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Varying Relapse Rates in Kawasaki Disease among Different Initial Therapies

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Keywords: Kawasaki disease, Relapse, Treatment, Intravenous immunoglobulin therapy, Coronary artery lesions.

ABSTRACT

Background: Kawasaki disease (KD) relapse is a risk factor for the development of coronary artery lesions (CALs). Varying relapse rates of KD have been reported among patients who receive different initial therapies. **Objective**: To clarify the usefulness of treatment with initial therapy using single intravenous immunoglobulin (IVIG) (2g/kg) with the delayed use of aspirin (DUA) in terms of the decrease in the risk of relapse in KD. **Materials and methods**: The KD relapse rates in four studies where the acute phase treatment was clarithromycin (CLA study), ciclosporin (KAICA study), prednisolone (RAISE study), and DUA (DUA study) for the initial IVIG therapy were statistically compared. Data of patients with IVIG resistance in the DUA study were compared with those of the KAICA and RAISE studies. **Results**: The relapse rates between the study group and the DUA study group were as follows: 12.5% vs. 2.4%, P = 0.012 (CLA study); 26.7% vs. 2.1%, P < 0.001 (KAICA study); and 10.7% vs. 2.1%, P = 0.116 (RAISE study). The relapse rates between the control group using IVIG therapy with concomitant use of aspirin and the DUA study group were as follows: 30.8% vs. 2.4%, P < 0.001 (CLA study); 8.0% vs. 2.1%, P = 0.260 (KAICA study); and 12.4% vs. 2.1%, P = 0.074 (RAISE study). **Conclusions**: The relapse rates in patients with KD were significantly different depending on the initial therapy used. An initial single IVIG therapy (2g/kg) with DUA may be useful for decreasing the relapse risk in KD.

INTRODUCTION

Kawasaki disease (KD) is an acute systemic vasculitis of unknown cause that mainly affects infants and children[1]. Coronary artery lesions (CALs) are a severe complication of KD, and disease relapse is a risk factor for CAL development[2].

Different relapse rates have been reported among KD patients who receive different initial therapies [3-6]. However, statistical analyses among these studies have not been performed. Therefore, the significance of the difference in KD relapse rates among different initial therapies remains unclear.

The standard therapy for the acute KD phase includes intravenous immunoglobulin (IVIG) therapy at 2 g/kg/dose with concomitant use of the medium- or high-dose aspirin[7]. However, the addition of medium- or high-dose aspirin is controversial, and 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[8,9].

Studies have suggested that aspirin may inhibit CAL prevention and that the delayed use of aspirin (DUA) may be beneficial for the prevention of coronary artery stenosis in KD[10-13]. The objective of this study was to clarify the significance of the difference in KD relapse rates among recent studies regarding acute phase treatment as well as to ascertain the usefulness of initial single IVIG therapy (2g/kg) with DUA for decreasing the rate of relapse in KD.

MATERIALS AND METHODS

The study protocol did not require approval by the institutional ethics committee because it involved comparative analysis among previously published studies.

This retrospective study included four recent studies regarding acute phase KD treatment using clarithromycin (CLA study)[4], ciclosporin (KAICA study)[5], prednisolone (RAISE study)[6], and DUA (DUA study)[3] for the initial IVIG therapy. The KD relapse rates were statistically compared among these studies. Data of the total population in the DUA study were compared with those of the CLA study, and the data of the patients with IVIG resistance in the DUA study were compared to those of the KAICA and RAISE studies. The rates of CAL development, using Japanese criteria[14] at week 4 after KD onset, were compared

between the KAICA and DUA studies.

KD presentations were considered as relapses when a second episode appeared within 2 months of the first and after the initial defervescence. Defervescence was defined as a body temperature < 37.5 °C for at least 24 h and the defervescence time was defined as the moment when the body temperature reached < 37.5 °C. IVIG resistance was defined as a fever that persisted or reappeared 24 h after the first-line treatment[15].

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.

