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Parameters to Guide Rescue Therapy for Intravenous Immunoglobulin-resistant Kawasaki Disease

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Author's contribution

The sole author designed, analyzed and interpreted and prepared the manuscript.

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ABSTRACT

Aims: To identify the most useful parameter to guide rescue therapy among the IVIG-resistant patients who received an initial single IVIG therapy dose with a delayed use of anti-inflammatory drugs (DUA) for Kawasaki disease.
Methods: The parameters of 174 patients who received the initial IVIG therapy at 2 g/kg/dose with DUA were investigated. These patients were divided into 135 IVIG-responders (responder group) and 39 IVIG-resistant patients. The 39 IVIG-resistant patients were further divided into two groups, a rescue group with 15 patients who received rescue therapies for initial IVIG therapy resistance and a non-rescue group with 24 children who did not receive the rescue therapy for resistance. Four parameters, including neutrophil counts, neutrophil %, neutrophil to lymphocyte ratio and C-reactive protein (CRP) value after initial IVIG therapy, were investigated retrospectively, as was the ratio of each parameter, defined as the ratio of the values after/before initial IVIG therapy.
Results: All four parameters and their ratios were significantly different among 3 groups ($P < .05$). Among these parameters, the ratio of CRP for the rescue group had the highest sensitivity and specificity, at 90.8%. Furthermore, the logistic regression analysis showed that only the ratio of

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CRP was an independent predictor for rescue group (P < .001, odds ratio: 66.807, 95% confidence interval: 7.468 ～ 597.655).
Conclusion: The ratio of CRP may be the most useful parameter for guiding rescue therapy among the IVIG-resistant patients who received an initial single IVIG therapy dose with DUA for Kawasaki disease.

Keywords: Kawasaki disease; intravenous immunoglobulin therapy; C-reactive protein; neutrophil; coronary artery lesions.

ABBREVIATIONS

CAL: Coronary artery lesions; IVIG: Intravenous immunoglobulin; CRP: C-reactive protein; NLR: Neutrophil to lymphocyte ratio; DUA: Delayed use of anti-inflammatory drugs.

1. INTRODUCTION

Kawasaki disease is an acute systemic vasculitis of unknown cause that mainly affects infants and children [1]. Coronary artery lesions (CAL) are one of the most important complications of this disease, and an intravenous immunoglobulin (IVIG) therapy resistance is one of the most important factors for CAL development during the acute phase of Kawasaki disease [2]. IVIG resistance was defined if either the fever persisted or reappeared at 24 hours after first-line treatment. However, the rescue therapies for IVIG-resistant patients and their guiding parameters have not yet been established [3].

A previous study showed that neutrophil counts and C-reactive protein (CRP) values might be useful for guiding rescue therapy [4]. Recent studies have demonstrated the usefulness of the neutrophil to lymphocyte ratio (NLR) for risk stratification after initial IVIG therapy in Kawasaki disease [3,5].

A previous study disclosed that anti-inflammatory drugs, including aspirin, appeared to have a negative impact on the suppressive effects of initial IVIG therapy for CAL development during the acute phase of Kawasaki disease; moreover, the study showed that an initial, single IVIG therapy dose with a delayed use of anti-inflammatory drugs (DUA) might be effective for CAL suppression [6]. A recent study regarding this regimen reported its safety and efficacy for the suppression of CAL development caused by Kawasaki disease [7]. The aim of this study is to identify the most useful parameter for guiding rescue therapy among the IVIG-resistant patients who received an initial single IVIG therapy dose with DUA for Kawasaki disease.

2. METHODS

This retrospective study included 174 consecutive patients who had received an initial 2 g/kg/dose of IVIG therapy with DUA (aspirin or flurbiprofen) for Kawasaki disease between January 2004 and February 2017 at our department. The retrospective data of those patients were collected. The diagnosis of Kawasaki disease was based on Japanese Criteria (Fifth Edition) [8].

Defervescence was defined as when a body temperature remained below 37.5°C for more than 24 hours, and the onset of defervescence was defined as the time point at which the body temperature reached below 37.5°C. IVIG resistance was defined if either the fever persisted or reappeared at 24 hours after first-line treatment.

