Acute Phase Treatment and Medium-Term Outcomes in Kawasaki Disease

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Abstract—An acute phase treatment for prevention of coronary artery stenosis caused by Kawasaki disease (KD) has not been established. The objective of this study was to clarify the medium-term outcomes of patients who received acute phase treatment in our department. This retrospective study included data from 214 patients with KD who received acute phase treatment from January 2009 to May 2020. A total of 196 (92.1%) received an initial single dose of intravenous immunoglobulin (IVIG) therapy. One patient with status epilepticus at presentation received initial IVIG plus steroid therapy. A total of 17 patients did not receive IVIG. The rate of coronary artery lesions (CALs) 1 month and 1 year after KD onset were 1.9% and 0.9%, respectively. Two patients had CAL 1 year after KD onset. However, no patients had coronary artery stenosis. One patient with a right giant CAL had a medium CAL before initial therapy. During a median follow-up period of 3 years and 4 months, no patients had cardiac events that required therapy.

Index Terms—Coronary artery lesions, Intravenous immunoglobulin therapy, Kawasaki disease, Outcomes.

I. INTRODUCTION

Kawasaki disease (KD) is an acute systemic vasculitis of unknown cause that mostly affects infants and children [1]. Coronary artery lesions (CALs) are a severe complication of KD. However, an acute phase treatment to prevent coronary artery stenosis has not been established. Studies regarding acute phase treatment for KD have been published [2]–[5]. However, a limitation is that their primary endpoints were the outcomes of CALs 6–8 weeks after KD onset, and the value of long-term outcomes of CALs require follow-up [6].

The standard therapy for the acute KD phase includes intravenous immunoglobulin (IVIG) therapy at 2 g/kg/dose with concomitant medium-dose or high-dose aspirin [7]. However, the addition of medium-dose or high-dose aspirin is now controversial [8]. A randomized controlled trial on the effectiveness of IVIG monotherapy and IVIG combined with high-dose aspirin in the acute KD stage is ongoing [9]. Studies suggest that aspirin may inhibit CAL prevention and that delayed use of aspirin (DUA) may be beneficial for the prevention of coronary artery stenosis in KD [10]–[13]. This study aimed to clarify the medium-term outcomes of patients who received acute phase treatment in our department and ascertain the usefulness of an initial single dose of IVIG therapy (2 g/kg/dose) with DUA to prevent coronary artery stenosis in patients without CALs before initial treatment.

II. PARTICIPANTS AND METHODS

Our institutional ethics committee approved the study protocol and waived the requirement of patient consent due to the retrospective nature of the study.

This retrospective study included data from 214 patients who received acute phase treatment for KD between January 2009 and May 2020. KD diagnoses were established based on the criteria (Japanese, 5th edition) mentioned in the diagnostic guidelines for KD until August 2019 and based on the revised criteria (Japanese, 6th edition) from September 2019 [14], [15]. Patients with a first episode of KD were included. One patient with heart failure at presentation who was transferred to another hospital was excluded because his detailed clinical data were not available. The remaining patients were divided into three groups: those with complications at presentation who received IVIG therapy (pre-complication group, $n = 5$), those without complications at presentation who received IVIG therapy with DUA (DUA group, $n = 192$), and those who received acute phase treatment without IVIG therapy (non-IVIG group, $n = 17$). The outcomes were the rates of CALs and coronary artery stenosis 1 year after KD onset.

IVIG resistance was defined as fever that persisted or reappeared 24 h after initial treatment [16]. KD presentation was defined as relapse when a second episode occurred within 2 months of the first episode after initial defervescence [17], [18]. Defervescence was defined as a body temperature $< 37.5^{\circ}\text{C}$ for at least 24 h, and the defervescence time was defined as the moment when the body temperature reached $< 37.5^{\circ}\text{C}$. Recurrent KD was defined as a secondary presentation of another episode 2 months after an initial episode [17], [18].

A. 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 initial therapy, whenever possible for the DUA group (Fig. 1). Prompt initial treatment was started for patients in the pre-complication group at presentation. If the patients had CALs, IVIG therapy with concomitant aspirin was started. Patients without inflammation or complications at presentation received acute phase therapy without IVIG.

