PREVENTION OF LARGE CORONARY ARTERY LESIONS CAUSED BY KAWASAKI DISEASE

Toshimasa Nakada

Department of Pediatrics, Aomori Prefectural Central Hospital

E-mail: toshimasanakada@yahoo.co.jp

Abstract

Appropriate therapy during the acute phase of Kawasaki disease to prevent large coronary artery lesions (CAL) has not been established. The aim of this retrospective study was to investigate the usefulness of initial intravenous immunoglobulin (IVIG) therapy with delayed administration of anti-inflammatory drugs (ADs). A total of 132 pediatric patients who received IVIG therapy with delayed administration of ADs for Kawasaki disease between 2004 and 2014 were enrolled at the Department of Pediatrics, Aomori Prefectural Central Hospital. An initial IVIG regimen of 2 g/kg/day, starting on day 5, was used as first-line therapy when possible. Second-line therapy was additional IVIG therapy, and third-line therapy was an urinastatin infusion or plasma exchange. All 132 patients received 2 g/kg/day initial IVIG therapy. 74 patients received aspirin and 58 patients received flurbiprofen after completion of initial IVIG infusion. Initial IVIG therapy resistance occurred in 31 of 132 patients (23%), and 10 patients (8%) received additional IVIG. One patient received urinastatin and one patient received plasma exchange as third-line therapy. Before the 30th day, the prevalence of CAL was 2% (2/132); after 30 days, it was 1% (1/132). The maximal internal CAL diameters were 4.8 mm (Z score = 6.3) among all patients. Initial single IVIG therapy with delayed administration of ADs may be useful for the prevention of large CAL caused by Kawasaki disease.

Key words: *Kawasaki disease, intravenous immunoglobulin therapy, coronary artery lesions, anti-inflammatory drugs, prevention*

1. INTRODUCTION

Myocardial ischemia due to coronary artery lesions (CAL) is one of the most important complications caused by Kawasaki disease. Long-term follow-up studies have shown that a maximum CAL size >5 mm was a statistically significant predictive risk factor for myocardial ischemia, and that all CAL ≤5 mm in size regressed to normal size (Mueller et al. 2009). Another study reported that the threshold diameter for acute phase CAL that developed into subsequent stenosis was 6.0 mm (Tsuda et al. 2005). Therefore, the prevention of CAL of >5 mm may be an important goal in the acute treatment of Kawasaki disease to prevent coronary artery stenosis in later stages of the disease.

Combination regimens of intravenous immunoglobulin (IVIG) and other drugs including steroids and infliximab have been tried as the initial therapy for patients with Kawasaki disease (Kobayashi et al. 2012; Tremoulet et al. 2014). However, the treatment for the prevention of large CAL has not been established, and not enough studies have been performed with regard to initial IVIG monotherapy in spite of the safety and effectiveness of this therapy.

The standard initial therapy for pediatric patients with Kawasaki disease is currently the combination of IVIG therapy and aspirin. However, recent research showed that anti-inflammatory drugs (ADs) including aspirin appeared to have a negative impact on the suppression of CAL development when administered with the initial IVIG therapy during the acute phase of Kawasaki disease. Initial IVIG monotherapy with delayed aspirin administration may be beneficial in the suppression of CAL caused by Kawasaki disease (Nakada 2015).

The hypothesis of this study was that initial IVIG monotherapy with delayed administration of ADs may be useful in the prevention of large CAL that were larger than 5 mm. Accordingly, this study investigated the outcome of CAL in patients that received initial IVIG monotherapy with delayed administration of ADs for Kawasaki disease.

2. METHODS

This retrospective study included 132 consecutive patients (64 boys, 68 girls; the mean age was 2 years and 10 months, and the age range was 2 months to 13 years and 3 months) who received 2 g/kg/day initial IVIG therapy with delayed administration of ADs for Kawasaki disease between January 2004 and December 2014 at the Department of Pediatrics, Aomori Prefectural Central Hospital. The diagnosis of Kawasaki disease was based on the Japanese criteria (Fifth edition) (The Japan Kawasaki disease research committee 2002). Patients with either disease recurrence or CAL before the start of therapy were excluded.

