Intravenous Immunoglobulin Therapy for Prevention of Coronary Artery Stenosis Caused in Kawasaki Disease

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Abstract

Kawasaki disease (KD) is an acute systemic vasculitis of unknown cause that affects mostly infants and children. Coronary artery lesions (CAL) are one of the most severe complications of KD. For the treatment of KD, intravenous immunoglobulin (IVIG) therapy, with its incompletely understood anti-inflammatory effects, remains important. The initial standard dose is 2 g/kg of IVIG. However, in terms of both the standard primary therapy and the implementation of strategies to prevent development of CAL, the acute treatment of KD remains controversial. In addition, it remains unclear what the most useful method of the administration of IVIG for CAL prevention is. Studies have shown that aspirin may interfere with CAL prevention if administered concomitantly with IVIG, and the delayed use of aspirin with a subsequent 2nd IVIG dose at 2 g/kg may be beneficial for the prevention of coronary artery stenosis in KD. Variable factors, including IVIG resistance, responsiveness, and disease relapse are associated with CAL complications and an initial single IVIG dose may prevent the coronary artery stenosis caused by different KD mechanisms. In this review, I discuss the use of IVIG therapy with delayed aspirin administration, and its efficacy for the prevention of coronary artery stenosis due to KD.

Keywords: Kawasaki disease, Intravenous immunoglobulin therapy, Coronary artery lesions, Aspirin, Risk stratification.

Introduction

Kawasaki disease (KD) is an acute systemic vasculitis of unknown origin affecting mostly infants and children [1]. Coronary artery lesions (CAL) are a severe complication of the disease. Furusho et al. described the use of intravenous immunoglobulin (IVIG) therapy for KD for the first time [2]. In addition, they published a randomized controlled trial showing the evidence for CAL suppression by the IVIG therapy [3].

Although the anti-inflammatory effects of IVIG treatment are incompletely understood, the therapy remains important for patients with KD [4].

The American Heart Association recommends a single IVIG infusion of 2 g/kg preferably during the first 10 days of illness [5], and that initial therapy is a global standard for KD.
However, both in terms of the standard primary therapy and the CAL prevention strategies, the acute treatment of KD remains controversial [6]. In addition, it remains unclear what the most useful IVIG administration method for CAL suppression is. In this review, I discuss the efficacy of IVIG therapy to diminish the risk of coronary artery stenosis that follows KD.

**Prevention of Large and Stenotic CAL**

The major goal of acute phase KD treatment is the prevention of large and stenotic CAL that may lead to myocardial ischemia. Long-term follow-up studies have shown that CAL > 5 mm are a significant predictive risk factor for myocardial ischemia, and that CAL ≤ 5 mm can regress back to normal [7]. The threshold diameter for acute phase CAL that develops into subsequent stenosis is 6.0 mm [8].

In addition, the cut-off values for a coronary artery aneurysm, within the first 100 days after the onset of KD leading to a stenotic lesion in the late period, were a diameter ≥6.1 mm in patients with a body surface area < 0.50 m², and a diameter ≥8.0 mm with a body surface area ≥0.50 m² [9].

The international criteria for CAL are based on z-scores [5]. The Japanese criteria, however, do not account for the patient size, that can substantially affect normal coronary artery dimensions, and their use lead to potential under-diagnosis and underestimation of the true prevalence of coronary artery dilation [5, 10]. However, z-scores are not available for distal CAL. Thus, for CAL in the distal coronary system, the Japanese criteria need to be applied [11].

**Initial IVIG Therapy for Stenosis Prevention of High-risk CAL Patients**

The initial IVIG therapy to prevent stenosis of high-risk CAL patients has not been established.

Steroids, a class of strong anti-inflammatory agent, have been used in combination with initial IVIG therapy for KD [12]. The RAISE study showed the incidence of CAL was significantly lower in the IVIG plus steroid group than in the IVIG group [12]. However, two case studies have shown that patients who received this therapy developed significant CAL with rapid defervescence after the initial therapy [13, 14]. In addition, a study using multivariable logistic regression analyses identified steroid therapy as an independent risk factor for significant CAL in patients with KD and high CAL risk [15].

Furthermore, a study regarding the combined use of infliximab and initial IVIG therapy showed the regimen leaves the high risk of stenosis with CAL unaffected [16].