Between January 2009 and November 2017, anti-inflammatory drugs (aspirin or flurbiprofen) were initiated within 24 h after the end of the initial IVIG infusion for patients in the DUA group (Fig. 1) [10]. Aspirin was initiated at a dose of 30 mg/kg/day and decreased to 5–10 mg/kg/day

once the patient was afebrile. Flurbiprofen was initiated at a dose of 3–5 mg/kg/day and decreased to 3 mg/kg/day once the patient was afebrile [10]. Each treating physician chose between aspirin and flurbiprofen after considering the patient's liver function and the risk of Reye syndrome during the influenza season. After December 2017, low-dose aspirin (5 mg/kg/day) was initiated on day 8 to 10 of illness after completion of the IVIG infusion, including the second course of therapy [18].

Fig. 1. Acute phase treatment for the DUA group.
IVIG: intravenous immunoglobulin, DUA: delayed use of aspirin.

B. 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 (Fig. 1). The decision was comprehensively made according to clinical parameters, including body temperature, major KD symptoms, general condition, and laboratory data [19]. The second course of therapy was rescue IVIG therapy at 2 g/kg/dose, and the third course of therapy was a ulinastatin infusion, a third course of IVIG therapy, or plasma exchange (Fig. 1) [13],[18].

C. Diagnosis of CAL

CALs were diagnosed using echocardiography based on the Japanese criteria according to Kobayashi *et al* [20]. A 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. A transient CAL was defined as the disappearance of a CAL within 30 days of the illness.

D. 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 P value of < 0.05 was considered statistically significant.

III. RESULTS

Of the 214 patients, 4 (1.9%) had a CAL before initial treatment (Table I). No patients in the DUA group had abnormal findings on the first echocardiogram. A total of 197 patients (92.1%) received IVIG therapy on a median 5th day of illness (Tables I and II). Of the 197 patients, 193 (98.0%)

received an initial 2 g/kg/dose of IVIG therapy (Table II), and 27 (13.7%) received rescue therapy after initial therapy. Of the 197 patients, 5 (2.5%) received third course of therapy, and 2 patients received plasma exchange (Table II). Of the 214 patients, 6 (2.8%) experienced KD relapse. However, no patients with relapse had a CAL. No patients experienced significant adverse effects due to acute phase treatment, such as shock, hemolytic anemia, and complications of severe infections (e.g., sepsis or osteomyelitis).

TABLE I: DEMOGRAPHIC DATA OF 214 PATIENTS

Variables	Data
Gender	Male/female = 109/105
Age at KD onset	Median 2 years and 2.5 months (range: 2 months–13 years and 3 months)
Incomplete type	41 (19.2%)
Patients with complications before initial treatment	CAL 4 (1.9%) Status epilepticus 1 (0.5%)
IVIG therapy	197 (92.1%)
Low-dose aspirin/medium-dose aspirin/flurbiprofen	41 (19.2%)/106 (49.5%)/67 (31.3%)
CAL	9 (4.2%)
Less than one month after KD onset	9 (4.2%)
One month after KD onset	4 (1.9%)
One year after KD onset	2 (0.9%)

Data are presented as n (%). KD: Kawasaki disease.
Incomplete type: major signs of KD ≤ 4 , IVIG: intravenous immunoglobulin, CAL: coronary artery lesion.

The rates of CALs less than one month and 1 month after KD onset were 4.2% and 1.9%, respectively, in the 214 patients (Table I). The rates of CALs in the pre-complication, DUA, and non-IVIG group patients less than 1 month after KD onset were 80.0%, 2.7%, and 0.0%, respectively, and those rates significantly differed among the three groups ($P < 0.01$). The rate of concomitant use of aspirin and initial IVIG therapy in the pre-complication group patients was significantly higher than that in the DUA group patients (Table III). The protocol of the initial IVIG therapies significantly differed between the pre-complication and the DUA group patients (Table III). The rates of CALs less than 1 month and 1 month after KD onset in the pre-complication group patients were significantly higher than those in the DUA group patients (Table III). Of the 214 patients, 2 (0.9%) had a CAL 1 year after KD onset (Table I), and their selective coronary angiograms showed findings with right CALs and normal left coronary arteries. No patients had coronary artery stenosis. Although not statistically significant, the rate of CALs in the pre-complication group patients 1 year after KD onset was higher than that in the DUA group patients (Table III).

