI, disease activity index score; PO, per os [by mouth]; RCT, randomised controlled trial; NA, not available.

[a]Data shown are of the high trough group.
[b]Two patients were excluded from efficacy analysis.

meta-analysis of observational studies demonstrated similarly high rates of short-term response to tacrolimus therapy, supporting the result of the meta-analysis of RCTs. The RCT undertaken by Ogata *et al.* demonstrated that tacrolimus is more effective when given at a high trough level of 10–15 ng/ml[10], and close therapeutic drug monitoring to keep it in that range is now standard care. However, some

A

	Risk ratio	Lower limit	Upper limit	Tacro high trough	Placebo	Risk ratio and 95% CI	Relative weight
Ogata 2006	6.84	1.77	26.39	13 / 19	2 / 20		34.33
Ogata 2012	3.75	1.41	9.95	16 / 32	4 / 30		65.67
Total	4.61	2.09	10.17				

Heterogeneity; $p = 0.48$, $I^2 = 0.00$

B

	Risk ratio	Lower limit	Upper limit	Tacro high trough	Placebo	Risk ratio and 95% CI	Relative weight
Ogata 2006	3.17	1.02	9.88	10 / 21	3 / 20		20.78
Ogata 2012	1.78	1.00	3.19	19 / 32	10 / 30		79.22
Total	2.01	1.20	3.37				

Heterogeneity; $p = 0.37$, $I^2 = 0.00$

C

	Risk ratio	Lower limit	Upper limit	Tacro high trough	Placebo	Risk ratio and 95% CI	Relative weight
Ogata 2006	3.15	0.14	72.88	1 / 19	0 / 20		100.00
Ogata 2012				0 / 32	0 / 30		
Total	3.15	0.14	72.88				

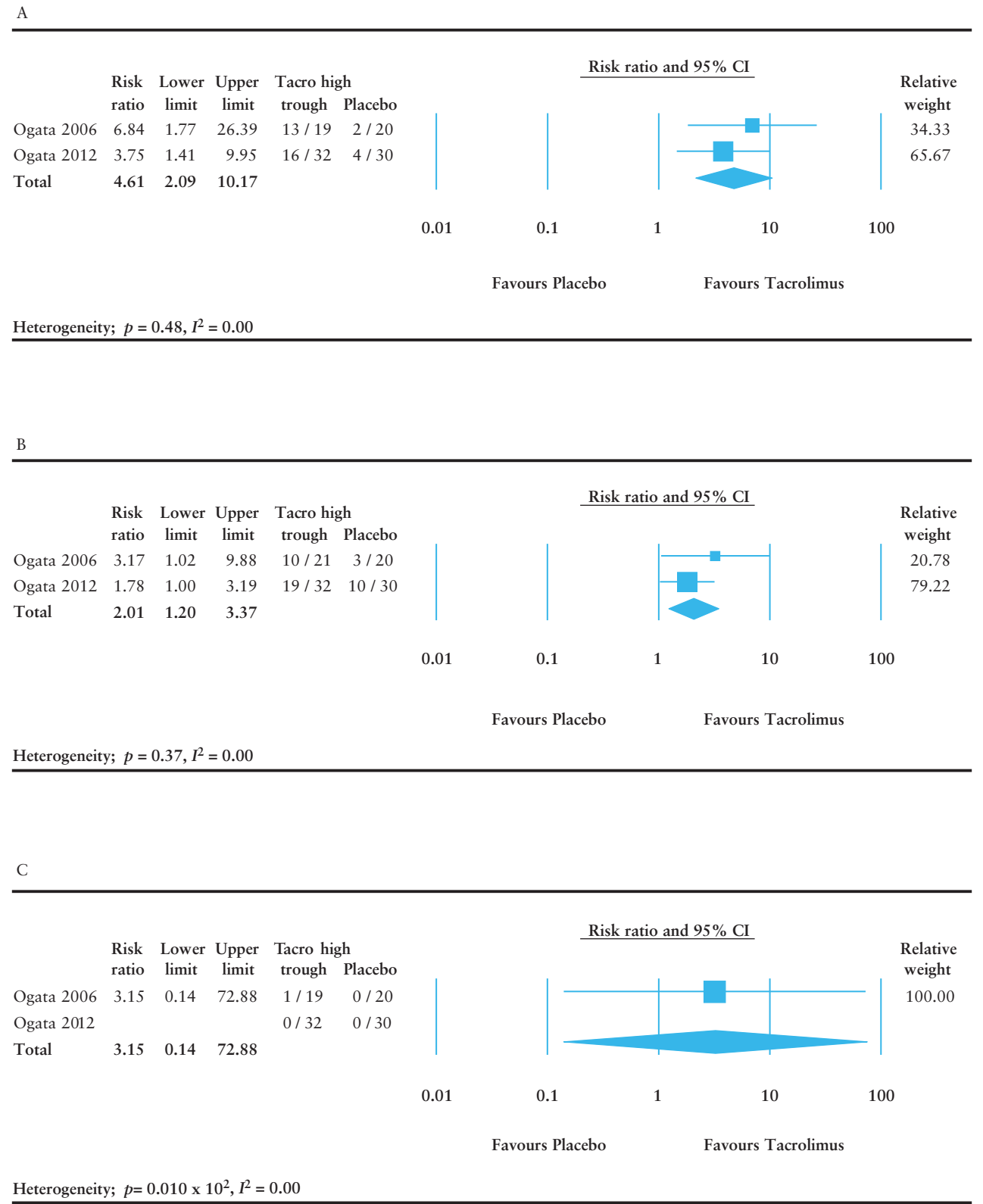Heterogeneity; $p = 0.010 \times 10^2$, $I^2 = 0.00$

