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Effect and Safety of TNF Inhibitors in Immunoglobulin-Resistant Kawasaki Disease: a Meta-analysis

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Abstract Previous studies showed that tumor necrosis factor (TNF) inhibitors might decrease the rate of coronary artery abnormalities in pediatrics with intravenous immunoglobulin (IVIG)-resistant Kawasaki disease (KD). Therefore, we aimed to evaluate the effect and safety of TNF inhibitors in IVIG-resistant KD. We undertook a meta-analysis of clinical trials identified in systematic searches of PubMed, EMBASE, Cochrane Database, and Google scholar through May 2016. Five studies were included. Overall, rate of coronary artery aneurysm was comparable between groups (relative risk (RR), 1.05; 95 % confidence interval (95 % CI), 0.60 to 1.81; $P = 0.87$). No significant differences were recorded between groups in coronary artery Z scores (standardized mean difference (SMD), 0.27; 95 % CI, −0.30 to 0.85; $P = 0.35$). Meanwhile, TNF inhibitors were not associated with a significant decreased risk of treatment resistance compared with IVIG treatment (RR, 0.65; 95 % CI, 0.37 to 0.15; $P = 0.14$). However, days of fever was significantly reduced in the TNF inhibitor group (SMD, −0.66; 95 % CI, −0.90 to −0.41; $P < 0.001$). Additionally, risk of serious adverse events was similar between groups. Therefore, TNF inhibitors could shorten the duration of fever in IVIG-resistant KD. However, TNF inhibitors appear to have no cardioprotective effect in patients with IVIG-resistant KD.

Keywords Kawasaki disease · Tumor necrosis factor inhibitor · Coronary artery aneurysm · Prognosis · Meta-analysis

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Introduction

Kawasaki disease (KD) is the most common vasculitis of childhood and 25 % of untreated KD may develop coronary artery aneurysm (CAA) [1]. Previous studies and meta-analyses have demonstrated that intravenous immunoglobulin (IVIG) plus aspirin reduces the risk of developing CAA [2, 3]. However, 10–20 % of patients with KD have persistence or reoccurrence of fever at least 36 h after initial IVIG therapy, which is referred to as resistant or refractory KD. Furthermore, resistant KD patients has an almost ninefold increased risk of developing CAA compared with those who responded to the initial IVIG infusion (12.2 vs. 1.4 %) [4]. Meanwhile, tumor necrosis factor-α levels are elevated in acute KD and highest in those who develop CAA [5], and tumor necrosis factor (TNF) inhibitors could decrease inflammation and endoarteritis, specifically the inhibition of neutrophil adhesion to endothelial cells [4]. Therefore, TNF inhibitors may have the cardioprotective effect in decreasing coronary artery abnormality in IVIG-resistant KD. In a prospective open-label trial, etanercept appears to be safe and well tolerated in children with KD [6]. In one two-center retrospective study, patients with IVIG-resistant KD whose first re-treatment is with infliximab, compared with IVIG, has faster resolution of fever and fewer days of hospitalization [7]. A randomized trial involving 196 children shows that the addition of infliximab in acute KD reduces left anterior descending

coronary artery *Z* scores by twofold, though the incidence of coronary artery abnormalities is similar between groups [8]. Owing to limited evidence, the effect of TNF inhibitors treatment in IVIG-resistant KD is still inconclusive. As the evidence base has recently increased, we undertook a meta-analysis to evaluate whether TNF inhibitors could decrease the risk of treatment resistance and CAA among patients with IVIG-resistant KD.

Methods

Data Sources and Search Strategies

We searched MEDLINE (source, PubMed from January 2005 to May 2016), EMBASE (January 2005 to May 2016), the Cochrane Library (to May 2016), Google Scholar (to May 2016), and the ClinicalTrials.gov website (to May 2016) using the terms "TNF inhibitor," "infliximab," "etanercept," "adalimumab," "golimumab," "Kawasaki disease," "intravenous immunoglobulin," "coronary artery abnormality," and "coronary artery aneurysm." No language restrictions were applied.

Study Selection

Studies were considered eligible if they met these criteria: (1) pediatrics with IVIG-resistant KD; (2)TNF inhibitor treatment, including infliximab, etanercept, etc.; and (3) outcome interest was risk of coronary artery abnormality and treatment resistance.

Data Collection

Two authors (L.J.X. and Z.C.F.) collected data about year of publication, first authors, patients' characteristics, the TNF inhibitor treatment strategy, IVIG treatment strategy, study quality, primary outcome, and secondary outcome using a standard data-collection form. All disagreements were resolved by discussion.

Primary outcomes were coronary abnormality, including coronary artery dilation, coronary artery aneurysm, and giant coronary artery aneurysm. Secondary outcomes were treatment resistance, days in hospital, days with fever, and serious adverse events. Serious adverse events included fever, coronary artery abnormality, headache following IVIG infusion, hemolytic anemia following IVIG infusion, abdominal pain, upper respiratory tract infection, desquamating rash, burn from hot object, seizure, electrolyte abnormality, hepatitis, hypertension, and coagulation [8].

Quality Evaluation

Methodological quality was evaluated by two reviewers (R.W. and Z.C.F.) using the Newcastle-Ottawa scale (NOS) [9]. NOS scale varies from 0 to 9 stars using eight criteria that cover three components: patient selection, study groups comparability, and outcomes assessment. Studies with a NOS score ≥6 were considered as "high quality," while studieswith a score <6 as "low quality." Additionally, we also followed the Preferred Reporting Items for Systemic Reviews and Meta-Analyses (PRISMA) statement [10].

