The strategy of immune globulin resistant Kawasaki disease: A comparative study of additional immune globulin and steroid pulse therapy

Shohei Ogata (MD)a, Yuki Bando (MD)a, Sumito Kimura (MD)a, Hisashi Ando (MD)a, Yayoi Nakahata (MD)a, Yoshihito Ogihara (MD)b, Tadahiro Kaneko (MD)b, Katsunori Minoura (MD)b, Miho Kaida (MD)c, Yukifumi Yokota (MD)c, Shinsuke Furukawa (MD)a, Masahiro Ishii (MD, FJCC)a.

a Department of Pediatrics, Kitasato University, 1-15-1 Kitasato, Sagamihara, Kanagawa 228, Japan
b Ebina General Hospital, Ebina, Kanagawa, Japan
c Sagamihara Kyodo Hospital, Sagamihara, Kanagawa, Japan

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KEYWORDS
Kawasaki disease; Intravenous immunoglobulin treatment; Steroid pulse therapy; Re-treatment; Coronary aneurysm; Vasculitis

Summary
Background: We compared the clinical utility of additional intravenous immune globulin (IVIG) therapy with the clinical utility of steroid pulse therapy in patients with IVIG-resistant Kawasaki disease.

Methods: We enrolled 164 patients with Kawasaki disease who were treated with a single dose of IVIG (2 g/kg) and aspirin (30 mg/kg per day). Twenty-seven of these patients (16%) were resistant to the initial IVIG treatment. We compared the effectiveness of treatment strategies for the initial IVIG-resistant 27 patients, 14 of these patients were treated with additional IVIG therapy, and the other 13 patients were treated with steroid pulse therapy (methylprednisolone 30 mg/kg per day for 3 days).

Results: Three patients in the group receiving additional IVIG treatment had coronary artery aneurysms (21.4%), no patients had coronary artery aneurysm in the steroid pulse therapy group; the difference in the incidence of coronary artery aneurysm was not statistically significant. The duration of high fever after additional treatment...
in the steroid pulse therapy group (1 ± 1.3 days) was significantly shorter than that in the additional IVIG treatment group (3 ± 2.4 days; \( P < 0.05 \)). The medical costs were significantly lower in the steroid pulse therapy group than in the additional IVIG treatment group.

**Conclusion:** Steroid pulse therapy was useful to reduce the fever duration and medical costs for patients with Kawasaki disease. Steroid pulse therapy and additional IVIG treatment were not significantly different in terms of preventing the development of coronary artery aneurysm.

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**Introduction**

Kawasaki disease (KD) is an acute febrile illness characterized by mucosal inflammation, skin rash, and cervical lymphadenopathy, and is observed most often in children younger than 4 years of age [1]. This is an acute vasculitis syndrome of unknown etiology that affects primarily small- and medium-sized arteries, particularly the coronary artery [2]. Treatment for KD has been the subject of many studies [3–6]. Recently, the administration of high-dose intravenous immune globulin (IVIG) has been observed to reduce both the duration of fever and the incidence of coronary artery aneurysms (CAA) when given within a few days of disease onset [7–9]. Nonetheless, approximately 10–20% of patients have persistent or recurrent fever despite IVIG treatment [3,6,10,11]. The risk of CAA is increased in these patients, and there have been few studies on the optimal management of such cases [3,6,10,11]. In a recent small-randomized trial, Hashino et al. compared the efficacy of additional IVIG treatment with the efficacy of steroid pulse therapy for IVIG treatment-resistant KD patients [3]. The aim of the present study was to compare the effectiveness of additional IVIG treatment with that of steroid pulse therapy for KD patients who showed resistance to initial IVIG treatment.

**Methods**

**Patients**

One hundred and sixty-four patients, ranging in age from 2 months to 10 years, were included in the study. They were treated at Kitasato University, Ebina General Hospital, and Sagamihara Kyodo Hospital between April 2004 and May 2007. The diagnosis of KD was made according to criteria established by the Japanese Kawasaki Disease Research Committee [12].

**Initial treatment**

All patients were initially treated with a single dose of IVIG (2 g/kg per day) in a single infusion over a 24-h period and were administered aspirin orally (30 mg/kg per day) within the first 9 days of the onset of fever. We defined a responder as a patient who showed resolution of fever (<37.5°C) and a fall in C-reactive protein (CRP) of more than 50% within 36–48 h after initial IVIG treatment [3,12–14]. These patients were treated with steroid pulse therapy or additional IVIG.