Figure 2. Meta-analysis of randomised controlled trials. Random-effects meta-analysis was performed to compare the efficacy between tacrolimus and placebo. [A] Clinical response at 2 weeks. [B] Treatment-related adverse event rate at 2 weeks. [C] Severe adverse event rate at 2 weeks.

Table 2. Characteristics of observational studies of tacrolimus in active UC.

	Study, year, [reference]	Age	Tacrolimus dosage and schedule of therapy	Mean tacrolimus treatment duration [months]	Concomitant medications for UC	Study design	Follow-up duration [months]	Definition of clinical response	Patients [n]	Steroid resistant/dependent [n]
High trough tacrolimus concentrations during induction therapy	Hogennauer *et al.* 2003[21]	Adult/paediatric	0.15 mg/kg/day PO, trough level of 1020 ng/ml	3.75	Steroids tapered by 10 mg/week. AZA was added after achieving improvement	Retrospective study	2–47	Reduction of modified Truelove Witts score ≥ 3	9	9/0
	Ziring *et al.* 2007[22]	Paediatric	0.2 mg/kg/day PO, trough level of 10–15 ng/ml for the first 2 weeks, followed by 7–12 ng/ml	5.62	Steroids tapered by 5–10 mg/week	Retrospective study	4–48	Absence of clinical symptoms	18	9/9
	Yamamoto *et al.* 2008[23]	Adult/paediatric	23 pts received 0.1 mg/kg/day PO, trough level of 10–15 ng/ml. 4 pts received 0.01 mg/kg/day IV, then switched to PO	11	NA	Retrospective study	2–65 [median 17]	NA	27	7/18
	Benson *et al.* 2008[24]	NA	0.2 mg/kg/day PO, trough level of 10–12 ng/ml	7	NA	Retrospective study	NA	NA	32	13/8
	Murano *et al.* 2011[25]	NA	0.1 mg/kg/day PO, trough level of 10–15 ng/ml	NA	NA	Retrospective study	NA	NA	27	22/5
	Inoue *et al.* 2012[26]	Adult	0.1 mg/kg/day PO, trough level of 10–15 ng/ml, followed by 5–10 ng/ml	5.25	NA	Retrospective study	4–20	Lichtiger score <1 0 and decrease ≥ 3	10	0/5
	Hiraoka *et al.* 2013[27]	Adult/paediatric	0.05–0.15 mg/kg/day PO, trough level of 10–15 ng/ml	NA	NA	Retrospective study	NA	NA	47	NA
	Matsuura *et al.* 2013[28]	Adult/paediatric	PO or IV, trough level of 10–15 ng/ml for induction and 5–10 ng/ml for maintenance	10	Steroids tapered and switched to AZA; 6 pts who did not respond received IFX	Retrospective study	2–107 [median 24]	NA	50	NA
	Miyoshi *et al.* 2013[29]	Adult	5 mg/day PO, trough level of 10–15 ng/ml for 2 weeks, followed by 5–10 ng/ml	7	NA	Retrospective study	3–29 [median 16]	Lichtiger score ≤ 10	51	30/18

