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Outcomes of Older Children with Kawasaki Disease Who Received Intravenous Immunoglobulin Therapy with Delayed Use of Anti-inflammatory Drugs

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Author's contribution

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

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Original Research Article

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ABSTRACT

Background: The prevalence of coronary artery lesions (CAL) is higher in older children compared with younger children. Anti-inflammatory drugs including aspirin appeared to have a negative impact on the suppressive effects of initial intravenous immunoglobulin (IVIG) therapy for CAL development during the acute phase of Kawasaki disease and an initial single IVIG therapy with the delayed use of anti-inflammatory drugs (DUA) might be effective for CAL suppression. The outcomes regarding CAL and non-cardiac complications after single IVIG therapy with DUA remain unclear.
Aims: To ascertain the outcomes of the older children with Kawasaki disease who received single IVIG therapy with DUA.
Methods: The retrospective data of 25 children who were ≧ 60 months old and received this therapy between 2004 and 2017 in our department were collected and outcomes were investigated. Anti-inflammatory drugs were initiated within 24 hours after the end of initial IVIG infusion.
Results: No patients were associated with CAL. However, three patients were associated with

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non-cardiac complications including transient blindness, intractable arthritis, and prolonged restriction of cervical movement caused by atlantoaxial rotatory fixation. All three children were IVIG therapy-resistant and had statistically higher C-reactive protein values (median: 9.64 interquartile range: 7.82-18.29 vs. 1.905: 0.76-4.77 mg/dL, *P* = 0.007), neutrophil counts (9545: 9312-9660 vs. 2766.5: 1936-3812 /mm3, *P* = 0.006), and neutrophil to lymphocyte ratios (10.38: 4.85-11.29 vs. 1.44: 0.92-2.69, *P* = 0.006) after IVIG therapy compared to those without complications.

Conclusion: Initial IVIG therapy-resistant three patients with high values of inflammatory biomarkers after initial therapy with DUA were associated with non-cardiac complications.

Keywords: Kawasaki disease; older children; intravenous immunoglobulin therapy; anti-inflammatory drugs; coronary artery lesions; complications; inflammatory biomarkers.

ABBREVIATIONS

CAL: Coronary artery lesions, IVIG: Intravenous immunoglobulin, DUA: Delayed use of anti-inflammatory drugs, NLR: Neutrophil to lymphocyte ratio, AARF: atlantoaxial rotatory fixation.

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. The previous study had disclosed that anti-inflammatory drugs including aspirin appeared to have a negative impact on the suppressive effects of initial intravenous immunoglobulin (IVIG) therapy for CAL development during the acute phase of Kawasaki disease and that an initial single IVIG therapy dose with the delayed use of anti-inflammatory drugs (DUA) might be effective for CAL suppression [2]. The recent study regarding this regimen disclosed the safety and efficacy for suppression of CAL development caused by Kawasaki disease [3]. However, outcomes of older children who received this therapy regarding CAL and non-cardiac complications remain unclear. The objective of this study is to ascertain the outcomes of the older children with Kawasaki disease who received this therapy.

2. PATIENTS AND METHODS

This retrospective study included 25 consecutive patients who were ≧ 60 months old and received an initial full dose IVIG therapy of 2 g/kg body weight/dose with DUA (aspirin or flurbiprofen) for Kawasaki disease between January 2004 and February 2017 in our department. The retrospective data of those patients were collected and outcomes, including CAL and non-cardiac complications required therapies, were investigated. I excluded one patient who developed left ventricular dysfunction with a different protocol, including plasma exchange in the early stage.

Diagnosis of Kawasaki disease was based on Japanese Criteria (Fifth Edition) [4]. IVIG therapy-resistance was defined if fever persisted or reappeared at 24 hours after first-line treatment. Neutrophil to lymphocyte ratio (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 were initiated within 24 hours after the end of initial IVIG infusion.

The choice between aspirin and flurbiprofen was made by each doctor after considering the patient's liver function and risk of Reye syndrome during the influenza season. Flurbiprofen was used in cases of severe aspirin hepatotoxicity, and Reye syndrome is not mentioned as an adverse effect or in flurbiprofen precautions [5]. Flurbiprofen was used in patients with liver dysfunction at risk for aspirin hepatotoxicity. Flurbiprofen was more commonly used before 2009 because of its advantage for hepatic dysfunction and Reye syndrome. Aspirin was more commonly used after 2009 because aspirin use became a global standard for Kawasaki disease. 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.

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 [2].

2.2 Rescue Therapy

The decision for using 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.

Second-line therapy was rescue IVIG therapy, and third-line therapy was ulinastatin infusion. Plasma exchange was adopted after 2014 as another third-line therapy option. This regimen has been approved in our institution [6,7].