Data Synthesis and Analysis

Data analysis was completed by three reviewers (L.J.X., R.W., and Z.C.F.). Pooled relative risk (RR) for dichotomous outcomes and standardized mean difference (SMD) for continuous outcomes was calculated with 95 % confidence intervals (CI). Heterogeneity was assessed by the I^2 statistic and the chi-squared test. I^2 values of 25, 50, and 75 % were considered as low, moderate, and high level of heterogeneity, respectively [11]. For outcomes with significant heterogeneity, the random-effects model was reported [11]; for all others, the fixed-effects models were reported [12]. Additionally, publication bias was tested using funnel plot with the Begg's and Egger's test (P for significant asymmetry <0.1) [13, 14]. Furthermore, sensitivity analysis was done by eliminating each study at one time to evaluate the influence of each trial on the primary outcome and the robustness of the result [12]. Additionally, subgroup analysis according different TNF inhibitors regimens (infliximab vs. other TNF inhibitors) was performed. All analyses were performed according to the intention-to-treat principle. Statistical significance was set at 0.05 for the Z test for RR. Results were analyzed quantitatively with STATA 12.0 (StataCorp LP, College Station, TX).

Results

Search Results

The process of study selection is shown in Fig. 1. Initially, 264 potential relevant papers were identified, of which 72 articles were considered to be of interest after reviewing the titles and abstracts. Then after full-text review, 27 articles were excluded owing to reviews ($n = 9$), incorrect comparisons ($n = 7$), animal studies ($n = 8$), and no clinical outcomes ($n = 3$). Ultimately, five studies were included in the qualitative analysis and four in the quantitative synthesis.

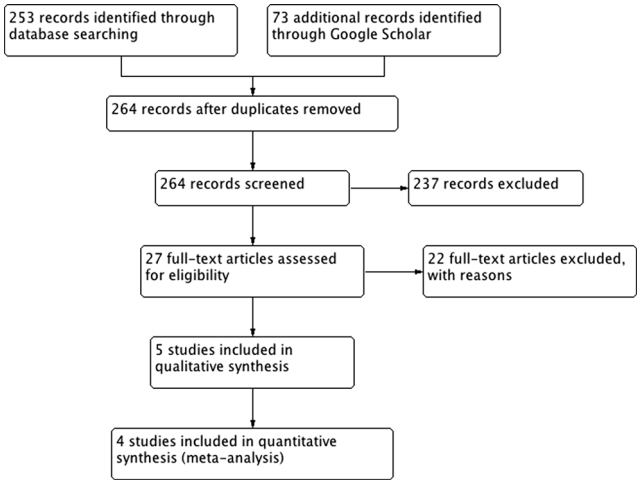

Fig. 1 Flow chart showing the study selection process

Study Characteristics

The characteristics of all include studies are summarized in Table 1. The five published studies [7, 8, 15–17] that included a total of 383 children were enrolled. The mean duration of follow-up was 5.8 weeks. The mean pediatric' ages was 15.8 months. Most were boy. The mean days of illness at enrollment were 6 days. Mean baseline CRP level was 7.8 mg/dL. The TNF inhibitors used was infliximab (single dose, 5 mg/kg) in all five studies. Meanwhile, IVIG (2 g kg^{-1} day^{-1}) was used in the control group for 6–10 days. One studies had been scored NOS <6 stars [15] and considered as low quality. However, the other four trials had been awarded ≥6 stars and qualified as high quality.

Primary Outcomes

Coronary Artery Abnormality

Three trials reported the rate of coronary artery dilation [7, 15, 18]. Overall, TNF inhibitor treatment was associated with similar incidence of coronary artery dilation compared with control group (RR, 1.09; 95 % CI, 0.68 to 1.75; $P = 0.71$) (Fig. 2). Furthermore, there were no significant differences in the risk of CAA (RR, 1.05; 95 % CI, 0.60 to 1.81; $P = 0.87$) (Fig. 3) or giant aneurysm (RR, 1.67; 95 % CI, 0.23 to 12.19; $P = 0.61$) between groups. Moreover, there was low level of heterogeneity ($I^2 = 0.0$ %). The funnel plot also showed no marked asymmetry in Begg's test ($P = 0.49$) and Egger's test ($P = 0.57$).

Additionally, three trials showed data about the coronary artery Z scores [7, 8, 15]. Overall, TNF inhibitor treatment was associated with similar maximum coronary artery Z scores compared with control group (SMD, 0.27; 95 % CI, −0.30 to 0.85; $P = 0.35$) (Fig. 4). Furthermore, there were no significant differences in the left anterior descending artery or right coronary artery Z scores (SMD, 0.14; 95 % CI, −0.49 to 0.77; $P = 0.66$ and SMD, −0.31; 95 % CI, −0.78 to 0.16; $P = 0.20$) between groups. However, there was high level of heterogeneity ($I^2 = 74.2$ %). The funnel plot also showed no marked asymmetry in Begg's test ($P = 0.29$) and Egger's test ($P = 0.38$).

Secondary Outcome

Treatment Resistance

Four trials provided data about the rate of treatment resistance [7, 8, 15, 17]. Overall, TNF inhibitors were associated with a trend of decreased risk of treatment resistance (RR, 0.65; 95 % CI, 0.37 to 1.15; $P = 0.14$) (Fig. 5). However, there was low level of heterogeneity ($I^2 = 0.0$ %). The funnel plot did not show marked asymmetry in Begg's test ($P = 0.30$) and Egger's test ($P = 0.23$).

Days of Hospital Stay and Days of Fever

Three trials provided data about days of hospital stay [7, 8, 17]. Overall, compared with IVIG therapy, the days of hospital stay was similar in patients with TNF inhibitor treatment (SMD, −0.29; 95 % CI, −0.78 to 0.20; $P = 0.24$) (Fig. 6). However, TNF inhibitors were associated with significantly decreased days of fever compared with control (SMD, −0.66; 95 % CI, −0.90 to −0.41; $P < 0.001$) (Fig. 7). Additionally, there was high level of heterogeneity ($I^2 = 69.1$ %). However, the funnel plot did not show marked asymmetry in Begg's test ($P = 0.29$) and Egger's test ($P = 0.26$).

Serious Adverse Events

Four studies mentioned the rate of severe adverse events [7, 8, 15, 17]. Overall, no significant differences were recorded between the two groups in serious adverse events (RR, 1.21; 95 % CI, 0.73 to 2.01; $P = 0.46$) (Fig. 8). Moreover, there was low level of heterogeneity ($I^2 = 0.0$ %). The funnel plot also showed no marked asymmetry in Begg's test ($P = 0.49$) and Egger's test ($P = 0.57$).