Table 2. *Continued*

| Study, year, [reference]	Age	Tacrolimus dosage and schedule of therapy	Mean tacrolimus treatment duration [months]	Concomitant medications for UC	Study design	Follow-up duration [months]	Definition of clinical response	Patients [n]	Steroid resistant/dependent [n]
Boschetti *et al.* 2014[30]	Adult	0.1–0.15 mg/kg/day PO, trough level of 10–15 ng/ml for 12 weeks, followed by 5–10 ng/ml for maintenance	NA	18 pts received 5-ASA, 4 pts received steroids. None received concomitant AZA/6-MP or biologicals	Retrospective study	12	Reduction of modified DAI ≥ 2	30	NA
Ikeya *et al.* 2015[31]	Adult/paediatric	0.1 mg/kg/day PO, trough level of 10–15 ng/ml for induction and 5–10 ng/ml for maintenance	NA	NA	Retrospective study	3 or more	NA	44	13/24
Minami *et al.* 2015[32]	Adult	0.1 mg/kg/day PO or 0.01 mg/kg/day IV, trough level of 10–15 ng/ml for induction	NA	21 pts received 5-ASA, 12 pts received PSL, 6 pts received AZA, 13 pts received leukocyte apheresis, 2 pts who did not respond received IFX	Retrospective study	0.5–118 [median 27]	NA	22	12/6
Kawakami *et al.* 2015[33]	Adult	0.1 mg/kg/day PO, trough level of 10–15 ng/ml for 2 weeks, and 5–10 ng/ml for maintenance	NA	5-ASA, steroids, and/or AZA or 6-MP	Prospective study	1	Lichtiger score < 10 and a decrease ≥ 3	49	38/13 [2 pts were included in both groups]
Nakamura *et al.* 2015[34]	NA	PO, trough level of 10–15 ng/ml for 2 weeks, 5–10 ng/ml for maintenance	7	NA	Retrospective study	NA	NA	71	71/0
Watanabe *et al.* 2015[35]	NA	PO, trough level of 10–15 ng/ml for 2 weeks, 5–10 ng/ml for maintenance	NA	NA	Retrospective study	NA	NA	47	47/0
Low trough tacrolimus concentrations during induction therapy									
Baumgart *et al.*2006[36]	Adult	0.1 mg/kg/day PO, trough level of 4–8 ng/ml; 2 pts with toxic megacolon initially received 0.01 mg/kg/day IV	25.2	NA	Retrospective study	NA	Reduction of modified clinical activity index ≥ 4	40	26/14

Table 2. *Continued*

| Study, year, [reference]	Age	Tacrolimus dosage and schedule of therapy	Mean tacrolimus treatment duration [months]	Concomitant medications for UC	Study design	Follow-up duration [months]	Definition of clinical response	Patients [n]	Steroid resistant/dependent [n]
Ng et al. 2007[37]	Adult	0.1 mg/kg/day PO, trough level of 5–10 ng/ml	NA	2 pts received steroids. 3 pts received balsalazide, 2 pts received 6MP, 1 pt received AZA	Retrospective study	Median 8	Inactive disease score on the TrueloveWitts criteria	6	NA
Schmidt et al. 2013[38]	Adult	0.1 mg/kg/day PO; 10 pts initially received 0.01 mg/kg IV with a fast switch to PO. Median trough concentration within 4 weeks in 78 pts was 6.9 ng/ml	NA	Steroids tapered individually. AZA [2–2.5 mg/kg/day] or 6-MP [1–1.5 mg/kg/day] continued in some pts. MTX [15–25 mg/week] used in 4 pts	Retrospective study	3	NA	130	130/0
Landy et al. 2013[39]	Adult/paediatric	0.1 mg/kg/day PO, trough level of 5–10 ng/ml	9	13 pts received PSL, 6 pts were concurrently treated with AZA	Retrospective study	3–66 [median 27]	Reduction of modified TrueloveWitts score ≥ 4	25	25/0
Navas-Lopes et al. 2014[40]	Paediatric	0.12 mg/kg/day PO, trough level of 5–10 ng/ml	4.7	NA	Retrospective study	24 or more	Improvement of clinical symptoms or laboratory parameters, or reduction of PUCAI ≥ 20	10	10/0
Tacrolimus trough concentrations unavailable									
Fellermann et al. 1998[8]	Adult/paediatric	0.01–0.02 mg/kg/day IV for 7 days, then switched to 0.1–0.2 mg/kg/day PO. Trough level: NA	7	PSL [1mg/kg IV till Day 7, 1mg/kg PO Days 7-14], 5-ASA [3–4 g/day], AZA [1.5–2.5 mg/kg]	Prospective study	4–16	NA	6	6/0
Fellermann et al. 2002[41]	NA	18 pts received 0.01–0.02 mg/kg/day IV up to 14 days, then switched to 0.1–0.2 mg/kg/day PO; 20 pts were started on PO. Trough level: NA	7.6	AZA or 6-MP added in some patients. Steroids were tapered after achieving improvement	Retrospective study	NA	NA	38 [5 indeterminate colitis]	38/0
Kimura et al. 2013[42]	NA	NA	NA	NA	Retrospective study	NA.	NA	42	42/0

