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Research Article

Usefulness of an Initial Single Intravenous Immunoglobulin Infusion with Delayed Use of Aspirin against Kawasaki Disease Relapse: A Single-Center Retrospective Study

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A B S T R A C T

Background: Kawasaki Disease (KD) relapse is a risk factor for Coronary Artery Lesion (CAL) development. However, the frequency and outcomes of patients with relapse remain unclear.

Objective: To determine the frequency and outcomes of patients with KD relapse and to ascertain the usefulness of treatment with initial single intravenous immunoglobulin (IVIG) therapy (2g/kg) with delayed use of aspirin (DUA).

Materials and Methods: The outcomes of 207 patients who underwent initial single IVIG therapy at 2 g/ kg/ dose with DUA for KD were analyzed retrospectively. The patient data were divided according to whether the patients had relapses (relapse group, n=5) or not (non-relapse group, n=202). KD presentations were considered as relapses when a second episode appeared within 2 months of the first one. Stat Flex version 6 for Windows was used for all statistical analyses. Chi-square, Fisher's exact, and Mann-Whitney U tests were used as appropriate, with sample size considerations.

Results: The frequency of patients with disease relapse was 2.4%. The five patients who experienced relapses (two boys and three girls; median age, 10 months; range, 3 months to 3 years 11 months) received initial IVIG therapy at 5 days of illness. The median day of illness for the relapse was 16 (range, 12-29). No patients with disease relapse developed CAL. The rate of incomplete type, IVIG resistance and CAL, and timing of initial IVIG therapy with regard to the days of illness were similar between the relapse group and the non-relapse group. Three parameters, including serum C-reactive protein, albumin values, and Neutrophil-to-Lymphocyte ratio (NLR) before and after initial IVIG, were similar between the two groups. Although not statistically significant (P=0.055), the median NLR after initial IVIG therapy of the relapse group was higher than that of the non-relapse group (2.48 vs. 0.84).

Conclusion: An initial single IVIG therapy (2g/ kg/ dose) with DUA for KD may lead to a low KD relapse frequency and to favorable patient outcomes.

Keywords: Coronary Artery Lesions, Intravenous Immunoglobulin Therapy, Kawasaki Disease, Relapse, Treatment

Introduction

Kawasaki Disease (KD) is an acute systemic vasculitis of unknown cause that affects mostly infants and children populations.[1] Coronary Artery Lesions (CALs) are a severe complication of KD. Disease relapse is a risk factor for CAL development.[2]

Recurrent KD is defined as recurring presentation of another episode after 2 months of the first one, and the incidence of recurrence was shown to be high among those with cardiac sequelae during the first episode.[3,4] Compared with patients who do not experience recurrence, patients with recurrent KD are more likely to be older, fulfill the atypical KD case definition, and develop CAL despite Intravenous Immunoglobulin (IVIG) treatment.[5,6] On the other hand, KD relapses defined as intervals between the first and second episodes of <2 months.[3,7] However, the outcomes of patients with relapse remain unclear.

The standard therapy for the acute KD phase has included IVIG therapy at 2 g/ kg/ dose with concomitant use of medium- or high-dose aspirin.[8] However, the addition of medium- or high-dose aspirin is now controversial.[9] A randomized controlled trial on the effectiveness of IVIG alone and of IVIG combined with high-dose aspirin in the acute KD stage is ongoing.[10]

Studies have suggested that aspirin may inhibit CAL prevention and the Delayed Use of Aspirin (DUA) may be beneficial for the prevention of coronary artery stenosis in KD.[11-14] This study was aimed to determine the frequency of KD relapse in patients treated with initial single IVIG therapy with DUA and outcomes in terms of CAL development of the patients with KD relapse and to ascertain the usefulness of an initial single IVIG therapy (2g/ kg/ dose) with DUA in patients with KD.

Materials and Methods

The institutional ethics committee approved the study protocol and waived the requirement of patient's consent because of the retrospective nature of the study.