Sensitivity and Subgroup Analysis

To determine the influence of individual trials on the overall pooled results, we performed the sensitivity analysis by removing each of the trials one at a time, which did not detect any influence on the overall result of CAA (Fig. 9). Furthermore, TNF inhibitors used in all trials included was infliximab, so the subgroup analysis for different treatment regimens (infliximab vs. other TNF inhibitors) could not be performed.

Table 1 Characteristics of IVIG-resistant KD patients

First author (ref.)	Year	Follow (weeks)	Patients no.	Age (months)	Male (%)	Illness day at enrolment	CRP (mg/dL)	TNF inhibitor group			Control group			
								TNF inhibitor	Dosage (mg kg^{-1} day^{-1})	Duration (days)	Treatment drug	Dosage (g kg^{-1} day^{-1})	Duration (days)	NOS
Burns [15]	2008	4	12/12	20/22	67/75	7/9	7/8	Infliximab	5	1	IVIG	2	N/R	5
Son [7]	2011	6	20/86	23/29	70/64	5/6	8/12	Infliximab	5	1	IVIG	2	6-10	6
Burns [16]	2013	6	7/7	3/3[a]	57/14	7/6	7/8	Infliximab	5	1	IVIG	2	N/R	6
Tremoulet [8]	2014	10	98/98	N/R	61/62	6/5	9/9	Infliximab	5	1	IVIG	2	<10	9
Youn [17]	2016	8	11/32	N/R	N/R	2–8	10/7	Infliximab	5	1	IVIG	2	2–8	6

mon month, *Num* number, *CRP* C-reactive protein, *TNF* tumor necrosis factor, *NOS* Newcastle-Ottawa scale, *IVIG* intravenous immunoglobulin, *KD* Kawasaki disease, *N/R* not reported

[a] Year old

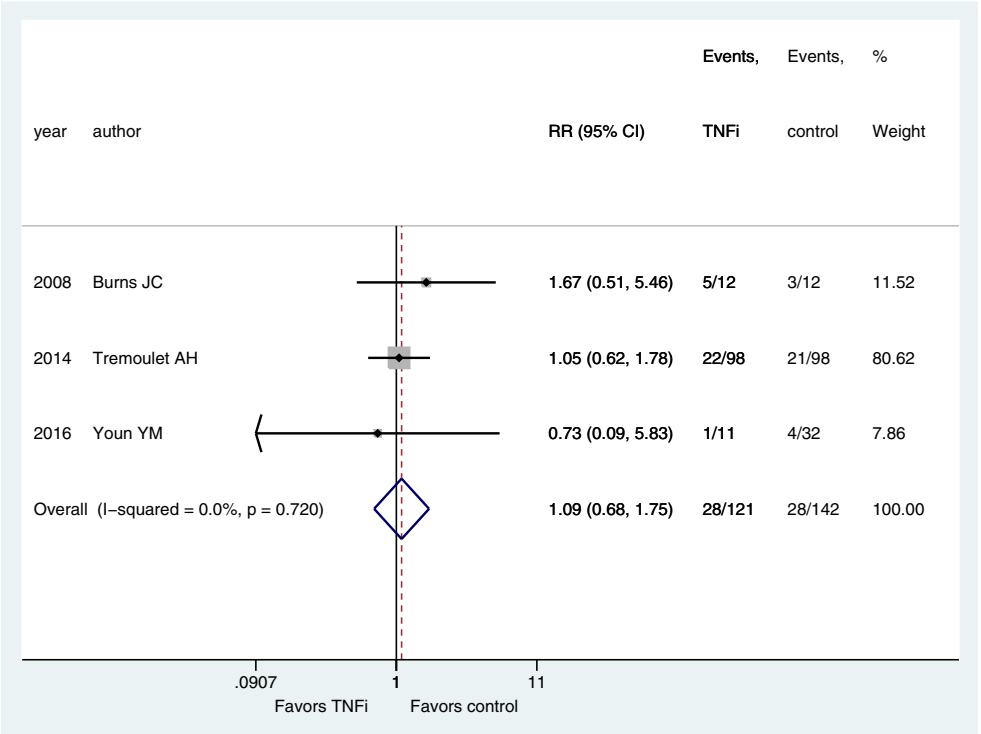

Fig. 2 Rate of coronary artery dilation identified in the meta-analysis of three trials using fixed-effect model. Test for overall effect, $z = 0.37$, $P = 0.70$; test for heterogeneity, $I^2 = 0.0$ %, $P = 0.72$. *TNFi* tumor necrosis factor inhibitor, *RR* relative risk, *CI* confidence interval

Discussion

Our meta-analysis shows that TNF inhibitors are associated with significantly faster resolution of fever, although rates of treatment resistance and coronary artery abnormality are similar between groups. Therefore, targeting systemic inflammation with TNF inhibitors appear to have no cardioprotective effect in patients with IVIG-resistant KD.

Patients with KD are associated with increased risk of CAA, especially in those with IVIG-resistant KD. KD is an