RESULTS

Patients in the CLA, KAICA, and RAISE studies received initial IVIG therapy with the concomitant use of aspirin (Table 1). The KD relapse rates ranged from 2.1% to 30.8% among the four studies (Table 1). The relapse rates between the study and the control groups were significantly different in the CLA study and the KAICA study (Table 1)[4,5]. The median day of illness at enrollment ranged from 4 to 5 (Table 1).

KD relapse rates among the study group, control group in the CLA study, and the DUA total study group were significantly different: 12.5% (5/40) vs. 30.8% (12/39) vs. 2.4% (5/207) ($P < 0.001$) (Figure no. 1). KD relapse rates between the study group in the CLA study and the DUA total study group were also significant: 12.5% (5/40) vs. 2.4% (5/207) ($P = 0.012$) (Figure no. 1). Furthermore, KD relapse rates between the control group in the CLA study and the DUA total study group were significant: 30.8% (12/39) vs. 2.4% (5/207) ($P < 0.001$) (Fig. 1).

KD relapse rates among the study group, control group in the KAICA study, and the DUA resistant study group were significantly different: 26.7% (23/86) vs. 8.0% (7/87) vs. 2.1% (1/47) ($P < 0.001$) (Figure no. 2). KD relapse rates between the study group in the KAICA study and the DUA resistant study group were also significant: 26.7% (23/86) vs. 2.1% (1/47) ($P < 0.001$) (Figure no. 2). However, the KD relapse rates between the control group in the

KAICA study and the DUA resistant study group were not significant: 8.0% (7/87) vs. 2.1% (1/47) (P = 0.260) (Figure no. 2).

Table No. 1. Kawasaki disease relapse rates among different studies

Study reference	Protocol	Relapse rate	P-value	Day of illness at enrollment
CLA study[4]				
Study group	CLA+IVIG+ASA	12.5% (5/40)	0.046	4 (2–8)
Control group	IVIG+ASA	30.8% (12/39)		5 (2–8)
KAICA study[5]				
Study group	Cicl+IVIG+ASA	26.7% (23/86)	0.016	4.2 (1.2)
Control group	IVIG+ASA	8.0% (7/87)		4.1 (1.1)
RAISE study[6]				
Study group	PLS+IVIG+ASA	10.7% (13/121)	0.84	4 (4–5)
Control group	IVIG+ASA	12.4% (15/121)		4 (3–5)
DUA study[3]				
Total patients	IVIG+DUA	2.4% (5/207)		5 (5–6)
IVIG-resistant patients	IVIG+DUA	2.1% (1/47)		5 (5–5.5)

P-value: Between the study vs. control groups in each study.

Day of illness at enrollment: Data are presented as median (range) in the CLA study, and as median (interquartile range) in the KAICA, RAISE, and DUA studies.

CLA: Clarithromycin, IVIG: Intravenous immunoglobulin, ASA: Concomitant use of aspirin, Cicl: Ciclosporin, PLS: Prednisolone, DUA: Delayed use of aspirin.