**Background Factors Regarding CAL Formation in the Acute Phase of KD**

IVIG therapy resistance is one of the most important factors for CAL development during the acute phase of KD [17]. However, variable factors, including IVIG resistance, responsiveness, and disease relapse have been associated with CAL complications and an initial single IVIG therapy may prevent large CAL in patients with KD [18]. As mentioned, the combined therapy of initial IVIG and steroids has not been shown to prevent large CAL [13, 14].
One reason for the development of large CAL may be the lack of appropriate rescue therapies once steroids have modified the clinical course of KD [18].

On the other side, a single IVIG therapy does not modify the clinical course of KD, and this allows clinicians to manage the treatment progress and to provide rescue therapies at appropriate times. Thus, based on these advantages and the reported CAL outcomes, the initial single IVIG therapy may be superior to combination treatment with initial IVIG and steroids [18].

Timing of Initial IVIG Therapy in Regards to Illness Onset

The American Heart Association guidelines recommend that patients with complete KD criteria and those who meet the algorithm criteria for incomplete KD should be treated with high-dose IVIG (2 g/kg given as a single intravenous infusion) within 10 days of illness onset but as soon as possible after diagnosis [5]. The Japanese guidelines recommend that initial IVIG therapy should be started on or before the seventh day after KD onset [19].

A retrospective study regarding the prevalence of CAL among patients who received initial IVIG therapy for KD within 5 to 7 days of illness onset showed that the prevalence of CAL was increased significantly in those receiving therapy after the 7th day of illness ($P = 0.024$). (Fig 1) [20]. These findings suggest the initial administration of IVIG before the 6th day of illness may be the most effective to prevent CAL.

Fig 1: Prevalence of coronary artery lesions among patients receiving initial intravenous immunoglobulin therapy on 5th, 6th, and 7th day of illness

The prevalence of coronary artery lesions of patients receiving intravenous immunoglobulin therapy on 7th day of illness is significantly higher than that for patients receiving the therapy prior to the 7th day of disease onset ($P = 0.024$). The prevalences for patients receiving initial therapy on the 5th day (4/79 = 5%), 6th day (3/42 = 7%), and 7th day of illness (5/19 = 26%) are shown.

Note: di, day of illness; 5th vs. 6th di, $P = 0.641$; 5th vs. 7th di, $P = 0.013$; 6th vs. 7th di, $P = 0.054$. The author has received permission to quote this figure from reference [20].
However, controversies remain regarding the early IVIG therapy within the first 4 days of illness [21–24]. A study has shown most patients with KD receiving IVIG treatment on days 1–4 of the illness onset have worse initial disease severity and, therefore, should be treated with IVIG as early as possible [23]. However, another study has shown the timing of IVIG therapy may not be associated with coronary outcomes; and, earlier IVIG therapy may be associated with a higher recurrence rate [22]. Muta et al. found that earlier IVIG therapy correlated with higher retreatment rate [21].

In addition, the most recent study has demonstrated that IVIG treatment by day 4 of illness is associated with the requirement for additional treatments even after adjustment for patients’ baseline characteristics [24]. The difference was more pronounced for the risk of relapse after initial fever resolution, and the risk of CAL did not differ significantly in this study [24].

In our institution, we use an initial single IVIG regimen of 2 g/kg/dose, starting on day 5 of the illness, whenever possible and the prevalences of rescue therapies for resistance and relapse were 9.1 and 2.2%, respectively [25]. These low prevalences of rescue therapies are consistent with the findings of the study mentioned above [24].

**Aspirin**

The appropriate use of aspirin with IVIG during the acute phase of KD is also the subject of debate. The standard therapy for the acute phase of KD has involved IVIG therapy at 2 g/kg/dose with concomitant use of medium- or higher-dose aspirin [5]. However, the concomitant use of medium- or higher-dose aspirin is now controversial [26].

A Cochrane review denounced a lack of evidence indicating that the use of aspirin as part of KD treatment regimen has any benefit for children [27]. A study has shown that medium- or higher-dose aspirin do not provide additional benefit over low-dose aspirin for CAL prevention [28]. In addition, another study has shown that low-dose aspirin is not inferior to high-dose aspirin for reducing CAL risks [29]. Moreover, other studies have suggested that aspirin may inhibit CAL prevention [30, 31].

The delayed use of aspirin (DUA) may be beneficial for the prevention of coronary artery stenosis in KD [25, 30, 32]. The delayed use of low-dose aspirin has been shown to reduce the incidence of large CAL caused in KD [32]. It has been suggested that the concomitant use of an anti-inflammatory drug may exert an inhibitory effect on the initial IVIG therapy at 2 g/kg/dose [25].