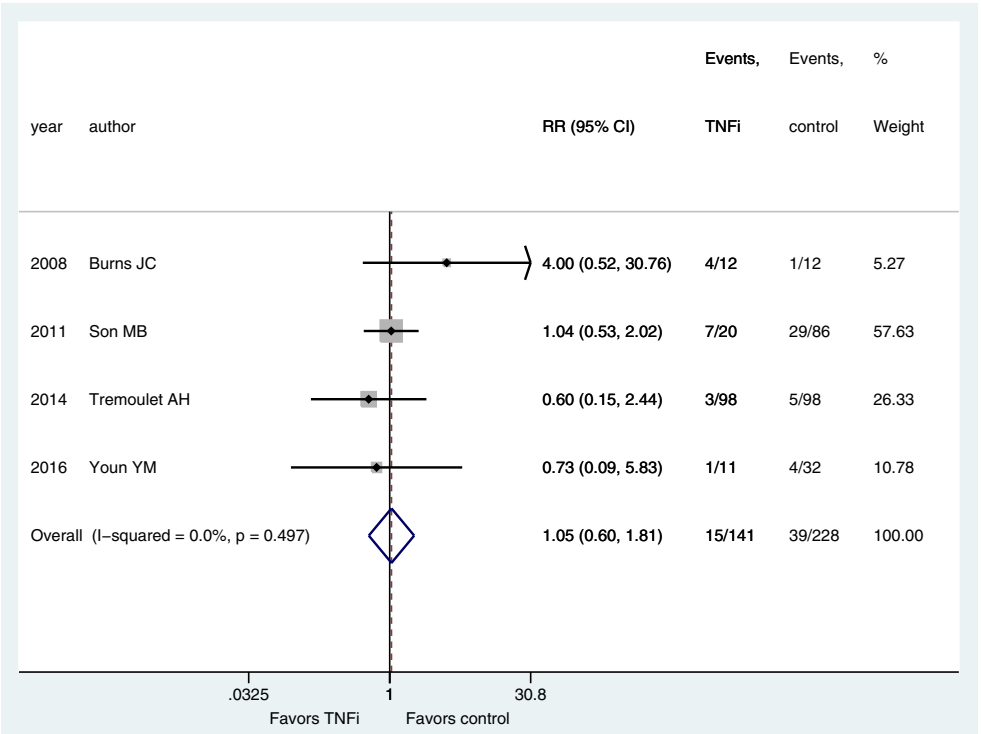

Fig. 3 Risk of coronary artery aneurysm in the meta-analysis of four studies using fixed-effect model. Test for overall effect, $z = 0.16$, $P = 0.87$; test for heterogeneity, $I^2 = 0.0$ %, $P = 0.49$. *TNFi* tumor necrosis factor inhibitor, *RR* relative risk, *CI* confidence interval

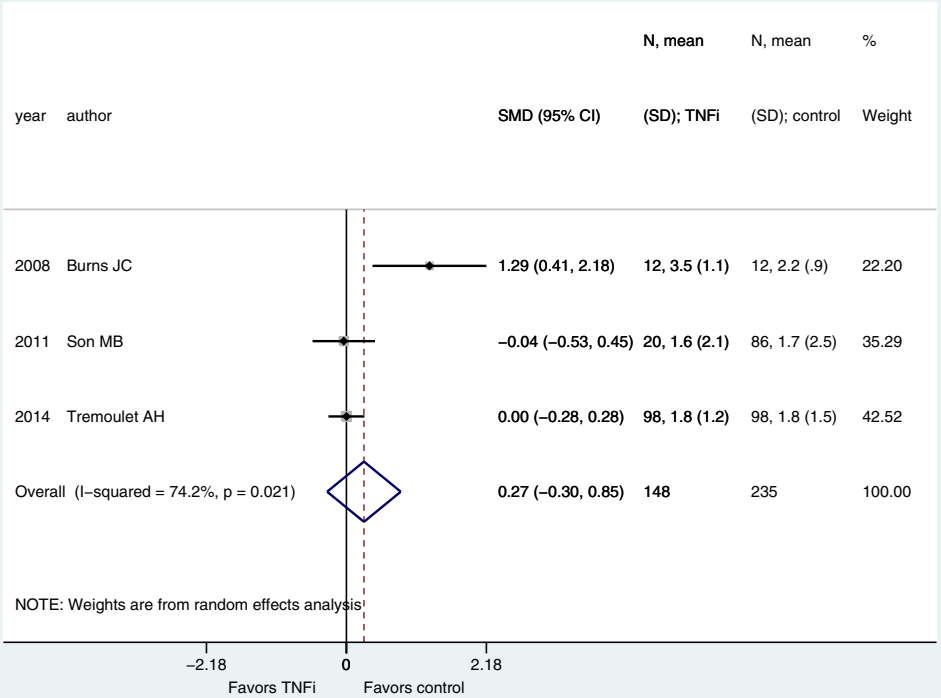

Fig. 4 Change of the coronary artery maximum *Z* scores in the meta-analysis of three trials using random-effect model. Test for overall effect, $z = 0.93$, $P = 0.35$; test for heterogeneity, $I^2 = 74.2\ \%$, $P = 0.02$. *TNFi* tumor necrosis factor inhibitor, *SMD* standardized mean difference, *CI* confidence interval

autoimmune disease found predominantly in children under 5-year old. Epidemiological studies show that KD incidence is higher in those who live in Asian or are of Asian descent. Treatment of KD remains mainly empirical at present. Timely administration of IVIG and aspirin are sufficient for most children with KD. However, approximately 10–30 % of patients fail to respond to the initial IVIG and will require further management with corticosteroid, immunomodulatory, or cytotoxic agents [18]. Although KD is usually self-limiting, children may develop cardiac abnormalities that can lead to