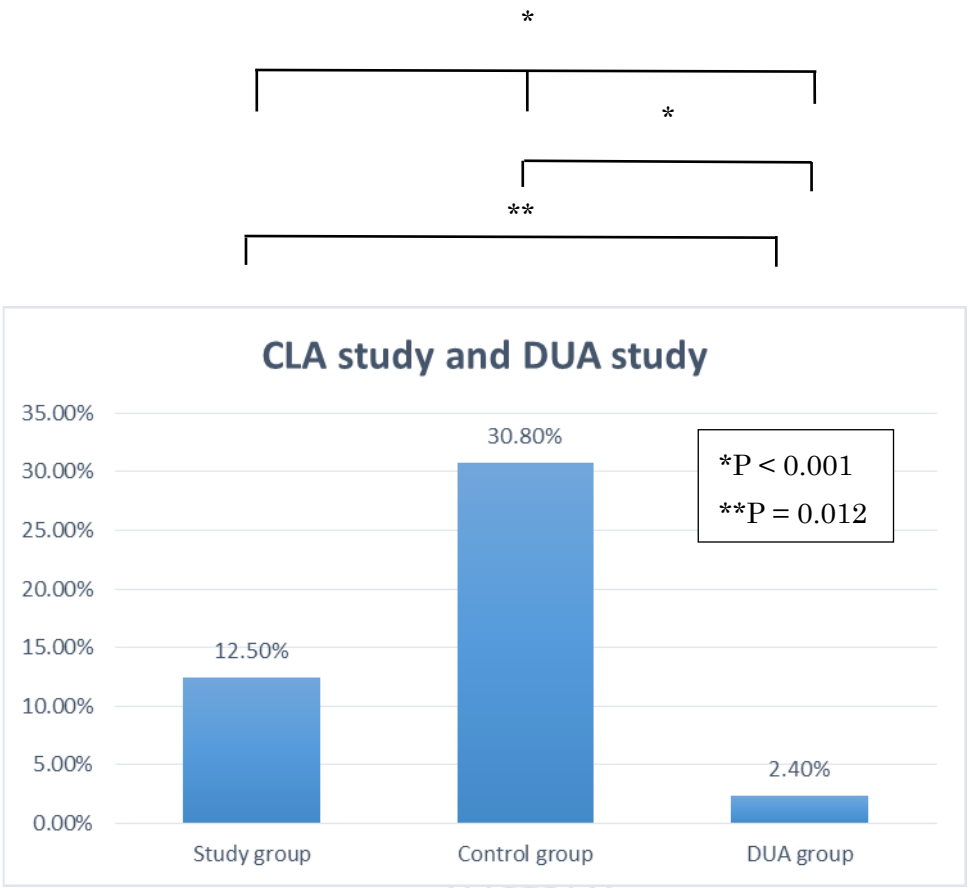

Figure No. 1. Comparison of Kawasaki disease relapse rates among the study group, the control group in the CLA study, and the DUA total study group