The patients were divided into 135 IVIG responders (responder group) and 39 IVIG-resistant patients. The 39 IVIG-resistant patients were further divided into two groups: a rescue group, comprising 15 patients who received the rescue therapies for initial IVIG therapy resistance; and a non-rescue group, comprising 24 patients who did not receive the rescue therapy for initial IVIG resistance.

Four parameters, including neutrophil counts, neutrophil %, NLR and CRP values after initial IVIG therapy, were investigated retrospectively, as was the ratio of each parameter, defined as the ratio of the values after/before initial IVIG therapy. The NLR was defined as the ratio of the neutrophil /lymphocyte counts.

2.1 Anti-inflammatory Drugs Therapy and Initial IVIG Therapy

During the study period, an initial single IVIG regimen of 2 g/kg/dose, starting on day 5 of the

illness, was used as first-line therapy, when possible. Anti-inflammatory drugs (aspirin or flurbiprofen) were initiated within 24 hours after the end of initial IVIG infusion [6].

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 patients became afebrile [6].

A regimen of the initial IVIG therapy with DUA was used after 2004. Some patients received this therapy with DUA between 2004 and 2008. The choice between DUA and concomitant use of anti-inflammatory drugs was made by each doctor during this period. After 2009, initial IVIG therapy with DUA was utilized for all patients [6].

2.2 Rescue Therapy

The decision to use rescue therapies in resistant patients was made between 48 and 72 hours after the end of the initial IVIG therapy. The decision was made comprehensively according to clinical parameters, including the body temperature, major symptoms of Kawasaki disease, general condition, and laboratory data [6].

Second-line therapy was rescue IVIG therapy at 2 g/kg/dose, and third-line therapy was ulinastatin infusion. Plasma exchange was adopted after 2014 as another third-line therapy option [3].

2.3 Diagnosis of CAL

CAL was diagnosed by echocardiography based on Japanese criteria according to Kobayashi et al. [2]. CAL was diagnosed when any of these examinations showed an internal lumen diameter ≧ 3 mm in a patient < 5 years of age or a diameter ≧ 4 mm in a patient ≧ 5 years of age; if the internal diameter of a segment was at least 1.5 times as large as 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.

2.4 Statistical Analysis

Statistical analyses were performed with StatFlex Version 6 for Windows (Artech Co., Ltd., Osaka, Japan). Chi-square, Fisher's exact, Mann–Whitney U, and Kruskal-Wallis tests were used as appropriate under sample size considerations. To determine the cut-off value of each parameter, receiver operating characteristic curves were used. Logistic regression analysis was used to determine independent predictor for rescue group. A value of $P < .05$ was considered statistically significant.

3. RESULTS

The clinical features regarding sex, age of onset, prevalence of incomplete types, and the sampling day of illness were similar among the three groups (Table 1). The neutrophil counts, neutrophil %, NLR, and CRP values before initial IVIG therapy were significantly different among the three groups (Table 1).

All 15 patients in the rescue group received rescue IVIG therapies on day 8 (based on median; range, 7-11) of illness for initial IVIG therapy resistance, and the duration between the first and second IVIG therapies had a median of 3 (range, 3-4) days. Two of the 15 patients received third-line therapy; one patient received an ulinastatin infusion, and another patient received plasma exchange.

The time until defervescence was significantly different among the three groups; the rescue group patients had the longest periods from the onset of the disease and from the initial IVIG therapy (Table 2). The neutrophil counts, neutrophil %, NLR, CRP values after initial IVIG therapy, as well as the ratios of each, were also significantly different among the three groups (Table 2).

The CRP ratio had the highest sensitivity and specificity for the rescue group among the abovementioned parameters based on the analytical results using receiver operating characteristic curves (Table 3). Furthermore, the logistic regression analysis showed that only the CRP ratio was an independent predictor for the rescue group among the parameters, including neutrophil counts, neutrophil %, NLR and CRP value after initial IVIG therapy, as well as the ratio of each parameter, defined as the ratio of the values after/before initial IVIG therapy (Table 4).

The highest cut-off value of the CRP ratio, which had 100% sensitivity for the rescue group, was 0.51, with a specificity of 86.7%.

