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Original Article

Effectiveness and risk associated with infliximab alone and in combination with immunosuppressors for Crohn's disease: a systematic review and meta-analysis

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Abstract: Objective: Infliximab (IFX) monotherapy and IFX combined with immunosuppressors have been used in the treatment of Crohn's disease. However, the differences between combination therapy and IFX alone remain controversial. The aim of this meta-analysis was to evaluate the effectiveness and risk associated with combination therapy and IFX monotherapy. Methods: Systematic searches were performed for randomized controlled trials with PubMed, Web of Science, OVID, and the Cochrane Library. The analyzed contents included induction of remission, short-term maintenance of remission, long-term maintenance of remission, and risks. The final results were estimated using statistical data of odds ratio (OR), relevant 95% confidence interval (CI), and *P* value. Results: 6 out of 1041 citations met the selection criteria. There was no statistical difference in the effectiveness of induction and long-term maintenance of remission between two groups (P=0.07, 0.12). However, for short-term maintenance of remission, there was mild statistical difference between two groups (P=0.02, OR=1.66). For risks, apart from the difference in the aspect of reaction to infusion (OR=0.43, 95% CI=0.29-0.65, P<0.0001), there was no statistical difference. Conclusions: There was no significant difference in effectiveness and risks between the therapy groups. However, these outcomes should be interpreted with caution. Specific categories of combination therapy and periodic medication should be paid more attention in future studies.

Keywords: Crohn's disease, combination therapy, infliximab, immunosuppressors, meta-analysis

Introduction

Crohn's disease (CD) is a chronic inflammatory bowel disease (IBD) with unknown etiology. Over the past several decades, medical therapy for CD has achieved significant advancements [1]. Conventional therapies for CD include aminosalicylates, corticosteroid and immunosuppressors (IS), such as methotrexate, azathioprine, 6-mercaptopurine, and anti-tumor necrosis factors (anti-TNFs) [2]. In mild CD, 5-aminosalicylate (5-ASA) and budesonide are considered as the first-line therapy [1]. For moderate to severe CD, systemic corticosteroids are used as the traditional medications. However, corticosteroids have several drawbacks which include inefficient remission maintenance and long-term side effects [3]. IS and anti-TNFs are usually considered in the treatment of CD by an increasing number of doctors, especially when traditional drugs are inefficient [4, 5]. Anti-TNFs include infliximab (IFX), adalimumab, certolizumab etc. Infliximab, the first anti-TNF used in patients with CD, was approved in 1998 and was recognized as an effective and safe drug in inducing and maintaining remission [6, 7]. Currently, IFX combined with IS is widely used in clinical practice. However, the effectiveness and/or risk tradeoff for the combination therapy as compared with IFX alone still exist as controversy. Some studies have demonstrated that combination therapy was superior to any of the monotherapies [8-10]. Whereas, others have testified that concomi-