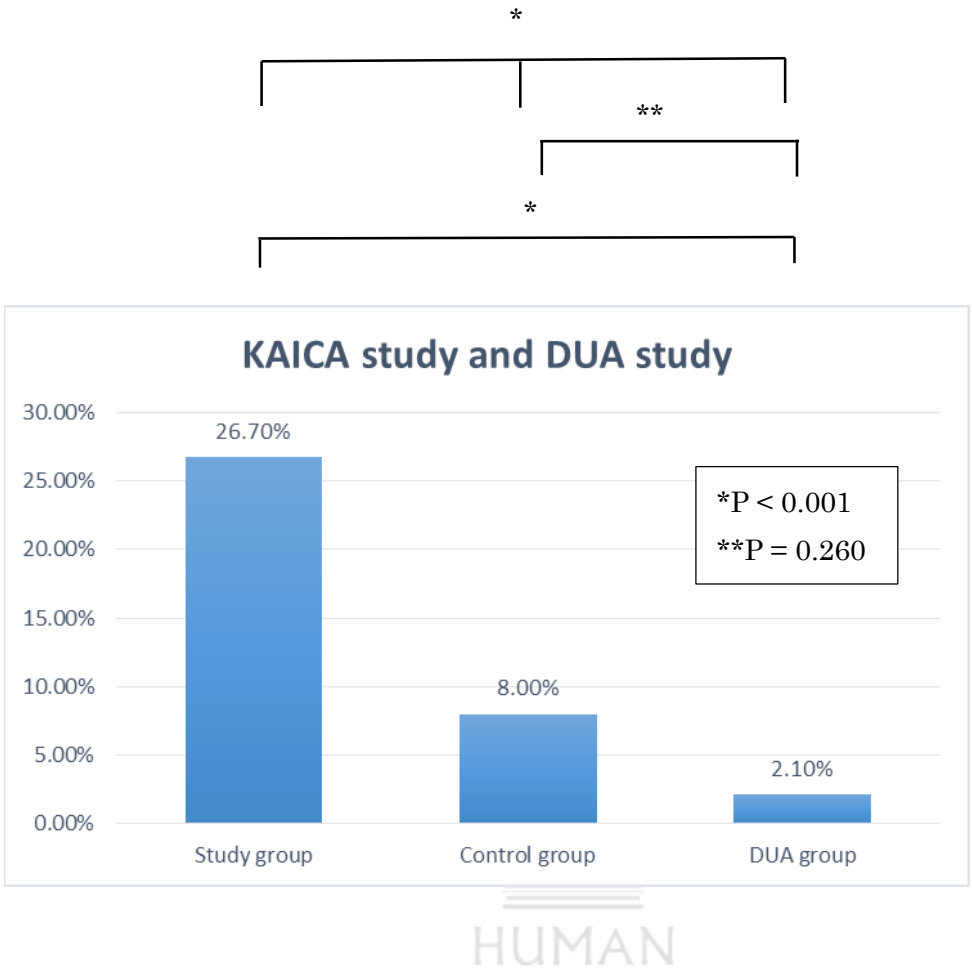

Figure No. 2. Comparison of Kawasaki disease relapse rates among the study group, the control group in the KAICA study, and the DUA resistant study group

The use of rescue therapies between the study group in the KAICA study and the DUA resistant study group were similar (Table 2). However, the use of the rescue therapies for resistance to initial therapy of the study group in the KAICA study was significantly lower than that of the DUA resistant study group. Inversely, the use of rescue therapies for relapse of the study group in the KAICA study was significantly higher than that of the DUA resistant study group (Table 2).

Table No. 2. Comparison of the use of rescue therapies between the study group in the KAICA study and the IVIG-resistant patients in the DUA study

	Study group in KAICA study (n = 86)	IVIG-resistant patients in DUA study (n = 47)	P-value
Rescue therapies	38 (44.2%)	21 (44.7%)	0.956
For resistance to initial therapy	15 (17.4%)	20 (42.6%)	0.002
For relapse	23 (26.7%)	1 (2.1%)	< 0.001

IVIG: Intravenous immunoglobulin.

The rates of CAL development, using Japanese criteria at week 4 after KD onset, were similar among the study group, control group in the KAICA study, and the DUA resistant study group: 2.3% (2/86) vs. 6.9% (6/87) vs. 4.3% (2/47) (P = 0.395) (Fig. 3). The rates of CAL development between the study group in the KAICA study and the DUA resistant study group [2.3% (2/86) vs. 4.3% (2/47), P = 0.614], and between the control group in the KAICA study and the DUA resistant study group [6.9% (6/87) vs. 4.3% (2/47), P = 0.713] were also similar (Fig. 3).

KD relapse rates among the study group, control group in the RAISE study, and the DUA resistant study group were similar: 10.7% (13/121) vs. 12.4% (15/121) vs. 2.1% (1/47) (P = 0.290) (Fig. 4). KD relapse rates between the study group in the RAISE study and the DUA resistant study group [10.7% (13/121) vs. 2.1% (1/47), P = 0.116], and between the control group in the RAISE study and the DUA resistant study group [12.4% (15/121) vs. 2.1% (1/47), P = 0.074] were also similar. (Fig. 4).