2.1 ADs therapy

The choice between aspirin and flurbiprofen was made by each doctor after consideration of the patient's liver function and the timing of the influenza pandemic. Flurbiprofen was more commonly used before 2009. Aspirin was initiated at a dose of 30 mg/kg/day and decreased to 5−10 mg/kg/day when the patients became afebrile. Flurbiprofen was initiated at a dose of 3–5 mg/kg/day and decreased to 3 mg/kg/day when the patient became

afebrile. The regimen with delayed administration of ADs was not used until after 2004. Some patients received the therapy regimen with delayed administration of ADs between 2004 and 2008. After 2009, this regimen was used for all patients. ADs were initiated within 24 h after the end of the initial IVIG infusion.

2.2 IVIG therapy

During the study period, an initial IVIG regimen of 2 g/kg/day starting on the fifth day of the illness was used as the first-line therapy when possible. The indication for additional therapy in resistant patients was determined between 48 and 72 h after the end of the initial IVIG infusion. The diagnosis was performed according to clinical parameters, including body temperature, major signs of Kawasaki disease, general condition, and laboratory data. Second-line therapy was additional IVIG therapy, and third-line therapy was urinastatin infusion. Plasma exchange had been adopted in 2014 as another third-line therapy option. Written informed consent was obtained from the parents or guardians of all the patients before initial therapy.

Response to IVIG therapy was defined as those patients who became afebrile (temperature < 37.5 °C for 24 h) within 24 h after the completion of the initial IVIG infusion. IVIG-resistant patients were defined as those not meeting these criteria.

2.3 Diagnosis of CAL

CAL was diagnosed by echocardiography according to the Japan Ministry of Health and Welfare criteria (Research committee on Kawasaki disease, 1994). CAL was defined as an artery diameter exceeding 3 mm in a child below 5 years of age or a diameter exceeding 4 mm in a child aged 5 years or older. Transient CALwas defined as the disappearance of CAL within 30 days of the illness. In this study, a CAL of size larger than 5 mm was defined as a large CAL.

3. RESULTS

All 132 patients received 2 g/kg/day initial IVIG therapy. 74 patients received aspirin and 58 patients received flurbiprofen after completion of initial IVIG infusion. The median start time of initial IVIG therapy was the fifth day of illness (day 4–16 of illness). Initial IVIG therapy resistance occurred in 31 of 132 patients (23%), and 10 patients (8%) received additional IVIG; nine patients for initial IVIG resistance and one patient for relapse, respectively. One patient received urinastatin and one patient received plasma exchange as third-line therapy. Among the patients that received third-line therapy, one patient received steroids after the urinastatin infusion because of prolonged fever and intractable arthralgia, and another patient received IVIG therapy as fourth-line therapy after the plasma exchange.

Before the 30th day, the prevalence of CAL was 2% (2/132); after 30 days, it was 1% (1/132). The maximal internal CAL diameters were 4.8 mm (Z score = 6.3) among all patients. The patient with the largest CAL diameter (Patient 1) had CAL on day 8, and she received a plasma exchange on day 9 at the hospital of Hirosaki University School of Medicine for 3 days. Her CAL diameter was 4.8 mm

on day 21 of her illness. However, echocardiography on day 52 of illness showed the regression of CAL and normal internal coronary artery size. The selective coronary arteriogram performed at 7 months after disease onset revealed no abnormal findings.

Table 1 showed comparison of the results describing the prevention of large CAL among four different studies (Kobayashi et al. 2012; Tremoulet et al. 2014; Newburger et al. 1991). Large CAL were prevented only in the present study, in which ADs were administered by delayed use. Among three previous studies, in which different three types of ADs were administered by concomitantly to initial IVIG, large CAL were not prevented.

Table 1. Comparison of results regarding prevention of large coronary artery lesions among four studies

	Present study	Previous studies		
		Study 1	Study 2	Study 3
IVIG protocol	2 g/kg	2 g/kg	2 g/kg	2 g/kg
ADs	Asp or Flur	Asp	Asp, Asp + Pred	Asp, Asp + Inf
	(n = 132)	(n = 273)	(n = 121) (n = 121)	(n = 98) (n = 98)
Use of ADs	delayed	concomitant	concomitant	concomitant
Prevention of large CAL	Yes	No	No No	No No