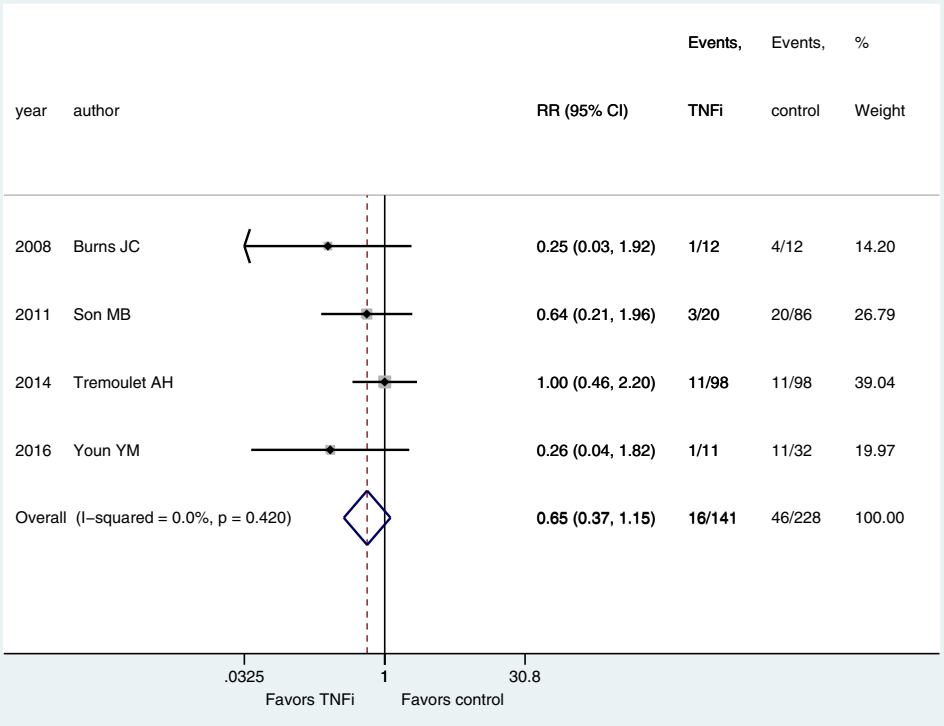

Fig. 5 Rate of treatment resistance in the meta-analysis of four studies using fixed-effect model. Test for overall effect, $z = 1.47$, $P = 0.14$; test for heterogeneity, $I^2 = 0.0\ \%$, $P = 0.42$. *TNFi* tumor necrosis factor inhibitor, *RR* relative risk, *CI* confidence interval

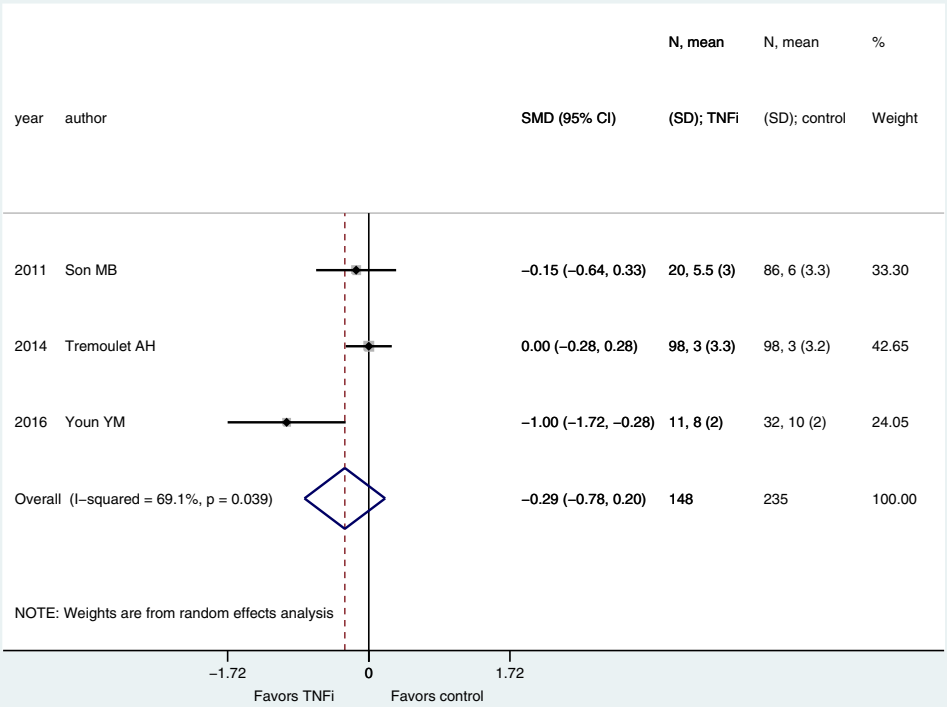

Fig. 6 Days in hospital in the meta-analysis of three studies using random-effect model. Test for overall effect, $z = 1.16$, $P = 0.24$; test for heterogeneity, $I^2 = 69.1\ \%$, $P = 0.03$. *TNFi* tumor necrosis factor inhibitor, *SMD* standardized mean difference, *CI* confidence interval

death [19]. Previous studies point out an increased incidence of myocardial infarction and increased cardiovascular mortality risk in KD [18]. Furthermore, resistance to IVIG portends much higher risk of aneurysm development. A multicenter study shows that IVIG nonresponders are prone to develop CAA (18.6 %), though initial sufficient IVIG therapy decreases the risk of IVIG nonresponse [19]. In a nationwide survey of 15,940 KD patients, IVIG nonresponders accountes for 20.3 % of them. In addition, IVIG nonresponders have significantly higher risks for CAA (odds ratio (OR), 10.38) or giant coronary artery aneurysms (OR, 54.06). KD has replaced rheumatic fever as the leading cause of acquired

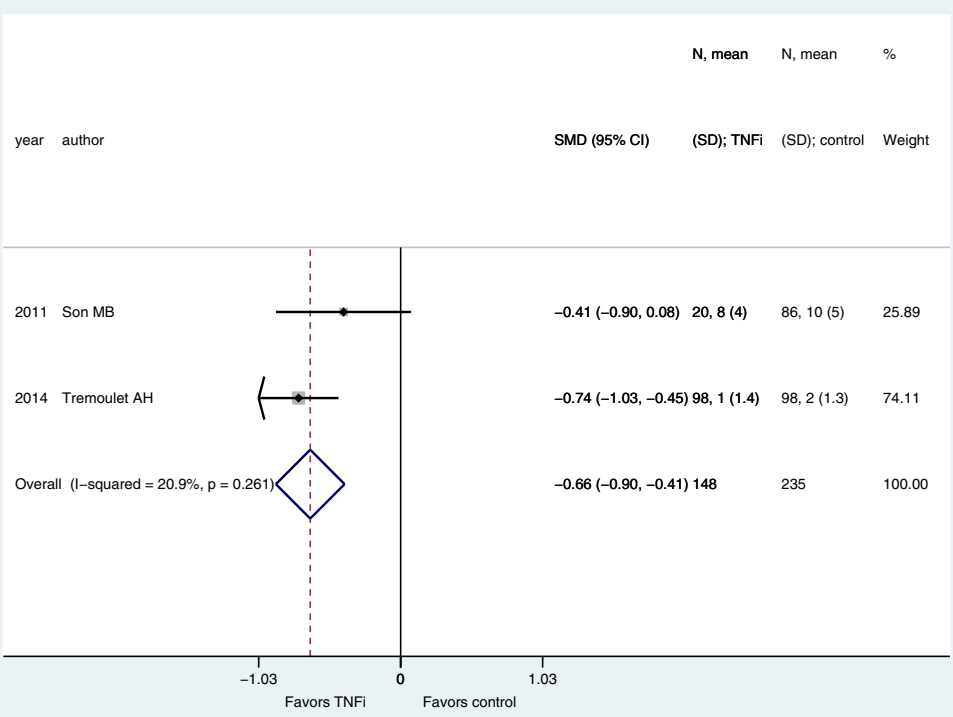

Fig. 7 Days with fever in the meta-analysis of only two studies using the fixed-effect model. Test for overall effect, $z = 5.16$, $P < 0.001$; test for heterogeneity, $I^2 = 20.9\ \%$, $P = 0.26$. *TNFi* tumor necrosis factor inhibitor, *SMD* standardized mean difference, *CI* confidence interval