This retrospective study included 207 consecutive patients who received an initial 2 g/ kg/ dose of IVIG therapy with DUA for KD from January 2004 to December 2018 at our department. The data of these patients were collected retrospectively. Those subjects were divided into those with disease relapse (Relapse group, n=5) and those without relapse (Non-relapse group, n=202).

The KD diagnoses were established based on the criteria (Japanese, 5th edition) mentioned in the diagnostic guidelines for KD.[15] Patients with first episode of KD were included. Five patients with CAL before therapy, and one patient with status epilepticus at the first presentation who received the combined therapy with initial IVIG and steroid were excluded. Another patient who developed left ventricular dysfunction and underwent a different protocol using plasma exchange in the early stage was excluded.

IVIG resistance was defined as fever that persisted or reappeared at 24 h after the first-line treatment. Defervescence was defined as a body temperature < 37.5 °C for 24 h and the defervescence time was defined as the moment when the body temperature reached < 37.5 °C. The Egami score, a risk score for predicting IVIG-resistance based on clinical findings such as age, illness days, platelet count, alanine aminotransferase level and C-reactive protein (CRP) level, was evaluated before the initial IVIG therapy.[16]

Parameter measured as outcome was the rate of CAL development.

Three parameters, including serum CRP, albumin values, and Neutrophil to Lymphocyte Ratio (NLR) were investigated retrospectively, as was the ratio of each parameter, defined as the ratio of the values after and before initial IVIG therapy. The NLR was defined as the ratio of the neutrophil and lymphocyte counts.

Initial Therapy

During the study period, an initial single IVIG infusion of 2 g/kg/dose, starting on day 5 of the illness, was used as first-line therapy, whenever possible.

Between January 2004 and November 2017, anti-inflammatory drugs (aspirin or flurbiprofen) were initiated within 24 h after the end of initial IVIG infusion. Aspirin was initiated at a dose of 30 mg/kg/day and decreased to 5–10 mg/kg/day once the patient became afebrile. Flurbiprofen was initiated at a dose of 3–5 mg/kg/day and decreased to 3 mg/kg/day once the patient became afebrile.[11] Each treating physician made a choice between aspirin and flurbiprofen after considering the patient's liver function and the risk of Reye syndrome during the influenza season.

A regimen of initial IVIG therapy with delayed use of anti-inflammatory drugs was used after 2004. Some patients received this therapy with delayed use of anti-inflammatory drugs between 2004 and 2008. The treating physicians chose between delayed use of anti-inflammatory drugs and concomitant use of anti-inflammatory drugs during this period. After 2009, all physicians prescribed initial IVIG therapy with delayed use of anti-inflammatory drugs for all patients until November 2017.[11,14] After December 2017, low-dose aspirin (5mg/kg/day) was initiated on the 8th to 10th day of illness after completion of the IVIG infusion, including second therapy.[14]

Rescue Therapy

The decision to use rescue therapies in resistant patients was made between 48 and 72 h after the initial IVIG therapy was completed. The decision was made comprehensively

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according to the clinical parameters, including body temperature, major KD symptoms, general condition, and laboratory data. The second-line therapy was rescue IVIG therapy at 2 g/kg/dose, and the third-line therapy was ulinastatin infusion, third IVIG therapy, or plasma exchange.[14]

Diagnosis of CAL

CAL was diagnosed using echocardiography based on the Japanese criteria according to Kobayashi et al.[17] CAL was diagnosed if any of the examinations showed an internal lumen diameter ≥3 mm in a patient younger than 5 years or a diameter ≥4 mm in a patient older than 5 years, if the internal diameter of a segment was at least 1.5 times that of an adjacent segment, or if the lumen appeared irregular. Transient CAL was defined as the disappearance of CAL within 30 days of the illness.

Statistical Analysis

Statistical analyses were performed using Stat Flex Version 6 for Windows (Artech Co., Ltd., Osaka, Japan). Chi-square, Fisher's exact, and Mann–Whitney U tests were used as appropriate, with sample size considerations. A value of $P < 0.05$ was considered statistically significant.