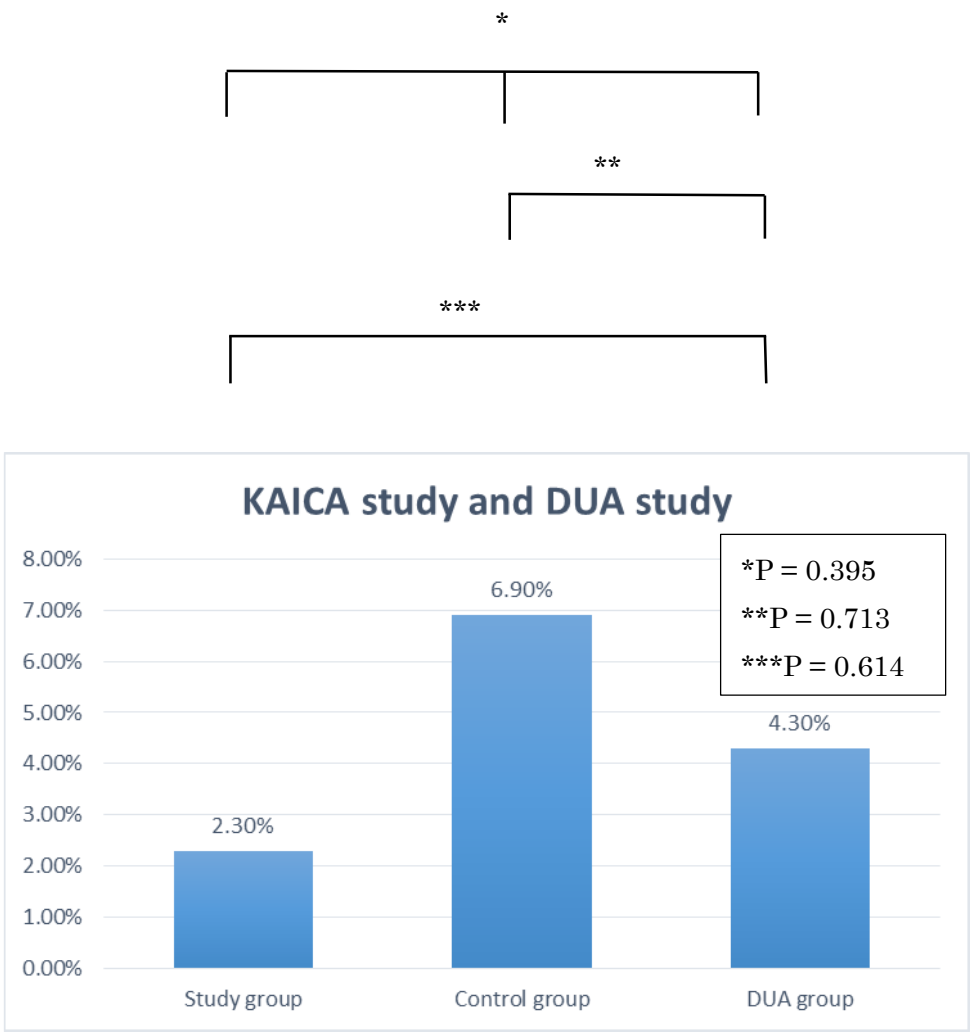

Figure No. 3. Comparison of the rates of coronary artery lesion development at week 4 after onset among the study group, control group in the KAICA study, and the DUA resistant study group