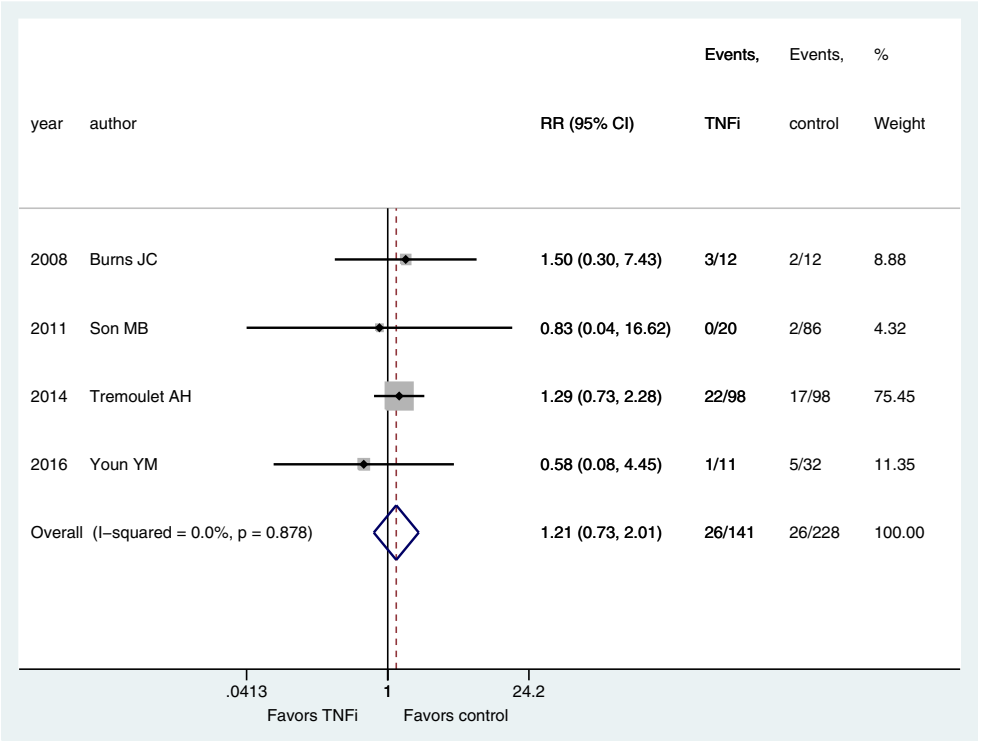

Fig. 8 Rate of severe adverse events in the meta-analysis of four studies using the fixed-effect model. Test for overall effect, $z = 0.74$, $P = 0.45$; test for heterogeneity, $I^2 = 0.0$ %, $P = 0.87$. *TNFi* tumor necrosis factor inhibitor, *RR* relative risk, *CI* confidence interval

cardiac disease in children in the developed world. Risk factors for development of CAA include both demographic variables and those related to the severity of vasculitis [4]. Various risk factors, including male gender, early IVIG treatment before day 5, laboratory parameters (e.g., increased CRP, low hemoglobin, low albumin and sodium and having recurrent KD are predictors for IVIG nonresponse [20, 21]. Therefore, physicians should consider potential IVIG nonresponder, particularly if they are boys and have laboratory values associated with nonresponse including low platelet count, elevated alanine aminotransferase, and C-reactive protein [20, 21]. These IVIG-resistant patients have a higher risk of developing CAA and require additional therapy to control inflammation [22].

The optimal treatment for IVIG-resistant KD remains controversial, and a second dose of IVIG 2 g/kg is recommended by most experts, including the American Heart Association (AHA) consensus guidelines, in patients for whom the initial dose has failed [23]. Previous studies reported that in up to 80 % of IVIG-resistant patients, a second dose of IVIG is effective in controlling disease activity [24]. Moreover, a meta-