Adult, age ≥ 18; paediatric, age <18 years.

UC, ulcerative colitis; pts, patients; PSL, prednisolone; AZA, azathioprine; 6-MP, mercaptopurine; MTX, methotrexate; IFX, infliximab; 5-ASA, 5-aminosalicylic acid; DAI, disease activity index; IV, intravenous; PO, per os [by mouth]; NA, not available; PUCAI, paediatric ulcerative colitis activity index.
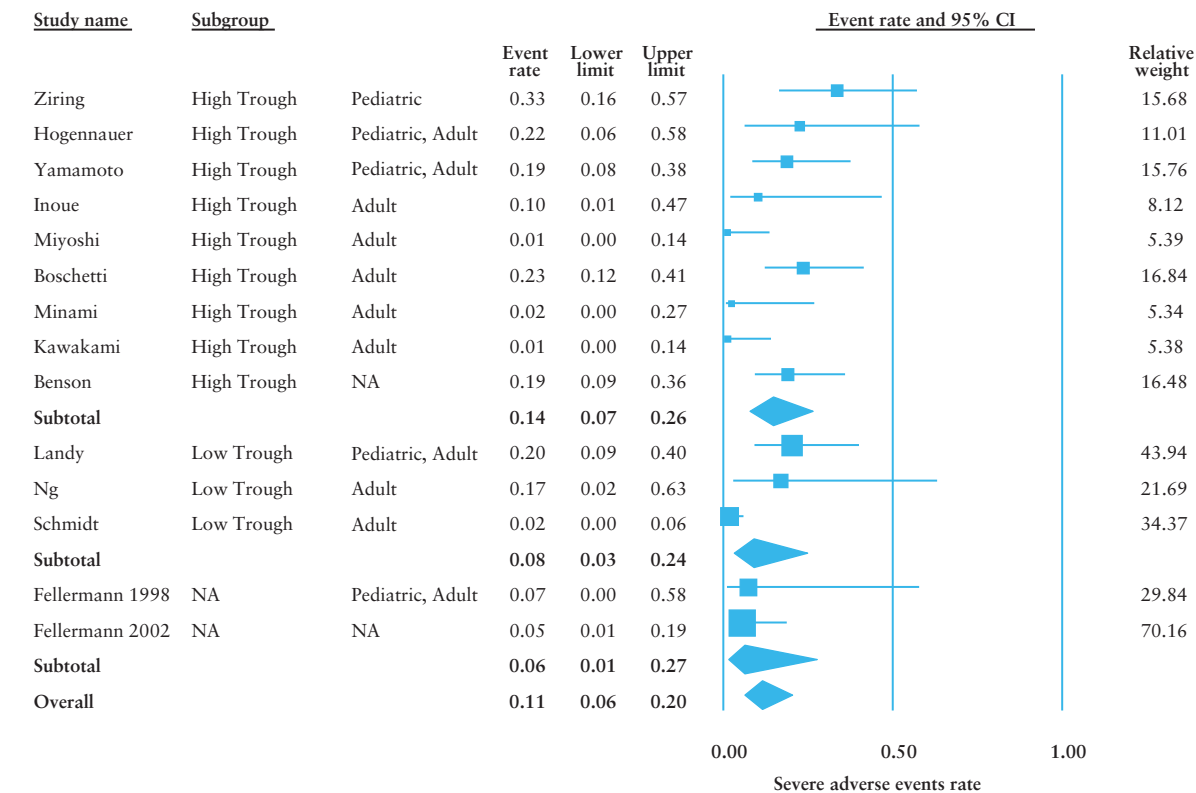
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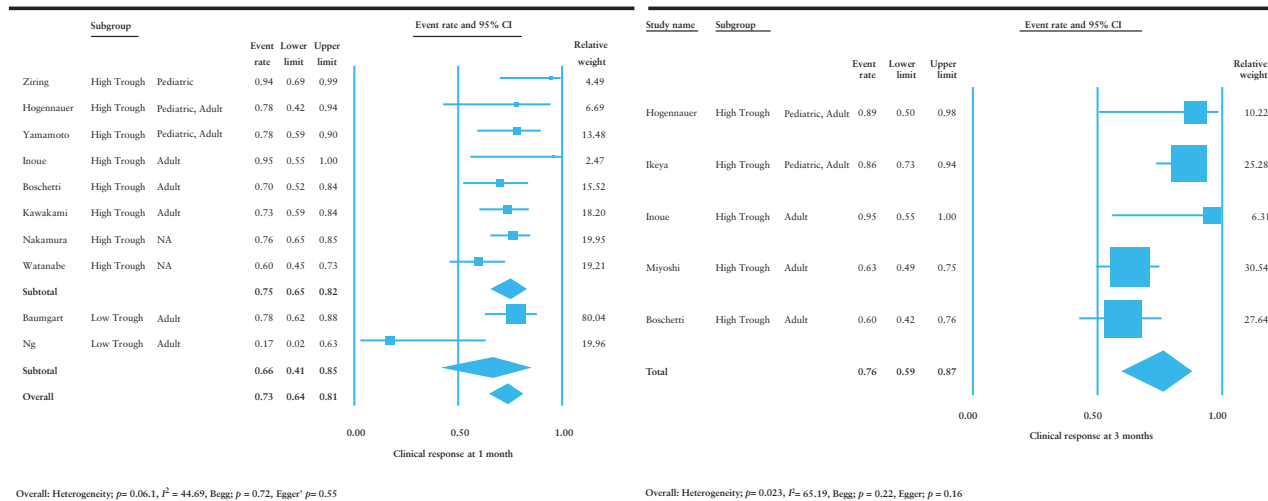