2.3 Diagnosis of CAL

CAL was diagnosed by echocardiography based on Japanese Criteria [8]. CAL was diagnosed when any of these examinations had an internal lumen 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 a disappearance of CAL within 30 days of illness.

2.4 Statistical Analysis

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

3. RESULTS

Table 1 showed the demographic data of the patients. No patients were associated with CAL. However, three patients were associated with non-cardiac complications, including transient blindness, intractable arthritis, and prolonged restriction of cervical movement caused by atlantoaxial rotatory fixation (AARF) (Table 2). All three children were initial IVIG therapy-resistant and received rescue therapies (Table 2).

The patients associated with complications had statistically higher C-reactive protein values, neutrophil counts, and NLR after initial IVIG therapy compared to those without complications (Table 3). Furthermore, the prevalence of resistance and rescue therapies for resistance in patients with complications were significantly higher than those without (Table 3).

4. DISCUSSION

Initial IVIG therapy-resistant patients with high values of inflammatory biomarkers after initial therapy with DUA might be associated with non-cardiac complications. Although no patients were associated with CAL, three patients associated with non-cardiac complications. Three patients were IVIG-resistant, and persistent inflammation after initial therapy might lead to non-cardiac complications.

Ocular involvement in the acute phase of Kawasaki disease typically involves the anterior segment of the eye, and its associated treatment outcomes are generally excellent. However, there are rare reports of posterior segment involvement, and these are associated with poorer outcomes [9-11]. The persistent inflammation caused by Kawasaki disease may lead to ocular posterior segment involvement [10]. The causes of transient blindness in the patient 1 (Table 2) were considered to be compression of the optic disc via increased intraocular pressure due to uveitis and possible subclinical optic perineuritis [12]. This patient did not receive corticosteroid therapy.

The prevalence of arthritis in the acute phase of Kawasaki disease was 7.5% [13]. Most cases of arthritis resolve without additional therapeutic intervention. Rescue therapy was necessary in 13% of the patients with arthritis, and 4% required additional corticosteroid treatment [13]. Patient 2 associated with intractable arthritis was also initial IVIG therapy-resistant and had high values of inflammatory biomarkers after initial therapy (Tables 2, 3). The additional corticosteroid treatment as 4th line therapy

Table 1. Demographic data of the 25 patients

Sex	**11 boys and 14 girls**
Age	Median: 6 years, 5 months (age range, 5 years to 13 years, 3 months)
Start time of initial IVIG therapy	Median: the sixth day of illness (range, day 4–13 of illness)
Aspirin / flurbiprofen	15/10 patients
Incomplete type	4/25 patients (16%)
Initial IVIG therapy resistance	8/25 patients (32%)
Rescue IVIG therapy for initial IVIG resistance	3/25 patients (12%)
Third-line therapy for resistance	1/25 patient (4%) received ulinastatin infusion.
Complications	
Coronary artery lesions	0/25 patients (0%)
Non-cardiac complications required therapies	3/25 patients (12%)

IVIG: intravenous immunoglobulin
Incomplete type: patients with fewer than five major symptoms of Kawasaki disease

Table 2. Clinical findings of the three patients associated with complications

Patient number	**1**	**2**	**3**
Sex	Female	Female	Male
Age	12 years, 4 months	8 years, 9 months	5 years, 4 months
Initial IVIG therapy	5th day of illness	7th day of illness	5th day of illness
Response	Resistant	Resistant	Resistant
Rescue IVIG therapy	9th day of illness	10th day of illness	9th day of illness
Symptoms after 12th day of illness	Transient blindness	Intractable arthralgia	Persistent restriction of cervical movement
Complications	Uveitis	Arthritis	Atlantoaxial rotatory fixation
	Increased intraocular pressure		
	Possible optic perineuritis		
Therapies for complications	Topical ß-blocker	Ulinastatin	Glisson traction
	Topical steroids	Steroids	
Outcomes	Recovered	Recovered	Recovered

IVIG: intravenous immunoglobulin

resolved intractable arthritis caused by prolonged inflammation due to Kawasaki disease (Table 2).

AARF is a rare complication of Kawasaki disease [14]. AARF is frequently observed in infants and school-age children; some reasons for this may include features pertaining to physical development and anatomy in children, such as insufficient bony structural support, loose capsule and large torsion angle as well as large proportion of soft tissue in atlantoaxial joint and direct connection of the pharyngeal lymph vessels to the venous plexus. These features predispose children to being susceptible to inflammation of atlantoaxial joint [15]. Inflammatory processes of Kawasaki disease at the neck might cause ligament hypermobility, with distension and abnormal laxity of ligaments surrounding the neck articulation and sternomastoid spasm [15]. Persistent inflammation after initial therapy might be the predisposing factor of the prolonged restriction of cervical movement caused by AARF in patient 3 (Tables 2, 3).