Result

The frequency of patients with disease relapse was 2.4% (5 of 207 patients). The five patients with relapse (two boys and three girls; median age, 10 months; range, 3 months to 3 years 11 months) had received initial IVIG therapy at 5 days of illness (Figure 1 and Table 1). One of the five patients was resistant to the initial IVIG therapy, and the median day of illness regarding relapse was 16 (range 12–29, Table 1). Two patients were resistant to IVIG therapy for relapse, and one patient received rescue IVIG therapy for resistance at relapse (Table 1). No patients with disease relapse developed CALs (Table 1). Among the total population, the frequency of patients who received initial IVIG therapy at days 5 and 4 of illness were 58.5% and 1.9%, respectively (Figure 1).

Table 1.Outcomes of the five patients with Kawasaki disease relapse

Patient No	1	2	3	4	5
Gender	Female	Male	Female	Male	Female
Age of onset	2 years 0 month	3 months	3 years 11 months	10 months	8 months
Number of major signs	5	5	6	3	6
Initial IVIG Start day of illness	5	5	5	5	5
Response	Responded	Responded	Resistant	Responded	Responded
Rescue therapy	None	None	None	None	None
Relapse					
Day of illness	16	12	16	29	23
IVIG					
Start day of illness	18	12	18	30	26
Response	Responded	Responded	Responded	Resistant	Resistant
Rescue therapy	None	None	None	None	2nd IVIG
CAL	None	None	None	None	None

IVIG, intravenous immunoglobulin; CAL, coronary artery lesions.

Table 2.Comparison of outcomes between the relapse and non-relapse groups

Variables	Relapse group (n = 5)	Non-relapse group (n = 202)	p-value
Gender (male)	2 (40.0%)	104 (51.5%)	0.677
Age (months)	10.0 (6.8-29.8)	24.5 (14.0-45.0)	0.147
Incomplete type	1 (20.0%)	27 (13.4%)	1.000
Egami score	2.0 (0.8-2.3)	1.0 (1.0-2.0)	0.928
Aspirin/Flurbiprofen			0.632
Low-dose aspirin	1 (20.0%)	19 (9.4%)	

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Medium-dose aspirin	1 (20.0%)	101 (50.0%)	
Flurbiprofen	3 (60.0%)	82 (40.6%)	
Timing of initial IVIG therapy with regard to day of illness	5 (5-5)	5 (5-6)	0.096
Resistant patients	1 (20.0%)	46 (22.8%)	1.000
CAL	0 (0.0%)	5 (2.5%)	1.000
TD	0 (0.0%)	3 (1.5%)	1.000
CCAL	0 (0.0%)	2 (1.0%)	1.000

Data are presented as n (%) or median (interquartile range); IVIG, intravenous immunoglobulin; CAL, coronary artery lesions; TD, transient CAL; CCAL, CAL at 30th day of illness; Incomplete type: patients with fewer than five major symptoms of Kawasaki disease.

The rates of incomplete type, Egami scores, and timing of initiating IVIG therapy with regard to days of illness were similar between the relapse and non-relapse groups (Table 2). The frequencies of patients with IVIG resistance and CAL were also similar between the two groups (Table 2). The rate of CAL development of the patients in the relapse group was 0.0% (Table 2).

Data are presented as median (interquartile range); IVIG, intravenous immunoglobulin; CRP, C-reactive protein; NLR, neutrophil-to-lymphocyte ratio; Ratio, the ratio of the values after/before initial IVIG therapy.

Discussion

This study showed low relapse rate and favorable outcomes of patients with KD who received initial single IVIG therapy (2g/ kg/ dose) with DUA. Disease relapse was a risk factor for CAL development.[2] Therefore, lowering the relapse rate may diminish the CAL frequency. The low relapse rate of patients with KD in this study may be due to the timing of initial IVIG therapy with regards to the days of illness.