The median follow-up period of the 214 patients was 3 years and 4 months (range: 13 days–9 years and 8 months). Among the 214 patients, 93 patients (43.5%) were still undergoing follow-up, and 80 patients (37.4%) had

completed follow-up at the last visit. A total of 21 patients (9.8%) were transferred to another hospital during follow-up, and 20 patients (9.3%) were lost to follow-up. Four patients with CALs 1 month after KD onset had ongoing follow-up at the last visit. During follow-up, 5 of the 214 patients (2.3%) experienced KD recurrence. However, no patients with recurrence had CALs. Two patients had chest pain syndrome, and one patient had mild aortic valve regurgitation 6 years after KD onset. However, no patients had cardiac events that required therapy, such as myocardial infarction/ischemia, heart failure, or life-threatening arrhythmia.

TABLE II: TREATMENT AND OUTCOMES OF 197 PATIENTS WHO RECEIVED IVIG THERAPY

Variables	Data
Day of illness at initial IVIG therapy	Median 5 (range: 3–16)
Protocol of initial IVIG therapy	2 g/kg/dose: 193 (98.0%) 2 g/kg/dose + steroid: 1 (0.5%) 1 g/kg/dose for 2 days: 3 (1.4%)
Non-responder	43 (21.8%)
Rescue therapy	2 nd IVIG therapy: 27 (13.7%) For non-responder: 20 (10.2%) For relapser: 6 (3.0%) For responder: 1 (0.5%) 3 rd course therapy: 5 (2.5%) Plasma exchange: 2 (1.0%) 3 rd IVIG therapy: 2 (1.0%) Ulinastatin: 1 (0.5%)

Data are presented as n (%). KD: Kawasaki disease.
IVIG: intravenous immunoglobulin, CAL: coronary artery lesion.

IV. DISCUSSION

The main findings of this study were that the medium-term outcomes of patients with KD who received acute phase treatment in our department were favorable and that the rate of CALs and coronary artery stenosis 1 year after onset were 0.9% and 0.0%, respectively. Moreover, an initial single dose of IVIG therapy (2 g/kg/dose) with DUA for patients without complications before initial treatment was useful for the prevention of coronary artery stenosis.

An initial single dose of IVIG therapy (2 g/kg/dose) with DUA has benefits regarding prevention of coronary artery stenosis, low rates of KD relapse, cost-effectiveness, and protection against severe infections.

The major goal of acute phase KD treatment is the prevention of coronary artery stenosis that may lead to myocardial ischemia [21]. During the median follow-up period of 3 years and 4 months, no patients had cardiac events that required therapy, such as cardiac infarction and myocardial ischemia. CAL size is significantly related to the occurrence of myocardial infarction/ischemia [22]. Therefore, CAL size during the acute phase of KD is an important factor for late phase outcomes. The cut-off values for CALs within the first 100 days after KD onset leading to a stenotic lesion in the late phase of KD, were a diameter $\geq$

6.1 mm in patients with a body surface area $< 0.50 \text{ m}^2$ and a diameter $\geq 8.0 \text{ mm}$ in patients with a body surface area $\geq 0.50 \text{ m}^2$ [23]. One study regarding initial IVIG therapy with DUA showed that the diameters of CALs in the DUA group patients were not larger than these cut-off values two months after KD onset [13]. Moreover, another study demonstrated an initial single dose of IVIG therapy with DUA was useful for prevention of CALs $\geq 3 \text{ mm}$ in infants younger than 1 year of age who had a high risk of CAL during the acute phase of KD [24]. This cohort study confirmed the efficacy of initial single dose of IVIG therapy with DUA for prevention of coronary artery stenosis 1 year after KD onset.