Thus, patients receiving an initial IVIG with DUA may delay that inhibitory effect deemed adverse during the initial stages. Therefore, the combination order and timing of initial IVIG therapy with administration of anti-inflammatory drugs may be important to achieve the best outcome and inhibit the development of CAL. Initial single IVIG therapy with 2 g/kg with DUA may be useful for suppressing CAL [25].

**Rescue Therapy**

IVIG therapy resistance during the acute phase of KD has been implicated in CAL development [17]. IVIG resistance is identified in patients when the fever either persists or reappears 24 h after the first-line KD treatment [19]. However, effective rescue
therapies and guidelines for IVIG-resistant patients have not been established [33]. The early identification of patients likely to develop IVIG-resistance is also a challenge [34]. The rescue therapy for prevention of coronary artery stenosis has not been established either.

The treatment options for initial IVIG-resistant KD include the use of prednisolone, methylprednisolone pulse, ulinastatin, cyclosporine, methotrexate, plasma exchange, or rescue IVIG (the most commonly used strategy) [5, 19].

The appropriate timing for a rescue IVIG dose has not been established. A rescue IVIG dose on day 8 after disease onset (based on a median; range, 7–11) has been shown to yield favorable results for large CAL prevention [33]. An early-administered IVIG has been associated with a higher rate of treatment resistance and may be more likely to lose its effect before the inflammation subsides [24].

An initial sharp rise in the serum immunoglobulin concentration after intravenous administration is followed by a rapid waning for 1 to 4 days due to the catabolism of immunoglobulin and distribution to extravascular spaces [35]. Meanwhile, a concentration-dependent immunomodulatory effect of IVIG in KD has been demonstrated [36, 37].

The median defervescence day after illness onset has been shown to be day 10 in patients receiving IVIG therapy on days 5 and 8 (medians), and none of those patients displayed large CAL [38]. It is possible that the administration of IVIG on days 5 and 8 after illness onset may help maintain an effective serum immunoglobulin concentration to inhibit large CAL formation. A study has shown that steroid therapy is an independent risk factor for significant CAL and that it should be used carefully for treating patients with high risks of CAL [15].

Another study has shown that patients resistant to initial IVIG therapy and receiving infliximab as their first retreatment had shorter fever duration and fewer hospitalization days compared to patients receiving a second IVIG dose; however, the coronary artery outcomes and adverse events were similar in both groups of patients [39].

Takahara T, et al. found that rescue therapies, including plasma exchange before 10 days of illness, were useful for preventing large CAL in KD [40]. Moreover, rescue therapies using plasma exchange are considered useful for CAL suppression during the late KD stages [41]. We have had similar findings in our experience [38].

Our patient was a 2-year-old girl presenting CAL 8 days after symptoms onset; she received plasma exchange for three days, beginning on day 9, at the Hirosaki University School of Medicine hospital. The CAL diameters of the right proximal artery were 4.8 and 2.9 mm on days 21 and 40, respectively. However, an echocardiography on day 52 after disease onset showed the regression of CAL and a normal internal coronary artery size. The selective coronary arteriogram performed 7 months after the disease onset was normal [38].

**Different Subgroups in Initial IVIG-Resistant Patients**

IVIG resistance is one of the most important...
factors for CAL development during the acute phase of KD. Therefore, risk stratification after initial IVIG therapy is important for appropriate rescue therapies and for stenosis prevention in high risk patients. However, the risk stratification after initial IVIG therapy during the acute phase of KD has not been established, and one of the reasons for this is the fact that it remains unclear what the clinical outcomes of initial IVIG-resistant patients are.

Two studies have demonstrated different subgroups in initial IVIG-resistant patients [42, 43]. Downie ML, et al. divided non-responders into partial (axillary temperature decreased to <37.5°C but fever recurred) and complete non-responders (axillary temperature consistently ≥37.5°C throughout IVIG treatment) [42]. They found defervescence was achieved with a second IVIG dose in 72% of partial non-responders and in 58% of complete non-responders (P = 0.001) [42]. The complete non-responders were more likely to develop coronary artery aneurysms than the partial non-responders were (odds ratio, 2.4 [1.1–5.4]; P = 0.03) [42].