Study 1: *N Engl J Med* 1991; 324: 1633–9, Study 2: *The Lancet* 2012; 379: 1613–20, Study 3: *The Lancet* 2014; 383: 1731–38,

IVIG: intravenous immunoglobulin, ADs: anti-inflammatory drugs, Asp: aspirin, Pred: prednisolone, Inf: infliximab, Use of ADs: use of ADs to initial IVIG therapy, Large CAL: large coronary artery lesions with internal diameters of larger than 5 mm or of larger than Z score 6.5

4. DISCUSSION

This study identified the usefulness of initial IVIG monotherapy with delayed administration of ADs for the prevention of CAL of more than 5 mm in size and the prevention of subsequent coronary artery stenosis caused by Kawasaki disease. The establishment of a safe and effective regimen for the initial IVIG therapy and the prevention of the development of large CAL during the acute phase is clinically important. As shown in Table 1, use of delayed administration of ADs appeared to be the important factor for prevention of large CAL. The different type of ADs did not appear to be the important factor. Recent study used by logistic regression analysis, including the patients who received IVIG therapy with and without delayed administration of ADs, showed that the significant variable for CAL development was the delayed administration of ADs and 2 g/kg IVIG therapy and that type of ADs was not a significant variable (Nakada T 2015). These findings are consistent with the results of Table 1. ADs appeared to have a

negative impact on the suppressive effects of initial IVIG therapy on CAL development in the acute phase of Kawasaki disease (Nakada T 2015). Therefore, knowledge regarding the technique of using ADs may be a breakthrough for the prevention of large CAL caused by Kawasaki disease.

Patients who received initial IVIG monotherapy with delayed administration of ADs may not receive a negative impact on the suppressive effects of ADs to IVIG therapy until the start time of ADs administration. However, patients who received initial IVIG therapy with concomitant use of ADs may receive a negative impact of ADs during IVIG therapy. This difference may be a mechanism that the combination order of initial IVIG therapy with administration of ADs may lead to the prevention of large CAL.

It was previously reported that ADs affected the immunological function of T-cells. A recent study suggested that the pathway including T-cells may play a role in the mechanism of action of IVIG. Furthermore, a recent immunological study highlighted that T cell activation in the early and middle stages was involved in the mechanism underlying cardiovascular injury in Kawasaki disease. These findings suggest that ADs can alter the effects of IVIG on Kawasaki disease (Nakada T 2015).

IVIG monotherapy does not modify the clinical course of Kawasaki disease. This characteristic permits clinicians to easily manage the treatment progress and to provide additional therapies at the appropriate time. With these advantages and the reported outcomes of CAL, initial IVIG monotherapy appears to be superior to combination treatment with initial IVIG and steroids.

A recent study reported that the long-term efficacy of plasma exchange treatment for refractory Kawasaki disease was excellent (Hokosaki et al. 2012). Another study also identified the efficacy of plasma exchange after the initial and additional IVIG monotherapy treatment for large CAL prevention (Takahara et al. 2014). These findings were consistent with the clinical course of Patient 1, whose CAL size was the largest among those in this study.

The optimum start time of the initial IVIG therapy for the prevention of large CAL caused by Kawasaki disease has not been established. An epidemiological study in 15,940 patients in Japan showed that receipt of initial IVIG before day 5 of the illness was significantly associated with IVIG non-response and CAL (Uehara et al. 2008). Another study reported that there was no evidence that IVIG therapy on day 4 or earlier had greater efficacy in preventing cardiac sequelae than therapy on days 5–9, and that early treatment would more likely require additional IVIG (Muta et al. 2004). The favorable outcome of CAL and the low prevalence of additional IVIG in this study showed that the start time on day 5 was not too late to prevent large CAL caused by Kawasaki disease. A recent study regarding CAL ruptures in Kawasaki disease reported that the children who received initial IVIG therapy on day 4 were associated with rupture at a rate similar to those who received IVIG after day 5 (Miyamoto et al. 2014). Cytokine modulation is considered to be one of the mechanisms of IVIG therapy in Kawasaki disease (Gupta et al. 2001). It is possible that cytokine modulation provides more effective suppression for CAL development with

higher levels of cytokines. Cytokine levels on day 4 or earlier in Kawasaki disease may be lower than those on day 5. High cytokine levels on day 5 may be one of the factors for the effective suppression of CAL development by IVIG therapy.