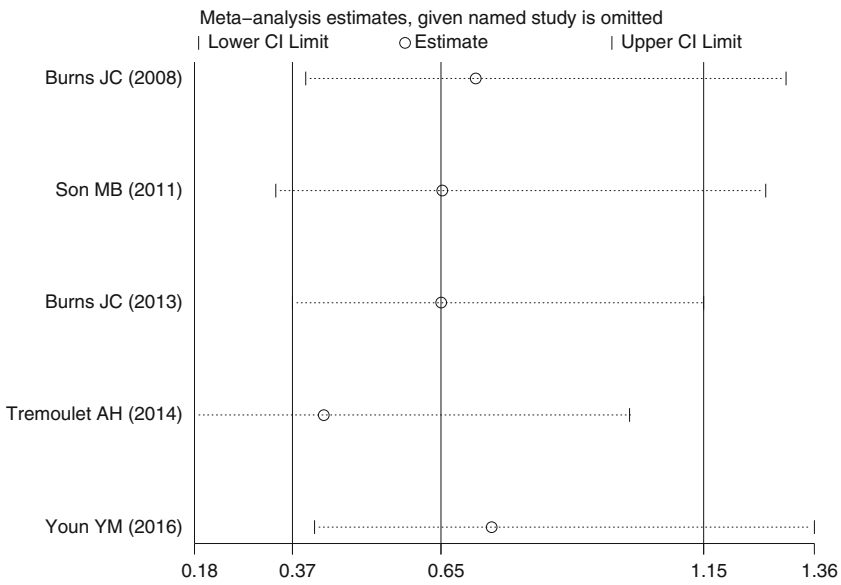

Fig. 9 Sensitivity analysis of coronary artery aneurysm

analysis of North America and Japanese studies demonstrates that the rate of the coronary artery abnormalities is inversely related to the total IVIG dose [25]. In a multicenter, retrospective survey of 378 children with KD in North America, Bruns et al reports that IVIG-resistant patients retreated with 2 g/kg infusion has a significantly lower risk of CAA, compared with those retreated with infusions of 1 g/kg (5.9 vs. 57.1 %, $P = 0.014$) [26]. On the basis of these results, a dose of 2 g/kg is recommended in most medical centers. However, no data from randomized controlled trial exist to guide and evaluate the efficacy and safety of re-treatment with IVIG. Additionally, the precise mechanism of action of IVIG in KD remains unknown but is presumed to be related to direct anti-inflammatory effect and specific activity against the aetiologic agent.

Additionally, adjunctive therapy, usually with a corticosteroid, might need to be considered in patients at high risk of coronary abnormalities. Hashino et al. performs a small randomized controlled trial examining the efficacy and safety of additional IVIG with steroid plus therapy in patients with IVIG-resistant KD. Seventeen patients did not respond to the IVIG treatment are randomized to receive a 3-day course of intravenous methylprednisolone (30 mg kg^{-1} day^{-1}) or IVIG infusion (1 g/kg). There is no significant difference in rate of CAA between groups (44.4 vs. 62.5 %). However, the duration of high fever is significantly decreased in the steroid group. Furthermore, the medical costs are significantly lower in patients treated with steroid pulse treatment [27]. In 2005, Miura et al. conducted another small randomized controlled trial about steroid treatment. Twenty-two patients are randomized to receive steroid (30 mg kg^{-1} day^{-1} of methylprednisolone for 3 days), or additional IVIG (2 g/kg). The antipyretic effect of steroid therapy is superior to that of additional IVIG on day 2 ($P = 0.02$), but not on day 3 and later. However, this study is halted prematurely because of adverse effects of steroid treatment. Sinus bradycardia (82 vs. 18 %, $P = 0.01$) and hyperglycemia (55 vs. 0 %, $P = 0.01$) occurs more frequently in the steroid group [28]. Two recent important Japanese studies evaluates the effect of adjunctive steroids in IVIG-resistant KD patients identified by the Egami score [29, 30], which includes age (<6 months), days of illness (≤4 days), platelet count ($<30 \times 10^4$/L), CRP (>8 mg/dL), and alanine aminotransferase level (>100 U/L). More patients in the steroid group has a prompt defervescence compared with IVIG group (86.4 vs. 23.1 %). Furthermore, higher coronary artery Z scores are noted in 9.1 % of patients receiving steroids, compared with 39 % in the IVIG group ($P = 0.04$) [29]. The most comprehensive and best-powered study of steroids treatment in patients with KD is the 2012 RAISE study [30]. This prospective, randomized, blinding trial involves 248 patients from 74 Japanese hospital, who are predicted to have a high risk of resistant to IVIG using the Kobayaski score. Patients receive standard IVIG and aspirin treatment with or without intravenous prednisolone (2 mg kg^{-1} day^{-1} for 5 days). The risk of coronary artery abnormalities is significantly lower in the steroid group after 1 to 2 weeks of disease onset (3 vs. 23 %, $P < 0.001$). At 4 weeks, four of 121 patients (3 %) and 15 of 120 patients (13 %) in the steroid and control groups, respectively, has coronary artery abnormalities ($P < 0.014$). Furthermore, coronary artery luminal diameter Z scores are markedly lower, fever subsided more quickly, fewer patients needed re-treatment with IVIG (13 vs. 40 %, $P < 0.0001$), and nonresponse rates are lower (5 vs. 30 %, $P < 0.0001$) in the steroid versus standard treatment groups, respectively [30]. Zhu et al performs a meta-analysis of randomized controlled trials to investigate the effect of corticosteroid therapy in KD [31]. Overall, corticosteroid combined with IVIG in primary treatment or as treatment of IVIG-resistant patients reduces rate of initial treatment failure (OR, 0.50, $P = 0.003$) and duration of fever (MD, −1.30, $P = 0.0005$). However, the incidence of coronary artery lesions (OR, 0.87, $P = 0.78$) or CAA are similar between groups (OR, 0.67, $P = 0.23$), which is consistent with another meta-analysis [32]. However, combining 11 randomized controlled trials and observational studies, Chen et al shows that IVIG plus corticosteroid therapy significantly reduces the risk of coronary abnormality (OR, 0.3; 95 % CI, 0.20 to 0.46). Similar results are also observed in subgroup analyses of randomized controlled studies (OR, 0.3; 95 % CI, 0.18 to 0.5) and studies focused on patients with a high risk of IVIG resistance (OR, 0.32; 95 % CI, 0.19 to 0.55). Moreover, there is no significant difference in rate of severe adverse events between groups (OR, 1.24; 95 % CI, 0.33 to 4.67) [22]. Hence, steroids may be an attractive option as adjunctive therapy in IVIG-resistant KD. However, differences in steroid dosing and duration, the lower aspirin doses used in Japanese studies compared with those used outside Japan, different pharmaceutical formulations and particularly the difficulty of identifying "high-risk" patients in non-Japanese patients make broad-scale implementation of adjunctive steroids challenging outside of Japan [33]. The Kobayashi and similar scoring systems to predict children at high risk of developing coronary artery abnormalities in North America has shown low sensitivity around 33–42 % [34]. Therefore, the AHA recommends restriction of pulse steroids to children in whom two or more IVIG infusions have been ineffective [23].