Table 3.Laboratory findings comparison between the relapse and non-relapse groups

Variables	Relapse group (n=5)	Non-relapse group (n=202)	p-value
Before initial IVIG therapy			
Sampling day of illness	5 (4.8-5)	5 (5-6)	0.414
CRP (mg/ dL)	8.81 (4.46-17.97)	6.63 (3.94-11.15) (n=201)	0.473
Albumin (g/ dL)	3.4 (3.28-3.65)	3.4 (3.2-3.7) (n=200)	0.768
NLR	2.95 (2.22-5.12)	2.85 (1.65-4.87) (n=174)	0.923
After initial IVIG therapy			
Sampling day of illness	8 (8-8)	8 (8-9)	0.241
Days after initial IVIG therapy	3 (3-3)	3 (3-3)	0.900
CRP (mg/ dL)	3.66 (0.98-5.07)	2.17 (0.97-4.53) (n=202)	0.786
Albumin(g/ dL)	3.3 (2.58-3.45)	3.05 (2.7-3.3) (n=200)	0.827
NLR	2.48 (1.87-3.99)	0.84 (0.51-1.38) (n=199)	0.055
CRP ratio	0.33 (0.23-0.37)	0.31 (0.2-0.46) (n=201)	0.939
Albumin ratio	0.88 (0.78-0.99)	0.89 (0.8-0.97) (n=198)	0.923
NLR ratio	0.91 (0.21-1.84)	0.29 (0.16-0.49) (n=171)	0.170

The median values of three parameters, including serum CRP, albumin values, and NLR before and after initial IVIG, were similar between the two groups (Table 3). Although not statistically significant (P = 0.055), the median NLR after initial IVIG therapy of the relapse group was higher than that of the non-relapse group (Table 3).

Controversies remain regarding the early IVIG therapy within the first 4 days of illness.[18-21] A study has shown that most patients with KD diagnosed on days 1–4 of the illness onset have worse initial disease severity and, therefore,

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should be treated with IVIG as early as possible.[20] However, another study has shown that the timing of IVIG therapy may not be associated with coronary outcomes, and earlier IVIG therapy may be associated with a higher recurrence rate.[19] Muta H et al. found that earlier IVIG therapy correlated with higher retreatment rate.[18] In addition, a new study has demonstrated that IVIG treatment by day 4 of illness is associated with the requirement for additional treatments even after the adjustment for patients' baseline characteristics.[21] 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.[21]

The patients, whose data were analyzed in this study, received initial single IVIG regimens of 2 g/ kg/ dose, starting on day 5 of illness, as first-line therapy whenever possible. The median timing of initial IVIG therapy with regard to the day of illness among the total population was 5 days (range, 4-16) (Figure 1). The rates of patients who received initial IVIG therapy at days 5 and 4 of illness were 58.5% and 1.9%, respectively (Figure 1). The number of patients who received rescue therapy for relapse was 5 of 207 (2.4%). The low prevalence of the rescue therapy for relapse may be related to the timing of the initial IVIG therapy as has been mentioned.[21] No patients with disease relapse had CAL in this study. This suggests that the rescue therapies for relapse in this study were appropriate. A single IVIG therapy does not modify the clinical course of KD, and this allows clinicians to perform a precise disease severity evaluation after initial treatment and to provide rescue therapies at appropriate times.[14] This may be true not only for patients with IVIG resistance but also for those with relapses.

A study showed that IVIG plus clarithromycin therapy reduces the relapse rate in patients with KD.[22] The same study demonstrated that the relapse rate of patients in the IVIG plus clarithromycin group was significantly lower than the relapse rate in the patients of the IVIG group (12.5% vs. 30.8%, respectively; P=0.046).[22] All of the patients in the same study received IVIG therapy with concomitant use of medium-dose aspirin.[22] On the other hand, all of the patients in the present study received IVIG therapy with DUA, and the relapse rate of patients in the present study (2.4%) was lower than that of the patients in the IVIG plus clarithromycin study. Moreover, the relapse rate of patients in the present study (2.4%) was lower than that of the patients who received IVIG therapy with concomitant use of medium-dose aspirin (30.8%).[22] These findings suggest that the initial single IVIG therapy with DUA decreases the rate of KD relapse.