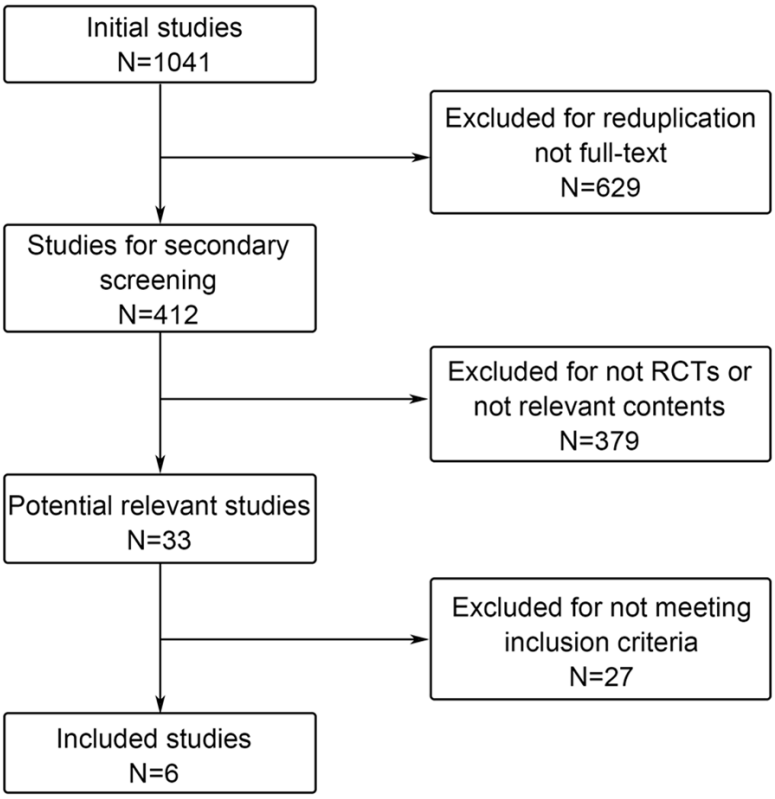

Figure 1. Screening process for the included citations. N = number of subjects.

tant immunomodulators were not effective in patients receiving maintenance IFX [11]. A recent randomized controlled trial demonstrated that combination therapy and IFX monotherapy were equally effective and safe in the treatment of CD [12]. Therefore, it is necessary to conduct a meta-analysis to evaluate whether there are any differences between the two kinds of treatment regimens.

Methods

Search source and select study

A systematic search for randomized controlled trials was conducted through PubMed, Web of Science, OVID, and the Cochrane Library from September 1990 to September 2014. The search key words were Crohn's disease, CD, combination therapy, drug polytherapies, monotherapy, anti-TNF, infliximab, immunosuppressants, immunosuppressors, randomized controlled trial, randomly, and random. To avoid missing any potentially relevant articles, mutual searches were conducted as a supplement to the main search.

Inclusion and exclusion criteria

Two investigators reviewed all the relevant citations. The titles and abstracts of these articles were reviewed to be identified as available articles related to: (1) randomized controlled trials (RCTs), (2) full text, (3) patients with Crohn's disease, (4) experimental groups consisting of IFX monotherapy and IFX combined with IS, (5) assessment of therapeutic effects containing one or more parameters such as remission rates and adverse events.

Data extraction

Two investigators executed further screening independently by intensive reading. Data was extracted from the eligible studies via mutual review. Disagreement on data extraction was resolved by the intervention of a third party. The data included was as follows: first author; year of publication; sample size; monotherapy; combination therapy; dosage; dose interval; induction numbers of remission; maintenance numbers of remission; follow-up duration; and adverse events.

Outcomes measurement

Extracted data of combination group and IFX monotherapy was sorted into four groups: induction of remission, short-term maintenance of remission, long-term maintenance of remission (including complete fistula response), and risks. Remission was mainly defined as Crohn's disease activity index (CDAI) <150 or corticosteroid-free clinical remission [13]. The induction of remission was chosen at week 12 to 16, when the induction treatment was completed. Short-term and long-term maintenance of remission were chosen at week 24 to 28 and >40 weeks respectively. For risk analysis, adverse events were analyzed during the treatment of CD. Five subgroups of adverse events were defined as follows: digestive system abnormalities, infections, other systemic disorders, reaction to infusion, and tumors.

Table 1. Characteristics of the included studies

Study	Case	Intervention	Dose	Interval	Duration (weeks)
Schröder et al. [16]	8	IFX	5 mg/kg	Week 0, 2	48
	11	IFX	5 mg/kg	Week 0, 2	
		Methotrexate	20 mg	Week 0-48	
Colombel et al. [15]	169	IFX	5 mg/kg	Week 0, 2, 6, 14, 22, 30, 38, 46	50
	169	IFX	5 mg/kg	Week 0, 2, 6, 14, 22, 30, 38, 46 (both)	
		Azathioprine	2.5 mg/kg		
Feagan et al. [12]	63	IFX	5 mg/kg	Week 1, 3, 7, 14, 22, 30, 38, 46	50
	63	IFX	5 mg/kg	Week 1, 3, 7, 14, 22, 30, 38, 46	
		Methotrexate	10 mg/kg	Week 1, 2	
			20 mg/kg	Week 3	
			25 mg/kg	Week 5-50	
Van et al. [17]	40	IFX	5 mg/kg	Week 0-104, 8 weekly	104
	40	IFX	5 mg/kg	Week 0-104, 8 weekly	
		IS	2-2.5 mg/kg#	Per day	
			1.5 mg/kg%	Per day	
			15 mg^	Per week	
ACCENT I [18, 19]	171	IFX	5 mg/kg	Week 0, 2, 6	54
			5/10 mg/kg*	Week 14, 22, 30, 38, 46	
	54	IFX	5 mg/kg	Week 0, 2, 6	
			5/10 mg/kg	Week 14, 22, 30, 38, 46	
		IS		NA	
ACCENT II [18, 20]	63	IFX	5 mg/kg	Week 0, 2, 6, 14, 22, 30, 38, 46	54
	28	IFX	5 mg/kg	Week 0, 2, 6, 14, 22, 30, 38, 46	
		IS		NA	