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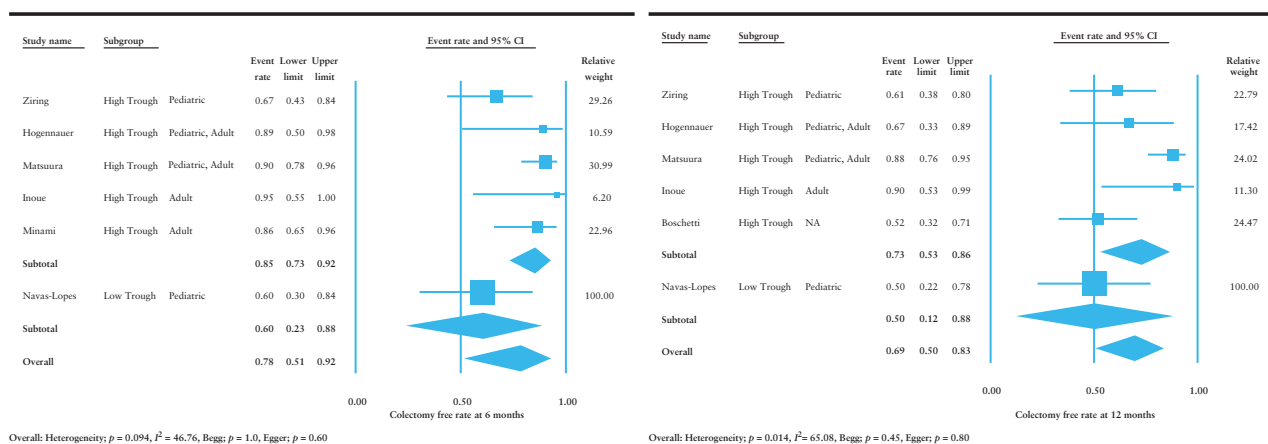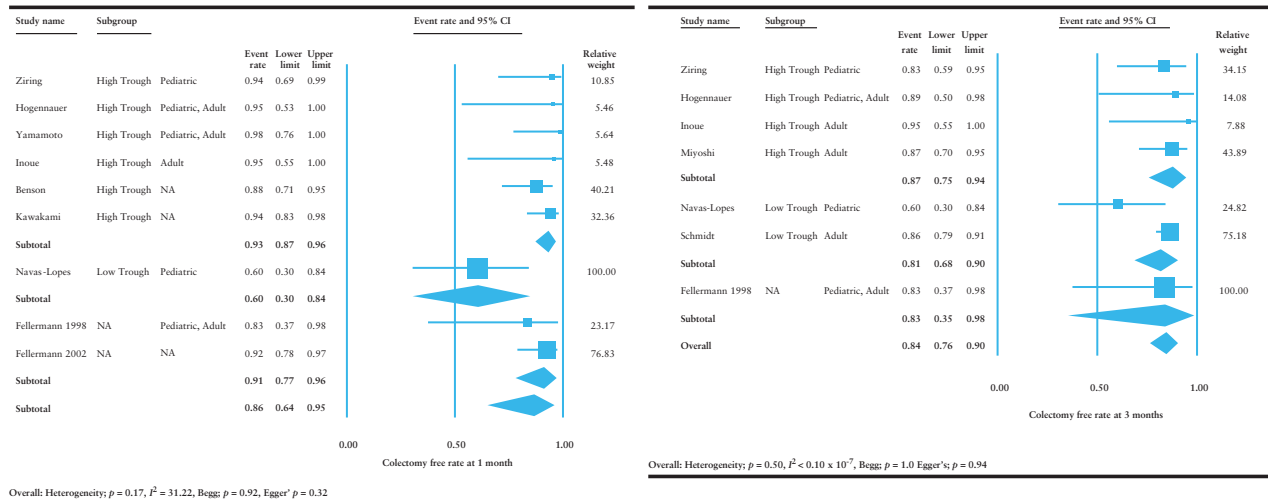
of the observational studies, especially those undertaken prior to the studies by Ogata *et al.* and paediatric studies, lacked information regarding the trough levels or administered it at a lower trough level. This may have underestimated its effect or led to higher rates of adverse reactions.