Another study on the different subgroups regarding the absence of rescue therapy in IVIG-resistant patients showed one patient of the rescue group (n = 11) developed CAL after 30 days of illness, and none of the patients in the non-rescue group (n = 22) developed CAL. The prevalences of persistent fever between rescue and non-rescue groups at 3 and 4 days after initial IVIG therapy were 100% vs. 77% (P = 0.144) and 100% vs. 18% (P < 0.001), respectively [43]. The C-reactive protein (CRP) value, neutrophil counts, serum albumin levels, and sodium levels were significantly different between two groups at the median 3 days after initial IVIG therapy. Two-thirds of the IVIG-resistant patients diagnosed 24 h after completion of the initial therapy did not develop CAL after 30 days of illness without rescue therapies [43].

The prevalence of the complete non-responders of the rescue group, in the Downie ML et al. study, was significantly higher than that of the non-responders of the non-rescue group in the second study (61.5% vs. 8.3%, P = 0.001) [42, 44].

Rescue therapy 24 h after completion of the initial IVIG therapy may lead to overtreatment [43]. But, the Japanese guidelines for acute-phase KD treatment recommend initiation of the rescue therapies 24 h after completion of the initial IVIG therapy [19]. However, a study has shown that fever in the first 36 h following the initial IVIG therapy completion does not predict CAL [45]. This study recommends refraining from rescue therapies until 36 h after completion of the initial IVIG therapy.

Another study defined IVIG-resistant patients as those with persistent fever who fail to achieve defervescence within 48 h after completion of the initial IVIG therapy [46]. Cho HJ et al. also defined IVIG resistance as persistent or recrudescent fever > 48 h after initial IVIG completion [32]. The description of the clinical outcomes of IVIG-resistant patients may lead to the appropriate timing of rescue therapies for these patients [43].

Risk Stratification after Initial IVIG Therapy

Universal rescue therapies and guidelines for IVIG-resistant patients do not exist [33].
Neutrophil counts and CRP values may be useful for guiding rescue therapy [47], and studies have demonstrated the usefulness of the neutrophil to lymphocyte ratio (NLR) for risk stratification after initial IVIG therapy in KD [32, 33, 48].

The CRP ratio defined as the ratio between the CRP values after/before initial IVIG therapy may be the most useful variable for guiding rescue therapy among the IVIG-resistant patients who have received an initial single IVIG therapy dose with DUA [38]. Studying 174 patients who received initial IVIG therapy at 2 g/kg/dose, researcher divided the patients into 135 IVIG-responders (responder group) and 39 IVIG-resistant patients [38].

The 39 IVIG-resistant patients were further divided into a rescue group with 15 patients receiving rescue therapies and a non-rescue group with 24 children who did not receive rescue therapy. Researcher found all four variables (neutrophil counts, neutrophil %, NLR, and CRP value after initial IVIG therapy) and their ratios (the ratio of the values after/before initial IVIG therapy) were significantly different among 3 groups (P < 0.05) [38].

Among these parameters, the CRP ratio for the rescue group had the highest sensitivity and specificity; and the logistic regression analysis identified the variable as an independent predictor for the rescue group (P < 0.001; odds ratio, 66.807; 95% confidence interval, 7.468–597.655).

Hypoalbuminemia is also considered a predictor of refractory disease [49]. The presence of both low serum albumin and high CRP levels increase the risk for CAL in adults after percutaneous coronary intervention in a synergistic manner [50]. Another study has reported that the CRP to albumin ratio predicts the mortality of septic patients [51], and a study has shown that the combined use of serum albumin and CRP after initial IVIG therapy may be useful for guiding rescue therapy among IVIG-resistant patients [52].

**CAL Prediction in the Acute KD Phase**

No predictors of CAL during the acute KD phase have been broadly accepted. A study using multivariate analysis revealed that the NLR 2 days after initial IVIG therapy independently predict CAL (P = 0.03) [48], and another one showed that NLR cannot predict CAL in the acute phase [32]. However, the change in NLR was significantly lower in the patients with CAL in the univariate analysis [32].

A study showed that coronary artery dilation alone and CAL differ in the total duration of inflammation, as measured by the number of days from fever onset to defervescence [53]. Another study demonstrated that the most important predictor of CAL in KD was a total fever duration of more than 8 days [54]. Therefore, day 8 may be an appropriate time-point for identifying high-risk CAL development patients. The NLR values from a median of day 8 were shown to be useful for risk stratification of KD and for identification of patients with CAL after 30 days of illness [33].