Footnotes: IFX: Infliximab; IS: Immunosuppressors; NA: Not available; #Azathioprine; %6-mercaptopurine; ^Methotrexate; *In ACCENT I 2002, patients received an infusion of infliximab either 5 mg/kg or 10 mg/kg every 8 weeks after week 6 until week 46.

Quality evaluation and publication bias analysis

Two researchers evaluated the included citations in terms of 5 items according to Jadad score [14]: (1) random allocation, (2) double-blind, (3) description of withdrawals and dropouts, (4) adequate follow-up, and (5) description of interventions. Each item was assigned as one score. A trial of more than 3 scores was defined as high quality, while 3 scores or less was referred to as low quality. Publication bias was assessed by the Begg's test and conducting funnel plot graph. This procedure was performed using STATA SE 12.0 statistical software.

Statistical analysis

The software Review Manager 5.2.6 (The Nordic Cochrane Center, 2008) was used to analyze the outcomes. The fixed effects model was used preferentially to compare the difference between the groups. When P value of the Cochran Q-test was lower than 0.1 or I^2 value was higher than 50%, it was switched to a random effects model for the assessment of heterogeneity. The results were described by forest plots and estimated by odds ratio (OR) and 95% confidence interval (95% CI). In the process of collecting data, the intention-to-treat method was adopted for indirect data collection.

Results

Search and selection results

Primary electronic database from PubMed, Web of Science, OVID, and the Cochrane Library yielded 1041 potential citations. 629 were excluded for reduplication. After secondary

Table 2. Quality analysis of the included studies

Study	Random allocation	Double-blind	Description of withdrawals and dropouts	Adequate follow-up	Description of interventions	Total
Schröder et al. [16]	1	0	1	1	1	4
Colombel et al. [15]	1	1	1	1	1	5
Feagan et al. [12]	1	1	1	1	1	5
Van et al. [17]	1	0	1	1	1	4
ACCENT I [18, 19]	1	1	1	0	0	3
ACCENT II [18, 20]	1	1	1	0	0	3

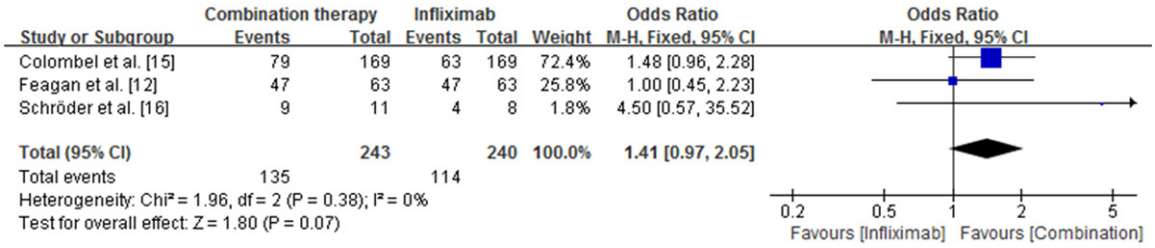

Figure 2. Forest plot of effectiveness for induction of remission.