TABLE III: COMPARISON OF CLINICAL FINDINGS, TREATMENTS AND OUTCOMES BETWEEN THE PRE- COMPLICATION GROUP AND THE DUA GROUP

Variables	Pre-complication group (n = 5)	DUA group (n = 192)	P-value
Male gender	4 (80.0%)	98 (51.0%)	0.370
Age at KD onset (months)	33 (5.8–35.5)	26.5 (14.0–47.0)	0.499
Incomplete type	2 (40.0%)	27 (14.1%)	0.158
CAL before initial therapy	4 (80.0%)	0 (0.0%)	< 0.001
Concomitant use of aspirin with initial IVIG therapy	4 (80.0%)	0 (0.0%)	< 0.001
Initial IVIG therapy			
Start day of illness	6.0 (5.3–9.8)	5.0 (5.0–6.0)	0.112
Protocol of initial IVIG therapy			< 0.001
2 g/kg/dose	1 (20.0%)	192 (100.0%)	
2 g/kg/dose + steroid	1 (20.0%)	0 (0.0%)	
1 g/kg/dose for 2 days	3 (60.0%)	0 (0.0%)	
Non-responder	0 (0.0%)	43 (22.4%)	0.358
Rescue therapy	1 (20.0%)	26 (13.5%)	1.000
CAL			
Less than one month after KD onset	4 (80.0%)	5 (2.7%)	< 0.001
One month after KD onset	2 (40.0%)	2 (1.0%)	0.003
One year after KD onset	1 (20.0%)	1 (0.5%)	0.050

Data are presented as n (%) or median (interquartile range)
DUA: delayed use of aspirin, KD: Kawasaki disease.
IVIG: intravenous immunoglobulin, CAL: coronary artery lesion.

Appropriate use of IVIG therapy and plasma exchange was useful for prevention of coronary artery stenosis in this study. Two patients who received plasma exchange had no CALs 1 year after KD onset. Although one patient had a CAL with a maximal size of 4.8 mm on the right proximal coronary artery

during the acute phase of KD, the CAL regressed 2 months after KD onset [13]. Another patient had no CALs during either the acute or late phases of KD in this study. Takahara *et al.* found that rescue therapies, including plasma exchange before 10 days of illness, were useful for preventing large CALs in KD [25]. Moreover, rescue therapies using plasma exchange are considered useful for CAL suppression during the late KD stages [26]. Results regarding the patients who received plasma exchange in the present study were consistent with those of previous reports [25], [26].

Early identification of patients likely to develop IVIG resistance is a challenge [27] and identifying patients with initial IVIG resistance after initial therapy is easier. Several factors, including IVIG resistance, responsiveness, and disease relapse, are associated with CAL complications [28]. Therefore, risk stratification after initial therapy for KD is important for prevention of large CALs [19]. Single IVIG therapy does not modify the clinical course of KD, and this characteristic allows clinicians to manage treatment progress and to provide rescue therapies for IVIG resistance and KD relapse at appropriate times. This point may be another factor for the favorable outcomes of the patients in this study.

A nationwide epidemiologic survey of KD in Japan (2015–16) demonstrated that the rate of the patients who received IVIG therapy was 93.5% [29]. This rate is similar to that in the present study (92.1%, Table I). The rate of CALs in the non-IVIG group patients was 0.0%. This finding suggests appropriate risk stratification before initial therapy and decision for using IVIG therapy among the patients in this study.

An initial single dose of IVIG therapy with DUA has a benefit regarding low rates of KD relapses. The rate of patients who received rescue therapies for KD relapses was 3.0% in the present study (Table II). IVIG therapy resistance during the acute phase of KD has been implicated in CAL development [20]. Trials have been performed to decrease the rate of IVIG resistance using the addition of prednisolone (RAISE study), infliximab, and cyclosporin (KAICA study) [2], [3], [5]. These trials were performed using IVIG therapy with concomitant use of medium-dose or high-dose aspirin [2], [3], [5]. The RAISE study and the KAICA study showed a significant decrease in the rate of IVIG resistance in the study group compared to that in the control group [2], [5]. However, the relapse rates in these studies were 5.1-fold to 12.7-fold higher than those in the study using DUA [2], [5], [18], [30]. Moreover, the KD relapse rate in the study group in the KAICA study was significantly higher than that in the IVIG-resistant patients in the study using DUA ($P < 0.001$) [5], [18], [30].