Table 1. Comparison of the clinical findings and laboratory values before initial IVIG therapy among the three groups

Variables	Rescue group	Non-rescue group	Responder group
	***n* = 15**	***n* = 24**	***n* = 135**
Sex (male) .	7 (46.7%)	15 (62.5%)	63 (46.7%)
Age (months)	24 (21–33.5)	34.5 (22–53)	22 (11–41.8)
Incomplete type	2 (13.3%)	4 (16.7%)	17 (12.6%)
Pre-IVIG laboratory values			
Sampling day of illness	5 (4-5)	5 (5-6)	5 (5-6) (*n* = 134)
Neutrophil counts[*[.015]] (/mm^3)	8811 (6816.5–13437.5) (*n* = 13)	10539 (6833.5–12559.8) (*n* = 21)	7645 (5179–9757.5) (*n* = 112)
Neutrophil %[***[.0000]]	80.1 (75.18–84.25) (*n* = 13)	73.9 (61.9–82.58) (*n* = 21)	61.25 (51.3–70.7)[###[.0001]] (*n* = 112)
NLR[***[.0000]]	5.76 (3.815–10.725) (*n* = 13)	4.18 (2.928–7.773) (*n* = 21)	2.245 (1.295–3.780)[###[.0001]] (*n* = 112)
CRP[*[.017]] (mg/dL)	9.76 (6.10–16.87)	7.93 (5.84–10.05)	6.18 (3.40–10.81)[##[.009]] (*n* = 134)

Data were presented as n (%) or median (interquartile range).
[*]P < .05, [**]P < .01, [***]P < .001, among the three groups. [P value]
[#]P < .05, [##]P < .01, [###]P <.001, vs the rescue group. [P value]
IVIG: intravenous immunoglobulin therapy.
Incomplete type: patients with fewer than five major symptoms of Kawasaki disease.
Sampling day of illness: day of illness when the blood samples for parameters were obtained.
NLR: neutrophil to lymphocyte ratio; CRP: C-reactive protein

Table 2. Comparison of the treatment, laboratory information, and outcomes after initial IVIG therapy among the three groups

Variables	Rescue group	Non-rescue group	Responder group
	n = 15	**n = 24**	**n = 135**
Day of illness at initial IVIG	5 (5-5)	5 (5-6)	5 (5-6)
Aspirin	5	12	77
Flurbiprofen	10	12	58
Defervescence			
Day of illness[***[.0000]]	10 (9–11.8)	8 (8–10)[###[.0005]]	6 (6-7)[###[.0000]]
Days after initial IVIG[***[.0000]]	5 (4–6.8)	3 (2.5-3)[###[.0000]]	1 (1-1)[###[.0000]]
Parameters after initial IVIG			
Sampling day of illness	8 (7.3-8.8)	8 (7.5–9)	8 (8-9)
Days at sampling after IVIG	3 (3-3)	3 (2-3)	3 (2-3)
Neutrophil counts[***[.0000]]	9660	5752.5	2524.5

Variables	Rescue group	Non-rescue group	Responder group
	n = 15	n = 24	n = 135
(/mm^3)	(6981–13695.5)	(3360–7196) $^{\#\#[.002]}$ (*n* = 22)	(1426–3727) $^{\#\#\#[.0000]}$ (*n* = 134)
Neutrophil %$^{***[.0000]}$	75.1 (63.33–78.90)	51.0 (42.30–60.30) $^{\#\#\#[.0007]}$ (*n* = 22)	36.65 (25.40–45.70) $^{\#\#\#[.0000]}$ (*n* = 134)
NLR$^{***[.0000]}$	4.85 (2.378–7.678)	1.645 (1.020-2.670) $^{\#\#[.002]}$ (*n* = 22)	0.745 (0.450-1.170) $^{\#\#\#[.0000]}$ (*n* = 134)
CRP$^{***[.0000]}$ (mg/dL)	9.33 (5.495–11.643)	3.945 (1.970–6.155) $^{\#\#\#[.0007]}$	1.50 (0.693–3.698) $^{\#\#\#[.0000]}$
Neutrophil counts ratio$^{***[.0000]}$	0.88 (0.74-1.45) (*n* = 13)	0.46 (0.40-0.70) $^{\#\#[.009]}$ (*n* = 19)	0.31 (0.18-0.53) $^{\#\#\#[.0000]}$ (*n* = 111)
Neutrophil % ratio$^{***[.0000]}$	0.90 (0.85-1.03) (*n* = 13)	0.69 (0.62-0.82) $^{\#\#[.002]}$ (*n* = 19)	0.58 (0.42-0.74) $^{\#\#\#[.0001]}$ (*n* = 111)
NLR ratio$^{*[.018]}$	0.69 (0.32-1.56) (*n* = 13)	0.28 (0.21-0.66) $^{\#[.046]}$ (*n* = 19)	0.29 (0.16-0.47) $^{\#\#[.005]}$ (*n* = 111)
CRP ratio$^{***[.0000]}$	0.76 (0.64-1.15)	0.46 (0.28-0.56) $^{\#\#\#[.0001]}$	0.24 (0.17-0.38) $^{\#\#\#[.0000]}$ (*n* = 134)
CAL before 30 di	1 (6.7%)	0 (0%)	1 (0.7%)
CAL after 30 di$^{*[.030]}$	1 (6.7%)	0 (0%)	0 (0%)