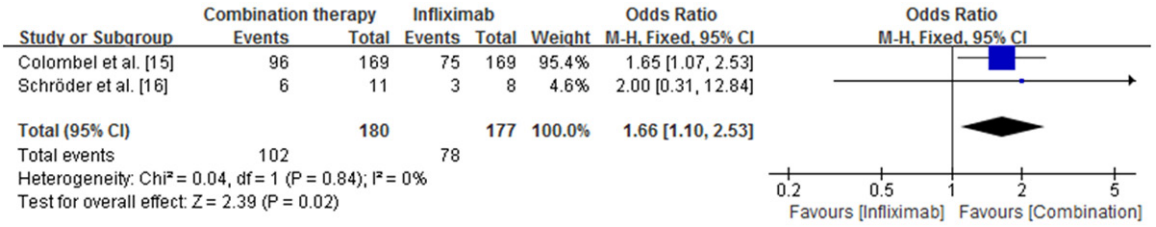

Figure 3. Forest plot of effectiveness for short-term maintenance of remission.

screening, 33 were reviewed for RCTs and relevancy. Eventually, 6 were included after complete full-text review [12, 15-20]. Moreover, the article by Lichtenstein et al. [18] was a summary and derivatives to articles of Hanauer et al. [19] and Sands et al [20]. The flow diagram demonstrating the whole search and selection procedure is given in **Figure 1**.

Study characteristics and bias analysis

The characteristics of the included studies are given in **Table 1**. The patients (N=879) were divided in two groups: IFX and combination group. Each group consisted of 514 and 365 patients respectively. The dose-intervals of IFX group were reviewed in detail. Two studies, ACCENT I [18, 19] and ACCENT II [18, 20], however, were not adequate for the review process for IS. The quality analysis for all the studies is given in **Table 2**. The funnel plot was constructed for the outcome of long-term maintenance of remission and included all the trials that provided results for this outcome. The funnel plot was symmetrical and the Begg's test did not indicate significant publication bias (P=0.260).

Outcome analysis

Effectiveness for induction of remission: Three studies, conducted by Feagan et al. [12], Colombel et al. [15], and Schröder et al. [16] respectively, which provided the available data, were considered for the subgroup evaluation. In the first trial, both combination and IFX group had same likelihood of inducing remission (OR=1.00; 95% CI: 0.45-2.33). In the second study, the remission rate of the combination group (79/169) was higher than the IFX group (63/169) (OR=1.48; 95% CI: 0.96-2.28). In the last study, 9 out of 11 patients in combination group and 4 out of 8 patients in IFX group

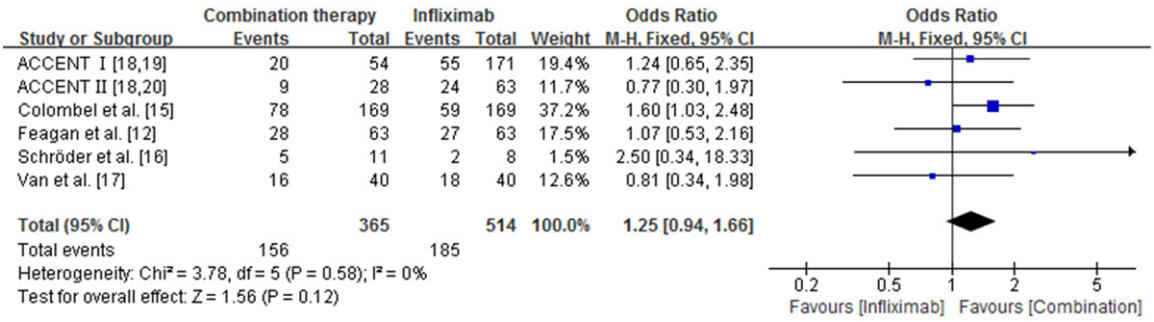

Figure 4. Forest plot of effectiveness for long-term maintenance of remission.

Table 3. Risk data of the included studies

Study	Total	Di.				In.	Ot.			Re.	Tumor
		A	B	C	Total		D	E	Total		
Schröder et al. [16]	Co 11	7	NA	NA	7	6	6	NA	6	NA	0
	Mo 8	1			1	2	3		3		0
Colombel et al. [15]	Co 179	NA	19	NA	19	75	NA	21	21	9	0
	Mo 163		30		30	75		32	32	27	0
Feagan et al. [12]	Co 63	0	21	9	30	40	8	26	34	1	0
	Mo 63	4	19	14	37	33	13	25	38	3	1
Van et al. [17]	Co 40	NA	NA	NA	NA	NA	NA	NA	NA	NA	0
	Mo 40										1
ACCENT I [18, 19]	Co 103	NA	NA	NA	NA	51	NA	NA	NA	17	NA
	Mo 282					143				92	
ACCENT II [18, 20]	Co 46	NA	NA	NA	NA	21	NA	NA	NA	8	NA
	Mo 92					53				14	

Footnotes: Di.: digestive system adnormalities; In.: Infection; Ot.: Other systemic disorders; Re.: Reaction to infusion; A: Elevated liver function tests; B: Worsening of Crohn's disease; C: Perianal disease; D: Dermatological disorders; E: Orthopedic disorders; Co: combination group; Mo: IFX monotherapy; NA: not available.

achieved remission respectively (OR=4.50; 95% CI: 0.57-35.52).