In addition, the Tenascin-C levels in patients who later developed CAL were shown to be significantly higher than those in patients who did not develop CAL (P = 0.010), and a cutoff value of 113.3 ng/ml on admission yielded a sensitivity of 63%, and a specificity of 84% for predicting CAL formation [55].
IVIG Therapy for Infants Younger than 6 Months

Infants with KD younger than 6 months have a high risk of developing CAL [56–58], even if they are administered treatment within the first 10 days [56]. A study has shown that initial IVIG therapy at 2 g/kg/dose before the 6th day of illness may reduce the prevalence of CAL in younger infants to a rate similar to that in older children [57]. This retrospective study included 231 patients who received initial IVIG therapy at 2 g/kg/dose.

Patients were divided into a younger group aged 6 months or younger (n = 25), and an older group older than 6 months (n = 206). The start time of initial IVIG therapy was significantly earlier in the younger group (ranging from 4 to 6 days after onset) than in the older group (ranging from 3–16 days after onset), \( P = 0.017 \). The prevalence of CAL was similar in the two groups both before (4.0% vs. 4.4%, \( P = 1.000 \)) and after 30 days of illness (4.0% vs. 1.5%, \( P = 0.370 \)).

The results of another study suggest that initial IVIG therapy before day 6 may be preferable for the suppression of CAL in infants younger than 6 months [58]. Another study also showed that infants treated appropriately may not have higher CAL risks [59].

The incomplete presentation of KD is a potential risk factor for delays in its diagnosis [60]. A Korean study with infants younger than 6 months showed that the prevalence of the incomplete presentation type was significantly higher in younger than in older children [58]. In contrast, the prevalence of the incomplete type was similar in the younger and older groups in a Japanese study [57]. In addition, the prevalence of major symptoms in infants younger than 6 months in this Japanese study was also higher than in infants in the Korean study [57, 58]. This may be a factor related to the differences in the studies. A study conducted in India with infants younger than 6 months also demonstrated a low prevalence of major KD symptoms and a high prevalence of the incomplete presentation type with diagnosis delays [61]. Differences in ethnicity may influence the different clinical features in infants younger than 6 months among these studies. The prevalence of infants younger than 6 months in the KD populations also differs among studies from different countries [61].

IVIG Therapy for Older Children

The prevalence of CAL is higher in older children than in younger children [59]. Moreover, the multivariate analysis in an epidemiological study showed that older age was also a risk factor for giant CAL [62]. The current standard therapy during the acute phase of KD is 2 g/kg body weight/dose IVIG therapy [5, 19].

However, the safety and efficacy of full dose IVIG infusion of 2 g/kg body weight/dose have not been established for older children. A study has shown that the 2 g/kg IVIG infusion may be safe and effective for suppressing CAL in older children (\( \geq 72 \) months-old) with KD, and their results showed the absence of CAL after 30 days in the older children [63].

In the same study, none of the children had any major complications, including thrombosis [63]. This clinical finding was consistent with the results of a study on
high-dose intact IVIG therapy showing inhibitory effects on platelet adhesion and thrombus formation [64].

A single infusion of high-dose IVIG during the KD acute phase increased blood viscosity [65]. However, the occurrence of thrombosis after IVIG therapy in the acute KD phase is rare in children [66]. It is possible that intact IVIG exerts an inhibitory effect on platelet adhesion and thrombus formation [64].

**Limitations of Sequential IVIG Therapy at 2 g/kg/Dose**

Studies have shown that initial IVIG therapy (2 g/kg/dose) with DUA and subsequent 2nd IVIG dose at 2 g/kg may be beneficial for stenosis prevention of high-risk CAL patients [25, 30, 32]. However, 1.6% of patients who received those therapies required 3rd line therapies and one of them required plasma exchange [25]. Furthermore, the decision to use plasma exchange has not been established [33]. The limitations of the studies on the use of IVIG with DUA included the inclusion of a small number of IVIG-resistant patients and the retrospective nature of the study designs [25, 30].

**Conclusions**

An IVIG therapy is a critically important therapy in the treatment of KD. A single IVIG therapy does not modify the clinical course of KD, and this allows clinicians to manage the treatment progress and to provide rescue therapies at appropriate times. The initial IVIG therapy (2 g/kg/dose) with DUA and subsequent 2nd IVIG dose at 2 g/kg may be beneficial for prevention of coronary artery stenosis in KD.

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