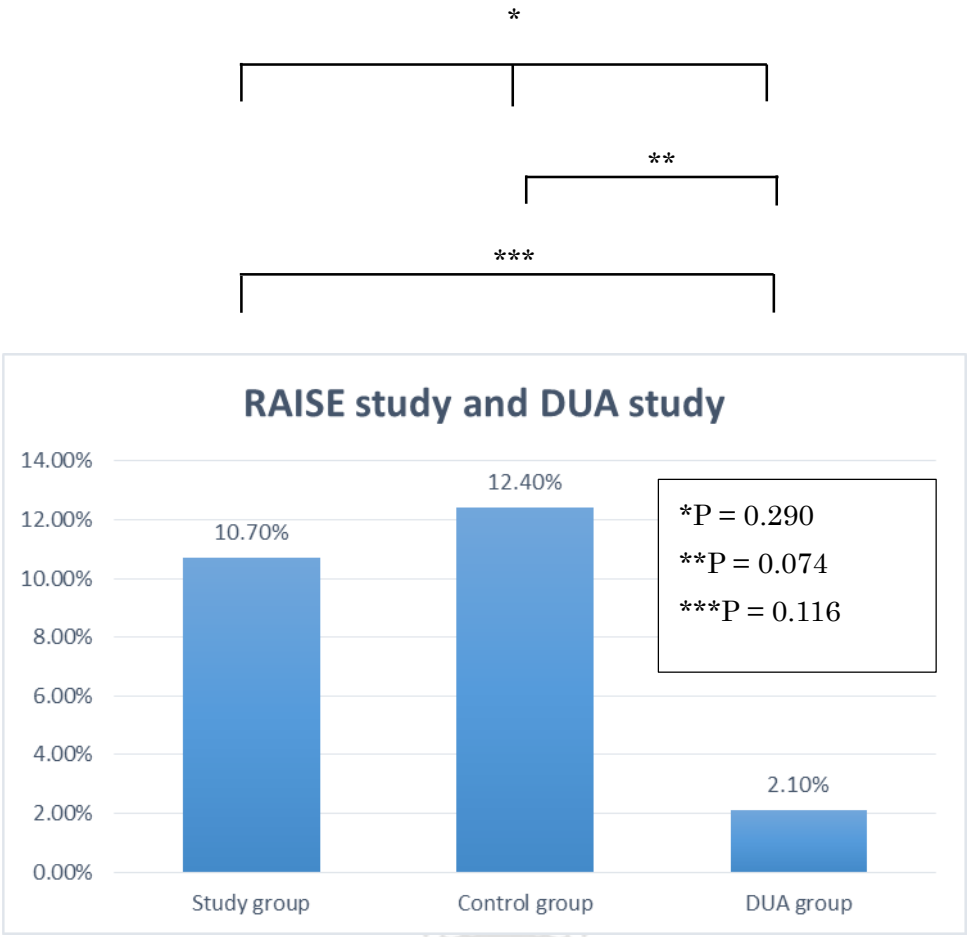

Figure No. 4. Comparison of Kawasaki disease relapse rates among the study group, the control group in the RAISE study, and the DUA resistant study group

DISCUSSION

The present study showed that KD relapse rates were significantly different among patients who received different initial therapies and that an initial single IVIG therapy (2g/kg) with DUA may be useful for decreasing the KD relapse risk.

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[2,16]. The KD relapse rate in the study group in the KAICA study was significantly higher than that of the resistant study group in the DUA study (Fig. 2). This finding suggests that the intensified initial IVIG therapy involving concomitant use of medium-dose aspirin and ciclosporin was unable to control the persistent inflammation and arteritis after the initial therapy. Moreover, the rates of CAL development using Japanese criteria at week 4 after KD onset were similar among the study group, control group in the KAICA study, and the DUA resistant study group (Fig.

3). This finding is consistent with the results of a recent study regarding intensified initial IVIG therapy in that the outcomes of CAL in terms of the size and regression rate 12 months after KD onset were similar among the patients who received IVIG only, IVIG plus infliximab, and IVIG plus corticosteroids[17].

IVIG therapy resistance during the acute phase of KD has been implicated in the development of CAL[14]. Trials have been performed to decrease the rate of IVIG resistance using treatment with the addition of prednisolone (RAISE study), infliximab, ciclosporin (KAICA study), and clarithromycin (CLA study) to the initial IVIG therapy[4-6,18]. These trials were performed using IVIG therapy with concomitant use of the medium- or high-dose aspirin[4-6,18].

The RAISE and KAICA studies showed a significant decrease in the rate of IVIG resistance in the study group compared to that in the control group[5,6]. However, the relapse rates of these studies were 5.1 to 12.7 fold of those observed in the DUA study (Figure no. 2, 4). Moreover, the KD relapse rates between the study group in the KAICA study and the DUA resistant study group were significantly different ($P < 0.001$) (Figure no. 2).

The RAISE study showed a significantly lower rate of CAL in the study group 4 weeks after KD onset compared to the control group[6]. However, giant CALs were not prevented by this regimen[6]. Another study showed that a patient who had received initial IVIG and prednisolone combination therapy developed a giant CAL after relapse[19].

