Treatment of Kawasaki Disease

Ling-Sai Chang

Abstract

The goal of treating acute Kawasaki disease (KD) is to treat inflammation and reduce cardiovascular sequelae by reducing the inflammation of the coronary arteries. We reviewed the clinical studies that focused on the efficacy of medications used for KD. Intravenous immunoglobulin (IVIG) is the standard treatments for KD. Some studies have the use of adjunctive corticosteroids in selective patients with KD. Corticosteroids were found to lower the progression of aneurysms in patients with *Z* scores ≥2.5. The efficacies of corticosteroids in KD remain controversial. Biologics, including etanercept and infliximab, have also been reported to exert benefits in patients with coronary artery abnormalities. Clinical trials with larger sample sizes are warranted to examine the efficacy of medications and clarify the role of acetylsalicylic acid in traditional treatments in KD.

Keywords

Coronary artery aneurysm · Corticosteroids Intravenous immunoglobulin · Kawasaki disease · Vasculitis · Treatment

L.-S. Chang (✉)
Kawasaki Disease Center and Department of Pediatrics, Kaohsiung Chang Gung Memorial Hospital, Kaohsiung, Taiwan
e-mail: 8702034@cgmh.org.tw

Intravenous Immunoglobulin

The American Heart Association (AHA) proposed the guidelines for the diagnosis and management of Kawasaki disease (KD) in 2004 based on the evidence including the summary provided by the meta-analysis published in the Cochrane in 2003 and the guideline was updated in 2017 [1–3]. Intravenous immunoglobulin (IVIG) is pooled from serum IgG. High-dose IVIG was applied in the therapy of KD in Japan in 1984 [4]. Then, Newburger et al. conducted a multicenter, randomized controlled trial study (RCT) confirmed that a single high dose IVIG can, indeed, reduce the coronary-artery abnormalities to <5% in then the USA [5]. Since then, KD is considered a nonfatal disease with good prognosis. There are many ways to use IVIG at the beginning, covering IVIG 400 mg/kg daily, for 5 days, or for 3–4 days, IVIG 1 g/kg for 1 or 2 days, IVIG 200 mg/kg per day for 5 consecutive days, IVIG 50–100 mg/kg for 5 days, or IVIG 2 g/kg [3]. Statistical analysis points out that prevalence of coronary artery abnormalities in KD is highly dependent on IVIG dose [3, 6]. The 2004 and 2017 treatment guidelines recommend IVIG 2 g/kg as a single infusion, usually given over 10–12 h [1, 2]. IVIG should be administered within 7 days of fever, and give it as soon as possible after the diagnosis of KD before developing histological arteritis. In a cohort study in Japan from 2011 to 2012, among 20,933 KD patients,

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patients with IVIG administered after 7 days of fever were prone to developing coronary artery dilations compared to those with IVIG before 7 days (odds ratio: 1.66) [7]. IVIG started ≦4 days of symptoms did not reduce the formation of coronary artery dilations. KD is considered a self-limited disease because the patient will go away from fever without treatment [8]. In a retrospective study, among 293 KD patients who had a fever for 5–10 days, the risk of coronary aneurysms after 1 month was significantly higher in 37 patients without IVIG treatment than that of patients who received IVIG (18.9% vs. 5.1%) [8]. Especially in patients younger than 1 year old and with elevated white blood cells, they were a high-risk group for coronary aneurysms. A retrospective study in Japan found that among 968 patients with KD, 71 patients had initial spontaneous defervescence within 7 days. If there was no abnormal coronary artery findings and persistent inflammation, the prognosis was relatively benign [9]. The current treatment recommendations are KD patients including those with spontaneous defervescence need IVIG treatment. However, we need further research to distinguish between high-risk groups and low-risk groups that do not require IVIG treatment for patients with spontaneous defervescence.

The high dose of IVIG has the effect of regulating immunity by lowering the high-affinity receptor FcγRI and ameliorating the inflammation of KD. At the same time, it also reduces the expression of FcγRII and other low-affinity receptors [10, 11]. IVIG also avoids autoimmunity caused by the combination of autoantibodies and Fcγ receptors [12]. The role of IVIG also includes enhancing the activity of regulatory T cells, inhibiting the production of antibodies and inflammation, and balancing type 1/type 2 inflammations [13–16]. The monoclonal antibodies against IgG Fc-dependent pathways have been undergoing clinical studies one after another [12, 17].

Serious adverse effects after treatment with IVIG are quite rare [18]. In 2017, Ibrahim et al. presented a patient with KD who developed transfusion-related acute lung injury after immunoglobulin infusion [19]. The patient's condition resolved with supportive care. Kemmotsu et al. conducted a retrospective analysis, 10-year period study in KD patients treated with high dose IVIG. They observed that acute treatment with high dose IVIG was related to aseptic meningitis in 4 out of 384 patients [20]. Mention of immediate reaction after infusion, one small-sample, cross-sectional study on high dose IVIG treatment reported one child developed skin rash in the 11 pediatric patients with KD [21]. A case series conducted at a tertiary care pediatric hospital identified five KD patients with severe anemia requiring transfusion with incidence of 0.36% [22].