KD relapse is caused by persistent inflammation and arteritis in the acute phase of KD and is a risk factor for CAL development as well as IVIG resistance [28]. These findings suggest that intensified initial IVIG therapies using concomitant medium-dose aspirin and cyclosporin/steroids are not able to control persistent inflammation and arteritis after the initial therapy. Moreover, the rates of CAL development using Japanese criteria were similar among the study group and the control group in the KAICA study and the IVIG-resistant patients in the study using DUA [30].

An initial single IVIG therapy with DUA has a benefit regarding cost-effectiveness. A recent Japanese nationwide

survey regarding KD patients in 2015 and 2016 showed that the rates of rescue therapy and cardiac sequelae 1 month after onset were 21.8% and 2.3%, respectively [29]. In the present study, those rates were 13.7% and 1.9%, respectively. Another study showed the cost-effectiveness of the initial IVIG therapy with DUA regarding rescue therapies for IVIG-resistant patients [30]. In the RAISE study and the KAICA study, patients who were predicted to be resistant to IVIG were enrolled [2], [5]. The patients were those with risk scores of five points or higher using a risk scoring system developed by Kobayashi *et al* [20]. The proportion of the predicted patients was 29.8% to 27.6% of the acute phase KD population [20], [31]. The proportion of the IVIG-resistant patients who received rescue therapies was 10.1% (21/207) in the study that utilized DUA [18]. The rate of the patients who received rescue therapy for IVIG resistance, response, and KD relapse in the DUA group was 13.5% in this study (Table III). This finding suggests the cost-effectiveness of the initial single IVIG therapy with DUA for KD.

Safety against severe infections is one of the benefits of single dose IVIG therapy. In the present study, no patients had complications of severe infections. In contrast to steroids/cyclosporin A, a single dose IVIG therapy has no immunosuppressive effects. This point may be important in the era of coronavirus disease 2019 (COVID-19). Adverse effects of the acute phase treatment for KD using steroids/cyclosporin A include severe infections, such as osteomyelitis and bacteremia [31], [32]. Immunosuppressive agents, such as steroids and cyclosporin A, have significant risk for complications of severe infections [31], [32]. A single IVIG therapy may be safer than the acute phase treatment using steroids/cyclosporin A against severe infections.

The rate of CAL in the pre-complication group patients was higher than that in the DUA group patients less than 1 month and 1 month and 1 year after KD onset (Table III). Four of five pre-complication group patients had CALs before initial therapy, whereas no patient in DUA group had abnormal findings on the first echocardiogram (Table III). A study showed that all patients with persistent CALs 1 year after KD onset already had an abnormal initial echocardiogram and that the presence of any abnormalities on the initial echocardiogram may contribute to early identification of patients with severe disease [33]. Another study using multivariable analyses demonstrated that the lack of CAL regression and persistent large CAL in the late phase were associated with large coronary artery diameters at diagnosis [34]. The study using logistic regression analysis of our KD patients also showed that CAL before initial treatment is an independent risk factor for persistent CAL in late-stage KD [35]. Therefore, the higher risk for CAL in the pre-complication group patients before initial therapy may contribute a higher rate of CAL. Furthermore, a low rate of 2 g/kg/dose initial single dose of IVIG therapy may also contribute higher rate of CAL (Table III).