The rates of CAL development, using Japanese criteria at week 4 after KD onset, were similar among the study group, control group in the KAICA study, and the DUA resistant study group ($P = 0.395$) (Figure no. 3). This finding suggests that the ability of the regimen utilized in the DUA study to suppress CALs may be similar to that in the KAICA study. Indeed, a recent study involving initial IVIG therapy with DUA demonstrated its ability to prevent coronary artery stenosis caused by KD[13]. Moreover, another study demonstrated that initial single IVIG therapy (2 g/kg) with DUA was useful for the prevention of CAL $\geq$ 3 mm in infants younger than 1 year of age who had a high risk for CAL[20]. These findings suggest the usefulness of initial single IVIG therapy with DUA for the suppression of CAL development, as well as the intensified initial IVIG therapy using prednisolone and ciclosporin.

In the RAISE and KAICA studies, the patients who were predicted to be resistant to initial IVIG therapy were enrolled[5,6]. These patients were defined as those with risk scores of 5 points or higher using the risk scoring system developed by Kobayashi and colleagues[14]. The frequency of the predicted patients ranged from 29.8% to 27.6% of the acute phase KD population[14,21]. In contrast, the frequency of the IVIG-resistant patients who received rescue therapies was 10.1% (21/207) in the DUA study (Table 1, 2)[3]. These findings suggest the socio-economic usefulness of initial IVIG therapy with DUA.

Although the early identification of patients likely to develop IVIG resistance is a challenge, the identification of patients with initial IVIG resistance after the initial therapy is easier[22]. Variable factors, including IVIG resistance, responsiveness, and disease relapse are associated with CAL complications[2]. Therefore, risk stratification after the initial therapy of KD is important for the prevention of large CALs[13]. 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 provide appropriate rescue therapies[13].

A recent study in which patients with initial IVIG resistance were assigned to two different subgroups according to resistance severity, showed that the clinical findings (fever pattern during initial IVIG therapy) and the laboratory findings after the initial therapy were significantly different between the two groups[23]. Moreover, risk stratification after initial IVIG therapy with DUA for IVIG resistance was useful for the prevention of KD coronary artery stenosis and for identifying patients who did not require rescue therapy for resistance[23].

Controversies remain regarding early IVIG therapy within the first 4 days of illness[16,24-26]. A recent 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[16]. The difference was more pronounced for the risk of relapse after initial fever resolution, and the risk of CALs did not differ significantly in this study[16].

Whenever possible, the patients whose data were analyzed in the DUA study, received initial single IVIG regimens of 2 g/kg/dose, starting on day 5 of illness, as first-line therapy. The median timing of the initial IVIG therapy, about the day of illness among the total population, was 5 days (range, 4–16)[3]. The rates of patients who received initial IVIG therapy at days 5 and 4 of illness were 58.5% and 1.9%, respectively[3]. The low prevalence of rescue therapy for relapse in the DUA study population may be related to the timing of the initial IVIG

therapy, as has been mentioned previously[16].

The KD relapse rate of the DUA total study group was significantly lower than that of the study and control groups in the CLA study (Figure no. 1). The total population in the CLA study received initial IVIG therapy with concomitant use of medium-dose aspirin, which is known to have an anti-inflammatory effect[4]. Furthermore, clarithromycin has anti-inflammatory activity that is not mediated through its traditional antimicrobial effect[4]. Previous studies have shown the negative impact of anti-inflammatory drugs on the initial IVIG therapy in acute phase KD[10,27]. The negative impact of anti-inflammatory drugs on initial IVIG therapy may go some way to explain the differences in the KD relapse rates among the patient groups in the CLA and the DUA studies.

The present study has some limitations. First, the DUA study is a retrospective study. Second, the subjects in the KAICA and RAISE studies were patients who were predicted to be IVIG-resistant based on the risk scoring system developed by Kobayashi et al[14]. However, the patients with IVIG resistance were used for comparison between the DUA study and the KAICA/RAISE studies.

CONCLUSIONS

The KD relapse rates were significantly different among patients who received different initial therapies. An initial single IVIG therapy (2g/kg) with DUA may be useful for decreasing the risk of relapse in KD.

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