Acetylsalicylic Acid

Before IVIG therapy has been established as the standard treatment for KD and the invention of cardiac ultrasound, acetylsalicylic acid was once believed to reduce the mortality of KD due to its effect on thrombotic occlusion of a coronary artery [23]. High-dose acetylsalicylic acid was applied from 80 to 100 mg/kg/day in the USA to 30–50 mg/kg/day in Japan, poses anti-inflammatory effect by blocking arachidonic acid producing prostaglandin E2, and converted to low-dose acetylsalicylic acid 3–5 mg/kg/day which had antiplatelet function by blocking cyclooxygenase producing thromboxane A2 48 h after defervescence for 6–8 weeks [24]. KD patients with coronary artery abnormalities are recommended to be treated until the cardiac ultrasound is normal and the inflammation index is completely improved.

Despite the lack of evidence provided by RCT, in contrast, traditional high-dose acetylsalicylic acid was considered to have no significant therapeutic effect in a 10-year retrospective study with 260 KD children [24, 25]. But it is still necessary to understand the preventive effect of low-dose aspirin on coronary artery lesions [26]. Kuo et al. designed a multi-center, randomized controlled, evaluator-blinded trial to compare the difference of coronary artery lesions between the two groups (IVIG alone vs. IVIG plus high-dose acetylsalicylic acid at acute stage) 1 month later [27].

Kuo et al. found that high-dose acetylsalicylic acid was associated with anemia [28]. The previ-

ous study involving 609 KD patients in Taiwan showed high dose acetylsalicylic acid posed no appreciable benefit in preventing the IVIG treatment failure, the formation of coronary artery lesions, or shortening the length of hospital stay. The use of acetylsalicylic acid is most prone to side effects of the digestive system (5.3% among 910 KD patients) in a retrospective study with large sample size [29]. Bleeding in the upper and lower gastrointestinal tract and abnormal liver function have been reported, and symptoms of abdominal discomfort may appear under the treatment of acetylsalicylic acid [30].

Adjuvant Therapy: Corticosteroids

Before knowing which way to treat KD, corticosteroids alone in the treatment of acute KD increased the incidence of coronary artery lesions (CAL) [23]. However, the current goal of precision medicine is to use adjuvant therapy for patients who are predicted to respond poorly to IVIG treatment. Two meta-analyses (one is limited to RCT and the other is not limited to) try to distinguish the effect of corticosteroids in KD [31, 32]. In selected high-risk patients with KD, initial combination with corticosteroids can reduce coronary artery abnormalities [33]. A 35-year retrospective analysis in the USA found that adjuvant therapy can effectively increase the CAL regression rate [34]. When 121 children diagnosed KD with a Z score ≥ 2.5 and <10, treatment plus corticosteroids or infliximab compared with IVIG alone can reduce the deterioration of coronary artery abnormalities [35]. Newburger and colleagues investigated the efficacy of initial methylprednisolone pulse therapy (30 mg/kg) combined with following IVIG in nonselective KD patients. This RCT found coadministration of methylprednisolone and IVIG cannot decrease the risk of coronary artery abnormalities [36].

Studies have investigated the use of initial adjunctive prednisolone with respect to its treatment effect in patients with severe KD in Japan. However, the results of these trials are conflicting.

Kobayashi and colleagues conducted an RCT called RAISE study and evaluated the efficacy of adjunctive initial prednisolone in selected high-risk KD patients evaluated by Kobayashi score [37]. They found that the effect of additional prednisolone was significant for coronary artery abnormalities (4/125 patients in combination group vs. 28/123 patients in standard group, $p < 0.0001$). Analysis of large-scale data from nationwide epidemiologic KD surveys which cannot identified the severity score found significantly decreased risk (estimated risk ratio 0.53) of coronary artery abnormality (74/1593 in combination treatment group with corticosteroids added to initial standard treatment vs. 140/1593 in IVIG group) and the requirement of retreatment for treatment failure (estimated risk ratio 0.65; 225/1593 in combination treatment group with corticosteroids added to initial standard treatment vs. 234/1593 in controls) [38, 39]. However, a Post RAISE study with a multicenter, prospective cohort design did not find different coronary outcomes between patients predicted IVIG resistance using Kobayashi score treated with combination treatment consisting of prednisolone and IVIG and placebo group [40].

Because the design of risk score varies from race to race, it also affects the clinical use of corticosteroids and related research [38, 41]. Since the therapeutic effect is equivalent to secondary IVIG, corticosteroids are also considered an option for refractory KD [42, 43].