Although not statistically significant (P = 0.055), the median NLR after initial IVIG therapy of the relapse group was higher than that of the non-relapse group. The NLR has been reported to be a powerful biomarker of systemic inflammation.[23] Moreover, the NLR is believed to predict CAL severity.[24] A study using multivariate analysis revealed that NLR after IVIG therapy independently predicted CAL development and IVIG therapy resistance.[25] Another study showed that the NLR values in patients with KD and CAL

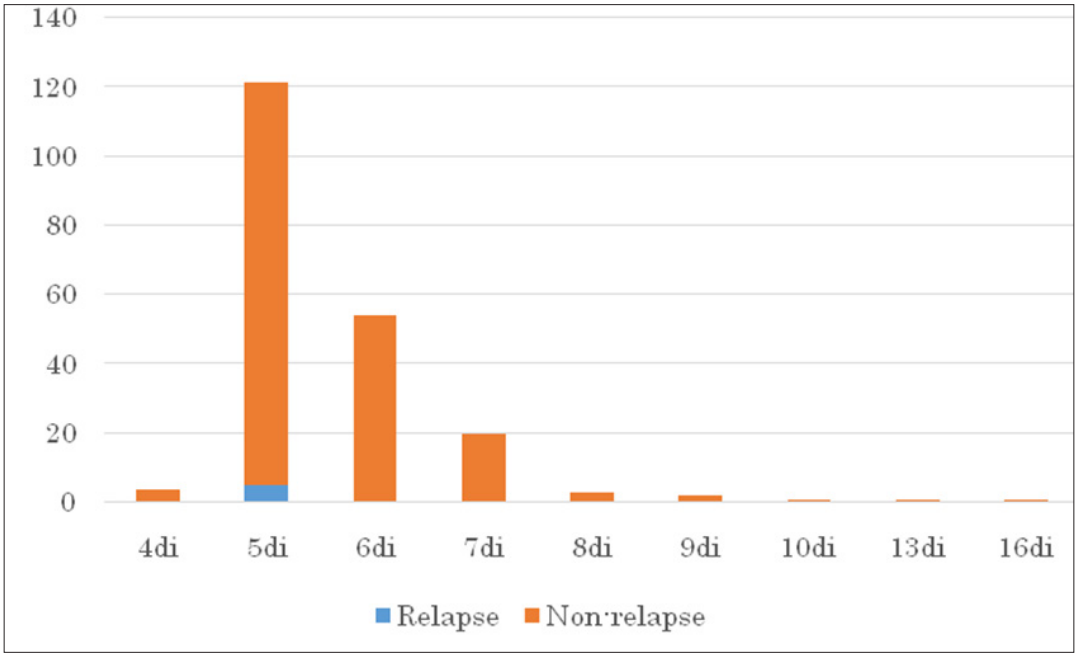

Figure 1.Histogram of the total population timing of initial intravenous immunoglobulin therapy with regard to the day of illness (di). Among the total population, the frequency of patients who received initial intravenous immunoglobulin therapy at 5th and 4th day of illness were 58.5% and 1.9%, respectively

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were significantly higher than those in patients without CAL.[26]

A high NLR value after initial IVIG therapy was identified among patients with CAL and those with non-cardiac KD complications.[27] Those complications are thought to be due to the prolonged inflammation in KD.[27] KD relapse is also thought to be due to prolonged inflammation in the acute phase of the disease.[21] A high NLR value after initial IVIG therapy in patients with relapse may indicate a prolonged inflammation in the acute KD phase. The NLR value after initial IVIG therapy may be a marker for KD relapse.

The limitations of this study include the inclusion of a small number of patients in the relapse group and its retrospective design. Furthermore, lack of in-built control group in this study to compare with those who received IVIG therapy with concomitant use of aspirin was another limitation.

Conclusion

An initial single IVIG infusion (2g/ kg/ dose) with DUA for KD may lead to low relapse frequency and to favorable patients' outcomes with regard to CAL development.

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Conflicts of Interest: None

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