One patient in the pre-complication group had a right giant CAL with a diameter ≥ 8 mm 1 year after KD onset (Table III). Although this patient had no stenotic lesions at the time this study was conducted, right coronary occlusion/stenosis may develop in the future because giant CALs have a risk for these lesions [22]. However, the prevalence of asymptomatic complete occlusion is significantly higher in the right

coronary artery, and a study showed a favorable outcome 5 years after KD onset in a patient with a right giant CAL [23], [36]. Most patients with giant CALs can lead ordinary lives with appropriate management [22]. Our patient with a right giant CAL had an uneventful course with aspirin and warfarin 1 year after KD onset.

Drug therapies have a limitation for the prevention of coronary artery stenosis caused by KD. The RAISE study showed the significantly lower rate of CAL in the study group 4 weeks after KD onset compared to that in the control group [2]. However, giant CALs were not prevented in the patients without CALs before initial therapy with this regimen [2]. A study showed that a patient who had received initial IVIG and prednisolone combination therapy developed a giant CAL after relapse [37]. Another study regarding intensified initial IVIG therapy showed the outcomes of CALs in terms of the size and regression rate 12 months after KD onset were similar among patients who received IVIG only, IVIG plus infliximab, or IVIG plus corticosteroids [38]. Furthermore, a study showed that the incidence and severity of CALs did not change notably after infliximab administration in Japanese patients with KD [39]. These findings suggest the limitation for prevention of coronary artery stenosis caused by KD among patients who received the mentioned pharmacotherapy regimens.

Rescue therapy with plasma exchange may be useful for prevention of coronary artery stenosis in high-risk patients based on the outcomes of the DUA group patients and the findings of previous studies [13], [25], [26]. Indication criteria for plasma exchange in patients with KD have not been established. However, biomarkers, such as the serum albumin level, C-reactive protein values, and neutrophil to lymphocyte ratio after initial therapy, may be useful for risk stratification after initial therapy [19], [40]–[42].

KD recurrence and development of arrhythmia are important problems after the acute phase of KD.

A nationwide epidemiologic survey of KD in Japan (2015–16) disclosed a 4.2% prevalence of KD recurrence [29]. The rate of KD recurrence was 2.3% in this cohort study. The incidence of KD recurrence is high among those with cardiac sequelae during the first episode [17]. The low rate of CALs during the first episode may be a factor for the lower rate of KD recurrence in this study. KD recurrence is a risk factor for CAL development [43]–[45]. In fact, 2 of 5 patients (40%) with recurrence between 1991 and 2003 had medium-size CALs one month after the second episode in our department [45]. In the present cohort study, no patients with recurrence had CALs. The higher rate of patients who received 2 g/kg/dose IVIG therapy may be a factor for the different rates of CAL development compared with previous rates.

A study of 165 patients with a history of KD using exercise stress testing showed that ventricular arrhythmias were uncommon and were seen only in patients with medium or large CALs [46]. This finding was consistent with the findings of the present study. No patients, including the two patients with CALs one year after KD onset, had any significant arrhythmias in the late phase. A case report showed a patient who had ventricular arrhythmia and possible myocardial ischemia in late-stage KD despite no association with CALs with KD onset [47]. This patient was treated with aspirin monotherapy and did not receive IVIG therapy during

the acute phase of KD [47]. Fortunately, the non-IVIG group patients in the present study had no significant arrhythmias or ischemic findings on exercise stress testing in the late phase. The complication of significant arrhythmias may be a rare event in patients without CALs in the late phase.

The limitations of this study include the small sample size and the retrospective study design.

In conclusion, the medium-term outcomes of patients with KD who received acute phase treatment in our department were favorable, and the rate of CALs and coronary artery stenosis one year after onset were 0.9% and 0.0%, respectively. Moreover, initial single IVIG therapy (2 g/kg/dose) with DUA for patients without CALs before initial treatment was useful for prevention of coronary artery stenosis. The majority of KD patients had favorable medium-term outcomes with acute phase management using risk stratification before and after initial treatment, initial single IVIG therapy (2 g/kg/dose) with DUA, and appropriate rescue therapies using IVIG and plasma exchange.

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The most recent publication is the article entitled “Preventive therapies using sodium channel blockers for congenital long QT syndrome” [World Journal of Pharmaceutical and Life Sciences 2020; 6 (6): 7-12].