Data were presented as n (%) or median (interquartile range).
$^{*}P < .05$, $^{**}P < .01$, $^{***}P < .001$, among the three groups. [P value]
$^{\#}P < .05$, $^{\#\#}P < .01$, $^{\#\#\#}P < .001$, vs the rescue group. [P value]
IVIG: intravenous immunoglobulin therapy.
Sampling day of illness: day of illness when the blood samples for parameters were obtained.
NLR: neutrophil to lymphocyte ratio; CRP: C-reactive protein.
CAL: coronary artery lesions.
di: day of illness

Table 3. Results of using analysis by receiver operating characteristic curves for detection of rescue group

Variables	Cut-off value	Sensitivity = specificity	Area under curve
Post neutrophil counts	4587	0.800	0.893
Post neutrophil %	56.5	0.840	0.906
Post NLR	1.78	0.836	0.902
Post CRP	4.54	0.800	0.925
Neutrophil counts ratio	0.62	0.777	0.865
Neutrophil % ratio	0.82	0.839	0.837
NLR ratio	0.43	0.692	0.734
CRP ratio	0.54	0.908	0.953

Post: parameters after initial intravenous immunoglobulin therapy.
NLR: neutrophil to lymphocyte ratio; CRP: C-reactive protein.
Ratio: the ratio of the values after/before initial IVIG therapy

One patient in the rescue group had the highest NLR value (12.65) on day 8 of illness and still had CAL after 30 days of illness (Table 2). This patient had CAL on day 8, and this 2-year-old girl received plasma exchange for three days, beginning on day 9, at the Hirosaki University School of Medicine hospital. Her CAL diameters of the right proximal artery were 4.8 and 2.9 mm on days 21 and 40, respectively, of her illness. However, echocardiography on day 52 of her illness showed regression of CAL and a normal internal coronary artery size. The selective coronary arteriogram performed at 7 months after disease onset revealed no abnormal findings.

Table 4. Results of logistic regression analysis for rescue group

Variables	*P* value	Odds ratio	95% confidence interval
Group 1			
Post neutrophil counts	.43	2.07	0.35–12.46
Post neutrophil %	.63	4.48	0.01–2007.82
Post NLR	.74	2.93	0.006–1459.27
Post CRP	.006	7.73	1.82–32.76
Group 2			
Neutrophil counts ratio	.14	6.64	0.55–80.80
Neutrophil % ratio	.12	8.17	0.58–114.90
NLR ratio	.54	0.40	0.02–7.32
CRP ratio	< .001	66.65	6.95–639.33
Group 3			
Post CRP	.15	3.15	0.65–15.21
CRP ratio	<.001	66.81	7.47–597.66

Post: parameters after initial intravenous immunoglobulin therapy.
NLR: neutrophil to lymphocyte ratio, CRP: C-reactive protein.
Ratio: the ratio of the values after/before initial IVIG therapy

4. DISCUSSION

This study identified the usefulness of the CRP ratio as a parameter for guiding rescue therapy for initial IVIG resistance. The establishment of this parameter is important for the suppression of CAL development caused by Kawasaki disease.

The early and definite determination of likely IVIG-resistant patients is still a challenge [9]. A previous study revealed that an increase in the CRP value after initial IVIG therapy was useful for the prediction of CAL [10]. Furthermore, a recent study showed that the lessened decrement of the NLR before and after IVIG therapy was significantly demonstrated in coronary artery abnormalities [11]. These studies suggest that using both parameters before and after initial IVIG therapy may be useful for identifying IVIG-resistant patients who require rescue therapies to reduce the development of CAL.