Adjuvant Therapy: Biologics

Tumor necrosis factor α (TNFα) is a well-known biomarker for KD. TNFα mediates endothelial cell activation and is involved in the CAL development [44]. Due to the breakthrough development of monoclonal antibodies, strong specificity can avoid systemic immunosuppression and other associated comorbidities [45]. Among the 16 refractory KD patients, 13 patients under infliximab were found to resolve their fever in a small series in 2005 [46]. A phase 3 RCT enrolled 196 patients and demonstrated no additional benefit of treatment resistance for the addition of infliximab, biologics as the format of chimeric murine/human IgG1, produced by hybridoma, to primary treatment in acute KD [47]. However, a meta-analysis for five RCTs with 494 participants

reported anti-TNFα has beneficial effects on treatment resistance [48]. The reduced transcripts of peptidase inhibitor-3, matrix metalloproteinase-8, chemokine receptor-2, and pentraxin-3 related to IVIG resistance after infliximab treatment support the use of infliximab in KD patients with IVIG resistance [49].

Another anti-TNF synthetic biologic, etanercept, binds only soluble TNF. A double-blind multicenter controlled trial on unselected KD patients who were treated with primary adjuvant etanercept demonstrated benefit in IVIG resistance in patients >1 year. It also has favorable effects on ameliorating coronary artery dilation in patients with baseline abnormalities (Z score > 2.5, $n = 22$ in etanercept group compared with $n = 24$ in placebo group $p = 0.03$) [50].

Adjuvant Treatments: Cyclosporin

Cyclosporin is a calcineurin inhibitor and then suppressed the activation of T cells by negative regulation of nuclear factor of activated T cells (NFAT) pathway, following signal transmission with functional polymorphism of *Inositol 1,4,5-trisphosphate 3-kinase C (ITPKC)* associated with the susceptibility and aneurysm formation in KD patients [51]. The high-risk *ITPKC* genotype involved in treatment failure is associated with the higher baseline and activated intracellular calcium and inflammatory biomarkers including IL-1β [52]. A phase 3 RCT collected 175 participants with Kobayashi risk score scale ≧5 points [53]. Combined primary therapy with IVIG and ciclosporin resulted in significantly lower incidence of CAL than IVIG group (12 [14%] of 86 patients; 27 [31%] of 87 patients; $p = 0.010$) [54].

Adjuvant Treatments: Clarithromycin

Immunological and epidemiological evidence strongly suggests characteristics of infectious disease for KD [55, 56]. *Mycoplasma pneumoniae* is the secondary bacterial etiology of pediatric pneumonia in Taiwan and may have association with KD and cardiac outcome [57, 58]. A retrospective Korean survey found 37 cases in 152 tested KD patients showed positive mycoplasma antibodies [59]. Current research cannot confirm that *Mycoplasma pneumoniae* is a possible trigger of KD or just a mere coincidental association [60].

Clarithromycin is a 14-membered ring macrolide with anti-inflammatory activity for respiratory tract infections in children [61]. In a phase 2 RCT involving nonselective patients with KD, IVIG plus clarithromycin showed the efficacy of improving relapse rate of patients (5/40 patients in additional clarithromycin group versus 12/39 patients in control group, $p = 0.046$) [61].

Second-Line Therapy of Refractory Kawasaki Disease

Refractory KD or IVIG resistance was defined as KD patients with fever ≥36 h and <7 days after the completion of their first IVIG treatment [1]. Ten to 20% of KD patients do not respond to gold standard treatment and have an increased risk of cardiovascular sequelae. Currently, there is no consensus regarding optimal adjunctive primary and second-line therapeutics for KD, especially in high-risk patients and patients with complications. Most patients still receive secondary IVIG treatment among more than 300 patients [43]. A meta-analysis identified no significant difference in the effect of intravenous pulse methylprednisolone, infliximab, or secondary IVIG on CAL [42]. Caution is still required in the use of intravenous pulse methylprednisolone due to the higher fever recurrence, higher rehospitalization rate and the higher CAL found in long-term follow-up in the methylprednisolone group [62, 63]. Infliximab's ability to reduce fever is even better than secondary IVIG [43]. The ongoing multicenter phase 3 RCT compares the therapeutic effects of infliximab and secondary IVIG on refractory KD [64]. The IL (interleukin)-1 pathway plays a significant role in KD pathogenesis. In the experimental mouse model of KD, it was found that both IL-1α and IL-1β can cause myocarditis and the

formation of aneurysm, which can be improved by anti-inflammatory drugs anakinra [52, 65]. In a phase 2, open-label study involving 16 patients with IVIG-resistant KD, anakinra, IL-1 inhibitors, showed clinical efficacy [66]. Only one patient stopped treatment because of swelling at the injection site. Highly invasive treatment of plasma exchange increases the risk of treatment. Plasma exchange is a therapeutic option (Class IIb; Level of Evidence C) reserved for patients failed to all other choices for refractory KD [1].

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