The total case numbers of the combination group and IFX group were 243 and 240 respectively. The corresponding remission numbers were 135 and 144. The overall OR for induction of remission was 1.41; and 95% CI was 0.97-2.05. The effectiveness for induction of remission between the two groups had no statistical difference (P=0.07) (**Figure 2**).

Effectiveness for short-term maintenance of remission: Colombel et al. [15] compared the short-term maintenance of remission at week 26, with remission being 96 and 75 patients in combination group and IFX group respectively (OR=1.65; 95% CI: 1.07-2.53).

Remission in the trial conducted by Schröder et al [16] was found in 6 out of 11 patients in combination group and 3 out of 8 patients in IFX group (OR=2.00; 95% CI: 0.31-12.84).

Overall, the accumulate remission number was 102 out of 180 patients in the combination group and 78 out of 177 patients in the IFX group (OR=1.66; 95% CI: 1.10-2.53). According to the data, there was mild statistical difference of remission number between the two groups (P=0.02) (**Figure 3**).

Effectiveness for long-term maintenance of remission: In 5 trials conducted by Schröder et al [16], Colombel et al [15], Van et al. [17], Feagan et al [12], and ACCENT I [18, 19], the long-term of remission, according to CDAI, was <150 without corticosteroid. The long-term of remission in the trial of ACCENT II [18, 20] was defined as complete fistula response without any draining. Each of the 6 trials demonstrated no obvious statistical difference between the two groups (P=0.12) (**Figure 4**).

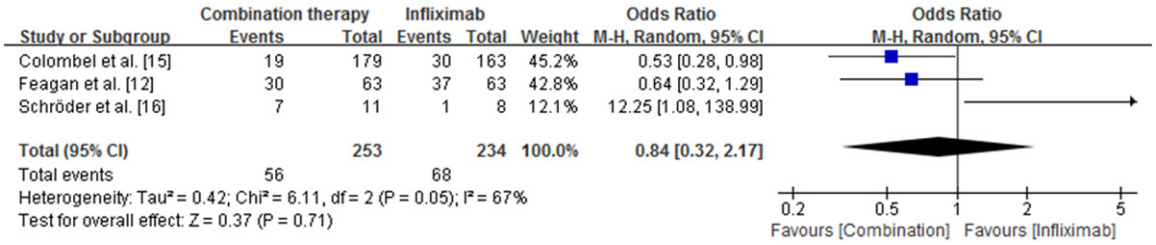

Figure 5. Forest plot of risks in digestive system abnormalities.

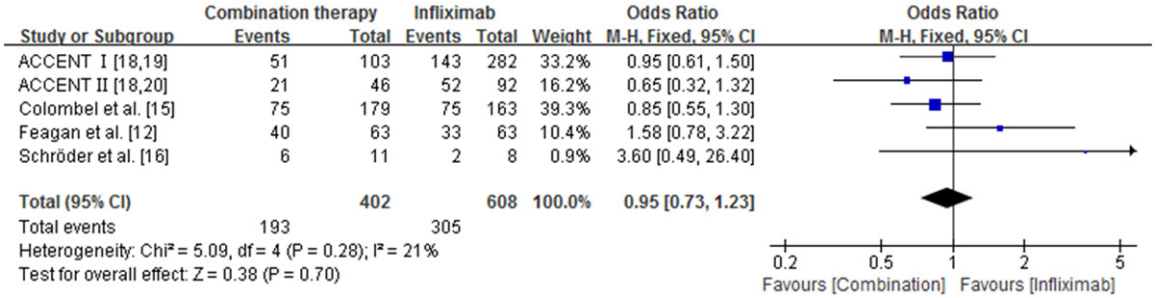

Figure 6. Forest plot of risks in infection.