In this study, the parameters before and after initial IVIG therapy were investigated, and the logistic regression analysis results showed a statistically significant relationship between the ratio of CRP values and the rescue therapies. Moreover, the CRP ratio had the highest sensitivity and specificity for the rescue group. A previous study showed the usefulness of using CRP values before and after initial IVIG therapy during the period prior to the utilization of the 2 g/kg regimen [10]. This study identified the usefulness of CRP values among patients who received an initial 2 g/kg/dose of IVIG therapy, which is the global standard at present.

The prevalence of IVIG-resistant patients receiving rescue therapies was 8.6% (15/174). This value was lower than the recent nationwide survey of Kawasaki disease in Japan (16%) and a recent Korean study which used IVIG therapy with the delayed use of aspirin (11.7%) [11,12]. In the present study, the prevalence of CAL after 30 day of illness was 0.6% (1/174). This value was lower than the recent nationwide survey of Kawasaki disease in Japan (3%) [12]. Furthermore, the prevalence of CAL larger than 5 mm in size was 0% (0/174). This value was lower than that of the recent Korean study (1.0%) [11]. Therefore, the decision to use rescue therapy in this study might be appropriate based on given the prevalence of the rescue therapy for IVIG-resistant patients and of CAL development. These findings suggest the usefulness of the CRP ratio as an appropriate guide for rescue therapies. The fever duration and the parameters regarding neutrophil counts and CRP values suggest that patients in the rescue group had the highest risk for CAL development among the three groups. Therefore, the use of the highest cut-off value (0.51) of the CRP ratio, which had 100% sensitivity, for the rescue group may be both safe and effective.

A recent study using multivariate analysis revealed that the NLR after IVIG therapy independently predicted coronary artery aneurysm development and IVIG therapy resistance [5]. In the present study, the NLR was

not an independent predictor for the rescue group. However, only one patient with CAL after day 30 of illness had the highest NLR value after initial IVIG therapy. This finding suggests that the NLR after initial IVIG therapy may be a possible predictor for CAL after day 30 of illness.

This study showed the favorable outcome of initial IVIG therapy with DUA in preventing large CAL. In addition to effective rescue therapies, including plasma exchange, removal of the negative impact of anti-inflammatory drugs during initial IVIG therapy by DUA may be another method for suppressing CAL. A recent study revealed that the concomitant use of medium- or higher-dose aspirin with IVIG therapy was inferior to the use of low-dose aspirin, which does not have the same effect as anti-inflammatory drugs, for the suppression of CAL in acute Kawasaki disease [13]. Another, more recent study also suggested the usefulness of the delayed use of low-dose aspirin for preventing large CAL [11]. These findings are consistent with the beneficial effect of removing the negative impact of anti-inflammatory drugs on initial IVIG therapy, and with the favorable outcome of CAL in the present study.

Myocardial ischemia due to 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 significant predictive risk factor for myocardial ischemia as well as that CAL 5 mm in size regressed to a normal size [14]. Another study reported that the threshold diameter for acute phase CAL that developed into subsequent stenosis was 6.0 mm [15]. Therefore, prevention of CAL of > 5 mm may be a major goal in the acute treatment of Kawasaki disease to prevent coronary artery stenosis in later stages of the disease [16]. In this study, CAL were evaluated in mm for the entire population because of the goal of preventing coronary artery stenosis in later stages.

Currently, international criteria for CAL is based on z-score [17]. Japanese criteria do not account for patient size, which can substantially affect normal coronary artery dimensions, potentially leading to underdiagnosis and underestimation of the true prevalence of coronary artery dilation [17,18].

The limitations of this study were the use of a small number of IVIG-resistant patients and the study's retrospective nature. The usefulness of the CRP ratio should be confirmed in a larger study.

5. CONCLUSION

The CRP ratio, defined as the ratio of after/before IVIG therapy, may be the most useful parameter for guiding rescue therapies among the IVIG-resistant patients who received an initial single IVIG therapy dose with DUA for Kawasaki disease.

CONSENT

It is not applicable.

ETHICAL APPROVAL

I received approval for this study from our institutional ethics committee with a waiver of consent.

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COMPETING INTERESTS

Author has declared that no competing interests exist.

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