TNF inhibitors are associated with cardioprotective effects in patients with inflammatory status, including juvenile idiopathic arthritis, rheumatoid arthritis, spondyloarthropathies, and other inflammatory conditions, including vasculitis [35]. TNF is a key cytokine-mediating effector pathway in both inflammatory disease target tissues and in atherosclerotic vessels [35]. A recently published study demonstrates that TNF inhibitors could significantly decrease the risk of cardiovascular events in psoriasis and psoriatic arthritis [36]. Moreover, Behnes shows that systemic anti-inflammatory therapy with TNF inhibitor could bring the spontaneous revascularization

of a chronic total occlusion lesion [37]. Therefore, treatment of inflammatory conditions with TNF inhibitors additionally modulates vascular risk factors and has beneficial effects on vascular outcomes. Given the known involvement of elevated TNF level in development of CAA in KD patients, TNF inhibitors, including infliximab and etanercept have been studies more recently for use in IVIG-resistant KD as primary adjunctive therapy. In a small, multicenter, randomized, prospective study of 24 children with IVIG-resistant KD, Burns et al found that TNF inhibitors were associated significantly reduction in CAA incidence compared with IVIG therapy [15], and Tremoulet et al. showed a decreased left anterior descending coronary artery *Z* scores by twofold [8]. These beneficial effects of TNF inhibitors have been attributed to the anti-inflammatory effect, the modulation of endothelial cell function, the reduction of vascular stiffness, and the expansion of regulatory T cells [16, 34]. However, in another two-center retrospective study of 106 patients with IVIG-resistant KD [7], Son et al. found that there is no significant difference in coronary artery outcomes in the first 6 weeks after illness onset, including absolute dimensions, *Z* scores, or differences in coronary measurements from baseline to follow-up. Additionally, the infliximab and IVIG re-treatment groups did not differ significantly in the percentage of patients with aneurysms (35 vs. 34 %) [7], which was also confirmed by a phase 3 randomized trial [8]. Combining all previous trials, our study demonstrates that rates of coronary artery abnormalities, including coronary artery dilation, CAA, and giant aneurysm, are similar between TNF inhibitor and control groups. However, five studies included in our meta-analysis are small sample size; moreover, only the infliximab is used in the TNF inhibitors group. Therefore, owing to limited data, the effect of TNF inhibitors in IVIG-resistant KD is still inconclusive.

However, TNF inhibitors could reduce the days of fever in KD. Previous studies demonstrate that administration of infliximab is associated with a more rapid decrease in CRP, fewer days of fever and shortened hospitalization [7]. Meanwhile, Tremoulet et al. also shows that the reduction in level of CRP and erythrocyte sedimentation rate at week 2 is greater in patients in the infliximab group [8]. Furthermore, days of fever or hospitalization are also significantly decreased in the TNF inhibitor group [8, 17]. Consistent with previous studies, we confirm that TNF inhibitors could markedly decrease the duration of fever in IVIG-resistant KD. However, the reduction of inflammatory factors, such as CRP, neutrophil count, and erythrocyte sedimentation rate, is not statistically significant at week 5 after TNF inhibitors treatment [8]. Moreover, most IVIG-resistant KD patients enrolled are followed up for no more than 3 months. PACE study suggests that TNF inhibitors have long-term efficacy in psoriatic arthritis. However, poor information on long-term outcomes on TNF inhibitors in KD is available. The time and/or duration of TNF inhibitors therapy might influence the outcomes in KD [38]. Therefore, more studies are needed to evaluate long-term effect of TNF inhibitor in KD.

Additional treatment options that might be considered in IVIG-resistant KD patients include plasma exchange [39], a single low dose of oral methotrexate (10 mg/m^2) [40], and ciclosporin (4–8 mg kg^{-1} day^{-1} for 14–21 days) [41]. Hokosaki et al. conducts a study to investigate the long-term efficacy of plasma exchange (PE) treatment for refractory KD. The primary endpoint is the incidence of coronary artery lesions before PE, in the acute period, and during the late period. The outcome of PE tends to be better when PE is begun in the early stage. Sequelae remains in 2.8 % of patients in whom PE is initiated prior to day 9 after onset and are present in 15 % of patients in whom PE is started on or after day 10 [39]. Meanwhile, Lee et al evaluates the efficacy of low-dose oral methotrexate in IVIG-resistant KD. They find that methotrexate treatment results in quick resolution of fever and rapid improvement of inflammation markers without causing any adverse effects [40]. Tremoulet et al. demonstrates that treatment of refractory KD with cyclosporine appears to be a safe and effective approach that achieves rapid control of inflammation associated with clinical improvement [41]. Furthermore, an anecdotal report describes the apparently successful use of IL-1 antagonist anakinra in a child with refractory KD complicated by macrophage activation syndrome [42]. The ongoing ANAKID trial will evaluate the safety and tolerability of anakinra as a strategy to prevent or attenuate coronary artery damage in infants and children with KD [43]. Besides, statins have the pleiotropic effects on endothelial function, inflammation, oxidative stress, platelet aggregation, and the risk of thrombosis, and maybe a possible option in refractory KD [44]. However, owing to the self-limited nature of KD, the limited number of patients with IVIG-resistant KD, and the lack of randomized controlled trials, more clinical trials are needed to adequately assess responses to the potential adverse outcomes of these treatment options.

Study Limitations

Our study has several limitations. First, most studies included are low-quality observational clinical trial, which could increase the risk of heterogeneity. Second, only one TNF inhibitor agent, infliximab, is used in all studies included, so we could not evaluate other TNF inhibitors' effect in IVIG-resistant KD. Third, although our inclusion criteria were broad, there remained slight differences across all studies in the characteristics of enrolled patients, treatment strategy used, and follow-up period. Fourth, most studies are with short-term follow-up (<3 months). Therefore, the long-term effect of TNF inhibitors is still unclear. Overall, based on the findings of our meta-analysis, large scale randomized trials with careful matching of

key clinical and technical variables, different TNF inhibitor regimens and duration are needed to definitively quantify the effect of TNF inhibitor treatment.

Conclusions

Given existing data, TNF inhibitors are not associated with reductions in the rates of coronary artery abnormalities in KD. Meanwhile, rate of treatment resistance is similar between groups. Therefore, TNF inhibitors could not provide cardioprotective effect in IVIG-resistant KD. More studies will need to be conducted to evaluate the effect of TNF inhibitors.

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Compliance with Ethical Standards

Conflict of Interest No conflict of interest.

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