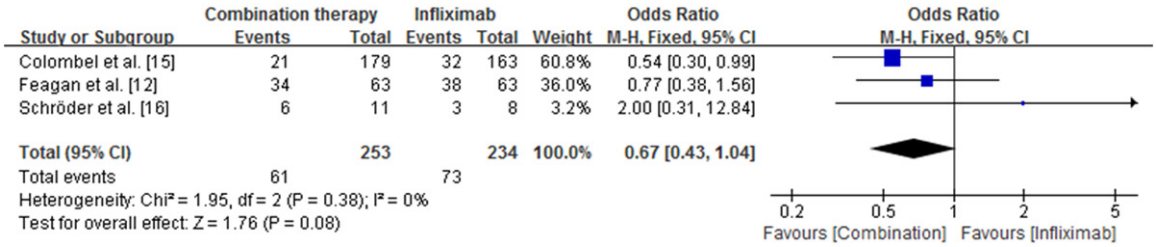

Figure 7. Forest plot of risks in other system disorders.

Risks of IFX monotherapy and combination therapy: In order to include adverse events as completely as possible, the risks of combination group and IFX group were evaluated in terms of five aspects: digestive system abnormalities, infections, other systemic disorders, reaction to infusion, and tumor. Instead of number of adverse events, the number of persons was used to describe adverse events.

We appropriately selected and merged one or more events considering that reduplication was inevitable while too many items were included. Representative items in each aspect were listed as follows: digestive system abnormalities group (elevated liver function indicators, worsening of Crohn's disease, and perianal disease), infections, other systemic disorders (skin rash, arthralgia), reaction to infusion, and tumor (**Table 3**).

The tumor data was extracted from the texts of Schröder et al [16], Colombel et al [15], and Feagan et al [12]; however, the data was calculated from the malignancy rate (1.2% discontinuation group) in the article of Van et al. [17]. The reaction to infusion data was computed from infusion-related reaction rate (1.6% combination therapy group and 4.8% infilixmab group) in the study of Feagan et al [12].

In the overall analysis, both combination and IFX group showed no significant difference in these 4 aspects: digestive system abnormalities (56/253, 68/234, OR=0.84; 95% CI: 0.32-2.17, P=0.71), infections (193/402, 305/608, OR=0.95; 95% CI: 0.73-1.23, P=0.70), other systemic disorders (61/253, 73/234, OR=0.67; 95% CI: 0.43-1.04, P=0.08), and tumor (0/293, 2/274, OR=0.33, 95% CI: 0.03-3.19, P=0.34). However, as for reaction to infusion, both gro-

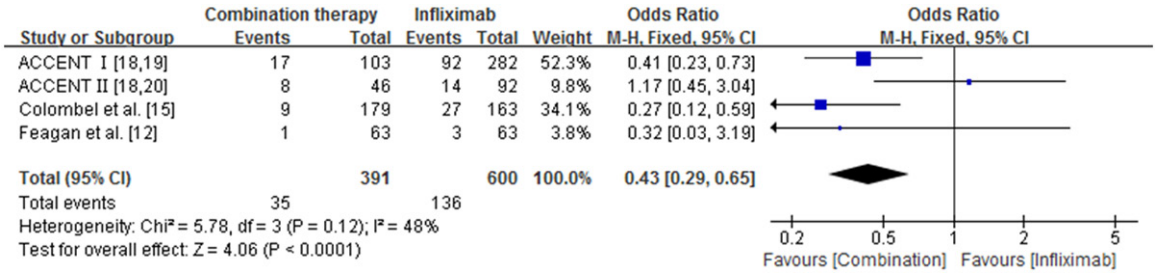

Figure 8. Forest plot of risks in reaction to infusion.