An onset at an older age is an independent risk factor for the development of cardiovascular sequelae in Kawasaki disease [16]. The prevalence of CAL is higher in older children than in younger children [17]. This study suggested

Table 3. Comparison of the clinical findings between patients with complications and those without

	Patients with complications n = 3	Patients without n = 22	*P* value
Sex (male)	1 (33.3%)	10 (45.5%)	1.0
Age (months)	105 (64-148)	76 (68-95)	.50
Incomplete type	2 (66.7%)	2 (9.1%)	.06
Initial IVIG therapy	5th (5-7) day of illness	6th (5-6) day of illness	.79
Aspirin	2	13	1.0
Flurbiprofen	1	9	
Resistance for initial IVIG therapy	3 (100%)	5 (22.7%)	.02
Sampling day of illness after initial IVIG therapy	9 (8-9)	9 (8-10)	.86
C-reactive protein value (mg/dL)	9.64 (7.82-18.29)	1.905 (0.76-4.77)	.007
Neutrophil counts (/mm3)	9545 (9312-9660)	2766.5 (1936-3812)(n = 20)	.006
Lymphocyte counts (/mm3)	920 (856-1922)	1942.5 (1429.5-2252) (n = 20)	.10
Neutrophil to lymphocyte ratio	10.38 (4.85-11.29)	1.44 (0.92-2.69)(n = 20)	.01
Rescue therapies	3 (100%)	0 (0%)	< .001
3rd line therapy	1 (33%)	0 (0%)	.12
Coronary artery lesions	0 (0%)	0 (0%)	1.0

Data were presented as n (%) or median (interquartile range).
Incomplete type: patients with fewer than five major symptoms of Kawasaki disease.
IVIG: intravenous immunoglobulin.

that an initial full dose IVIG therapy of 2 g/kg body weight/dose with DUA may be useful for suppression of CAL caused by Kawasaki disease in older children.

Patients who received initial IVIG with DUA may not receive a negative impact of the suppressive effects of anti-inflammatory drugs to IVIG therapy until the start time of anti-inflammatory drugs administration. However, patients who received initial IVIG therapy with concomitant use of anti-inflammatory drugs may receive a negative impact of anti-inflammatory drugs during IVIG therapy. This difference may be relevant to the superior efficacy of IVIG with DUA to that of IVIG with concomitant use of anti-inflammatory drugs [2,18]. Only one of 163 patients who received IVIG therapy with DUA had CAL after day 30 of illness in our recent study [19]. The prevalence of CAL was 0.6% (1/163); 95% confidence interval was 0.6 to 3.4%. On the other hand, the recent 22nd nationwide survey of Kawasaki disease in Japan, where the concomitant use of medium-dose aspirin was standard, showed that 3% of patients had associated CAL after 30 days of illness [20].

The recent study using logistic regression analysis showed that the type of anti-inflammatory drug (aspirin or flurbiprofen) was not a significant factor for CAL suppression [2].

The recent study showed the safety and efficacy of full-dose infusion of an initial 2 g/kg/dose IVIG therapy with DUA in older children with Kawasaki disease, and that none of the children had any major complications, including thrombosis [21]. These clinical findings were consistent with the results of a previous study; high-dose therapy with intact IVIG had inhibitory effects on platelet adhesion and thrombus formation [22]. A single infusion of high-dose IVIG during the acute phase of Kawasaki disease increased blood viscosity [23]. However, the prevalence of thrombosis after IVIG therapy in the acute phase of Kawasaki disease has been rare in children [24]. One factor for this finding may be due to an inhibitory effect on platelet adhesion and thrombus formation of intact IVIG [22].

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 [25]. Another study reported that the threshold diameter for acute phase CAL that developed into subsequent stenosis was 6.0 mm [26]. 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 [18]. In this study, CAL were evaluated in mm for the entire population because of the goal of preventing coronary artery stenosis in later stages.

Recent study showed that Kawasaki disease might frequently be undiagnosed especially in adult patients due to the factors including incomplete type and atypical complications such as renal impairment, acute surgical abdomen, and pleural effusion [27]. Our patients were not associated with those atypical complications and the prevalence of incomplete type was similar to that of previous study [16].

The limitations of this study were the small number of patients and the retrospective nature of the study.

5. CONCLUSIONS

Although no patients were associated with CAL, 3 of 25 patients were associated with non-cardiac complications after initial single IVIG therapy with DUA. Initial IVIG therapy-resistant patients with high values of inflammatory biomarkers after initial therapy with DUA might be associated with non-cardiac complications.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

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COMPETING INTERESTS

Author has declared that no competing interests exist.

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