In conclusion, this systematic review and meta-analysis showed that tacrolimus was effective in inducing short-term clinical response in active UC patients, with a durable effect of preventing colectomy without increased risk of severe adverse events. The use of tacrolimus is warranted in severe and steroid-refractory UC.

C

Study name	Subgroup		Event rate	Lower limit	Upper limit	Event rate and 95% CI	Relative weight
Ziring	High Trough	Pediatric	0.33	0.16	0.57		15.68
Hogennauer	High Trough	Pediatric, Adult	0.22	0.06	0.58		11.01
Yamamoto	High Trough	Pediatric, Adult	0.19	0.08	0.38		15.76
Inoue	High Trough	Adult	0.10	0.01	0.47		8.12
Miyoshi	High Trough	Adult	0.01	0.00	0.14		5.39
Boschetti	High Trough	Adult	0.23	0.12	0.41		16.84
Minami	High Trough	Adult	0.02	0.00	0.27		5.34
Kawakami	High Trough	Adult	0.01	0.00	0.14		5.38
Benson	High Trough	NA	0.19	0.09	0.36		16.48
Subtotal			**0.14**	**0.07**	**0.26**		
Landy	Low Trough	Pediatric, Adult	0.20	0.09	0.40		43.94
Ng	Low Trough	Adult	0.17	0.02	0.63		21.69
Schmidt	Low Trough	Adult	0.02	0.00	0.06		34.37
Subtotal			**0.08**	**0.03**	**0.24**		
Fellermann 1998	NA	Pediatric, Adult	0.07	0.00	0.58		29.84
Fellermann 2002	NA	NA	0.05	0.01	0.19		70.16
Subtotal			**0.06**	**0.01**	**0.27**		
Overall			**0.11**	**0.06**	**0.20**		

0.00   0.50   1.00

Severe adverse events rate

Overall: Heterogeneity; $p = 2.14 \times 10^{-3}$, $I^2 = 59.80$, Begg; $p = 0.043$, Egger; $p = 9.34 \times 10^{-3}$

Figure 3. Meta-analysis of observational studies. Random-effects meta-analysis was performed to assess the efficacy of tacrolimus. [A] Analysis of the rate of clinical response at 1 and 3 months. [B] Analysis of colectomy-free rates at 1, 3, 6, and 12 months. [C] Analysis of the rate of severe adverse events. Adult indicates patient population was ≥ 18 years old; paediatric indicates patient population was < 18 years old.

Conflict of Interest

None.

Author Contributions

YK and FK: analysis of data and drafting of manuscript; AI: critical review and approval of manuscript: AS, study concept and design, analysis of data, and writing of manuscript.

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