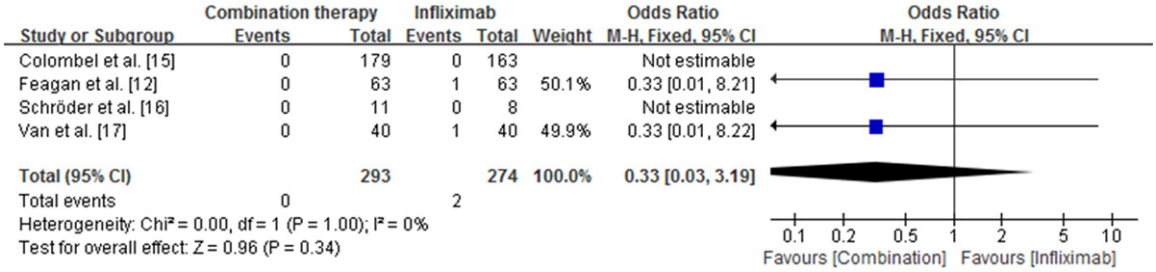

Figure 9. Forest plot of risks in tumor.

ups showed significant difference (35/391, 136/600, OR=0.43; 95% CI: 0.29-0.65, P< 0.0001) (**Figures 5-9**).

Discussion

In the past several decades, the treatment strategy for CD has always been changing and no optimized treatment program has been established. However, anti-TNF has become a landmark therapeutic application in the treatment of CD. Although anti-TNF has been used for a long time, maximization of benefits and management of toxicity still cannot be determined [21]. From the data analysis, there was no evident statistical difference between combination therapy and IFX monotherapy in induction and long-term maintenance of remission. Heterogeneity was not reported in these two aspects. In short-term maintenance of remission, a mild difference was observed between the two groups; however, heterogeneity was not demonstrated because of the small sample size of Schröder et al [16] group (combination therapy vs. infliximab, 11:8). Therefore, the impact of the trial on the whole outcome was subtle due to its low proportion. In addition, in the trial by Feagan et al [12], the choice of IS was methotrexate (MTX) and there was no significant difference in results between the groups at all 3 stages. Neeraj et al [22] reported that intrinsic lack of superior effective drug combination was the cause of the outcome. Laharie et al. [23] demonstrated that the clinical effects of IFX in combination with azathioprine (AZA) was superior as compared with the combination of IFX and MTX. In the trial by Colombel et al [15], AZA was used as the IS instead of MTX. From the above analyses, it was hypothesized that there was no significant difference between the two groups with the addition of MTX. Thus, it was concluded that there was no apparent difference in the induction and long-term maintenance of remission between the two groups. However, for short-term maintenance of remission, combination group was mildly superior to the monotherapy group. Although the difference in short-term maintenance of remission was meaningless, specific categories of combination therapy can be used in future to avoid mutual interference on the final outcome of different IS. On the other hand, assessment of specific joint protocols will have important guiding significance in clinical trials. Furthermore, the value of researching periodic medications should be emphasized due to the differences in the outcomes.

In terms of risks, digestive system abnormalities group reported heterogeneity (P=0.05),

and therefore it was described with random-effects model. The incidences of reactions to infusion were significantly different between the two groups; however, no statistical differences were observed for other aspects, such as digestive system abnormalities, infections, other systemic disorders, and tumors. Reactions to infusion, as an important adverse event during monoclonal antibody therapy, have been largely explored [24-26]. Vermeire et al [27] showed that combination group achieved lower incidence of patients generating antibodies to infliximab (ATIs) (53/115; 46%) than that of IFX monotherapy group (OR=43/59; CI: 73%; P<0.001). IS can reduce the infusion reaction by decreasing ATI's formation and improving the pharmacokinetics of IFX.

Certainly we should treat all the results cautiously, because of patients' inconsistency in the following aspects which might produce immeasurable impacts on the results: (1) condition of the patients including chronic situations, (2) usage of concomitant medications, especially corticosteroid, and (3) patients' response to IS.

Conclusions

In summary, the pooled results of this meta-analysis demonstrated that IS in combination with IFX was ineffective in induction as well as long-term maintenance of remission as compared with IFX alone. The mild difference in short-term maintenance of remission between the groups might be owing to the limitations, such as small sample size and ambiguous classification of IS, thereby it highlighted the need of more subgroup analyses [28]. For risks, the combination group was superior to IFX group in the aspect of reaction to infusion. Overall, there was no significant difference in effectiveness and risks between IS in combination with IFX and IFX alone. These findings should be interpreted with caution and confirmed with more randomized controlled trials with large sample sizes. Specific categories of combination therapy and periodic medications should be paid more attention in the future studies.

Disclosure of conflict of interest

None.

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