One limitation of this study was the small number of patients. In addition, this was a retrospective study. Finally, the use of Japanese Ministry of Health and Welfare criteria may have underestimated the true incidence of CAL due to Kawasaki disease (Zorzi et al. 1998).

5. CONCLUSION

Initial IVIG monotherapy with delayed administration of ADs may be useful for the prevention of CAL that are more than 5 mm in size during the acute phase of Kawasaki disease.

CONFLICT OF INTEREST

There are no conflicts of interest to declare.

ACKNOWLEDGEMENTS

I would like to thank the pediatric cardiologists of Hirosaki University School of Medicine for providing clinical information regarding patient 1, all those who were involved in the medical management of the patients included in this study, and Enago (www.enago.jp) for the English language review.

REFERENCES

Gupta M, Noel GJ, Schaefer M, Friedman D, Bussel J, Johann-Liang R. 2001. "Cytokine modulation with immune gamma-globulin in peripheral blood of normal children and its implications in Kawasaki disease treatment." *J Clin Immunol* 21:193–9

Hokosaki T, Mori M, Nishizawa T et al. 2012. "Long-term efficacy of plasma exchange treatment for refractory Kawasaki disease." *Pediatr Int* 54:99–103

Kobayashi T, Saji T, Otani T et al. 2012. "Efficacy of immunoglobulin plus prednisolone for prevention of coronary artery abnormalities in severe Kawasaki disease (RAISE study): a randomized, open-label, blinded-endpoints trial." *Lancet* 379:1613–20

Miyamoto T, Ikeda K, Ishii Y, Kobayashi T. 2014. "Rupture of a coronary artery aneurysm in Kawasaki disease: a rare case and review of the literature for the past 15 years." *J Thorac and Cardiovasc Surg* 147:e67–9

Mueller F, Knirsch W, Harpes P, Prêtre R, Valsangiacomo Buechel E, Kretschmar O. 2009. "Long-term follow-up of acute changes in coronary artery diameter caused by Kawasaki disease: risk factors for development of stenotic lesions." *Clin Res Cardiol* 98:501–7

Muta H, Ishii M, Egami K et al. 2004. "Early intravenous gamma-globulin treatment for Kawasaki disease: the nationwide surveys in Japan*." J Pediatr* 144:496–9

Nakada T. 2015. "Effects of anti-inflammatory drugs on intravenous immunoglobulin therapy in the acute phase of Kawasaki disease." *Pediatr Cardiol* 36:335–9

Newburger JW, Takahashi M, Beiser AS et al. 1991. "A single intravenous infusion of gamma globulin as compared with four infusions in the treatment of acute Kawasaki syndrome." *N Engl J Med* 324:1633–9

Research committee on Kawasaki disease. 1994. "Report of subcommittee on standardization of diagnostic criteria and reporting of coronary artery lesions in Kawasaki disease." Ministry of Health and Welfare, Tokyo

Takahara T, Yamagami Y, Oonishi S et al. 2014. "Therapeutic strategy for immunoglobulin refractory Kawasaki disease including plasma exchange therapy in 60 patients." *Prog Med* 34:1282–7

The Japan Kawasaki disease research committee. 2002. "Diagnostic guidelines of Kawasaki disease." 5th revised edn, Tokyo

Tremoulet AH, Jain S, Jaggi P et al. 2014. "Infliximab for intensification of primary therapy for Kawasaki disease: a phase 3 randomised, double-blind, placebo–controlled trial." Lancet 383:1731–38

Tsuda E, Kamiya T, Ono Y, Kimura K, Kurosaki K, Echigo S. 2005. "Incidence of stenotic lesions predicted by acute phase changes in coronary arterial diameter during Kawasaki disease." *Pediatr Cardiol* 26:73–9

Uehara R, Belay ED, Maddox RA et al. 2008. "Analysis of potential risk factors associated with nonresponse to initial intravenous immunoglobulin treatment among Kawasaki disease patients in Japan." *Pediatr Infect Dis* J 27:155–60

Zorzi AD, Colan SD, Gauvreau K, Baker AL, Sundel RP, Newburger JW. 1998. "Coronary artery dimensions may be misclassified as normal in Kawasaki disease." *J Pediatr* 133:254–8