**Additional IVIG treatment and steroid pulse therapy**

Twenty-seven patients (16%) showed no clinical response at 36–48 h after initial IVIG treatment. Thirteen non-responders were treated at Kitasato University Hospital, and these patients were treated with steroid pulse therapy (group 1: methylprednisolone 30 mg/kg per day for 3 days). The remaining 14 patients were treated at Ebina General Hospital and Sagamihara Kyoudo Hospital with additional IVIG treatment (group 2). There were no significant differences in gender, age, or duration of illness between the 2 groups (Table 1). During steroid pulse infusion and IVIG treatment patients underwent continuous cardiac monitoring and their blood pressure was determined every 30 min. Frequent evaluations were made after the infusion until vital signs were stable and within normal limits.

**Calculation of medical cost**

In calculation of medical cost the hospitalization basic charge, clinical test (laboratory test, electrocardiograph, echocardiography, etc.) costs, disposal costs, cost of procedures and cost of drugs were included. The medical costs were calculated from admission to discharge.
Table 1  Age, gender, and duration of illness on admission

<table>
<thead>
<tr>
<th>Group 1</th>
<th>Group 2</th>
<th>(P)</th>
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<tbody>
<tr>
<td>Age</td>
<td>1 year 2 months ± 1 year 5 months</td>
<td>2 years 9 months ± 2 years 0 month</td>
</tr>
<tr>
<td>Gender (male:female)</td>
<td>7:5</td>
<td>9:4</td>
</tr>
<tr>
<td>Duration of illness</td>
<td>5 ± 0.3 days</td>
<td>4 ± 1.3 days</td>
</tr>
</tbody>
</table>

Group 1, steroid pulse therapy group; group 2, IVIG treatment group.

**Statistical analysis**

All data are expressed as the median ± S.D. Mann–Whitney’s U-test was used for the two-way comparison of data. Values were considered significantly different at \(P < 0.05\).

**Results**

**Results of treatment**

One hundred and sixty-four sequential patients were treated with IVIG (2 g/kg) immediately after being diagnosed with KD. One hundred and thirty-seven of these patients (84%) were clinical responders to the initial treatment, and none of these patients showed coronary artery abnormalities. However, the remaining 27 patients (16%) showed no clinical response. These patients were treated with either steroid pulse therapy (methylprednisolone 30 mg/kg per day for 3 days) or additional IVIG (2 g/kg). The 13 IVIG-resistant patients at Kitasato University Hospital were treated with steroid pulse therapy (group 1), and the 14 IVIG-resistant patients at Ebina General Hospital and Sagamihara Kyodo Hospital were treated with additional IVIG treatment (group 2) within 36–48 h after initial IVIG treatment. Although 2 patients developed bradycardia in the steroid pulse group, these cases improved spontaneously.

**Incidence of CAA**

CAA occurred in 3 patients (21.4%) in the additional IVIG treatment group (group 2). One patient had a giant coronary aneurysm, and the other 2 patients had small aneurysms. No patients had CAA in the steroid pulse therapy group (group 1). There was no statistically significant difference in the incidence of CAA between the 2 groups.

**Duration of fever**

No significant difference was found between the 2 groups with regard to illness days before additional treatment (Table 2). The duration of fever (>37.5 °C) after additional treatment in patients treated with steroid pulse therapy (1 ± 1.3 days) was significantly shorter than that in patients treated with additional IVIG treatment (3 ± 2.4 days; \(P < 0.05\)). A significant difference was found in the total duration of fever between the 2 groups (8 ± 2.1 days in group 1 versus 11 ± 2.0 days in group 2; \(P < 0.05\)).

**Laboratory data**

Laboratory data on admission and after initial treatment are shown in Tables 2 and 3. Except for

Table 2  Illness day and laboratory data on additional treatment

<table>
<thead>
<tr>
<th></th>
<th>Group 1</th>
<th>Group 2</th>
<th>(P)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Illness day</td>
<td>7 ± 1.3</td>
<td>8 ± 2.4</td>
<td>NS</td>
</tr>
<tr>
<td>WBC ((\mu)l)</td>
<td>12,500 ± 1,029</td>
<td>10,700 ± 3,769</td>
<td>NS</td>
</tr>
<tr>
<td>Neutrophils (%)</td>
<td>67 ± 10</td>
<td>64 ± 16</td>
<td>NS</td>
</tr>
<tr>
<td>Ht (%)</td>
<td>32 ± 2</td>
<td>33 ± 2</td>
<td>NS</td>
</tr>
<tr>
<td>Platelets ((\times)10⁴)</td>
<td>32 ± 15</td>
<td>50 ± 15</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>CRP (mg/dl)</td>
<td>4.3 ± 1.7</td>
<td>5.9 ± 4.0</td>
<td>NS</td>
</tr>
<tr>
<td>AST (IU)</td>
<td>35 ± 16</td>
<td>34 ± 21</td>
<td>NS</td>
</tr>
<tr>
<td>ALT (IU)</td>
<td>28 ± 60</td>
<td>26 ± 44</td>
<td>NS</td>
</tr>
<tr>
<td>Na (mequiv./l)</td>
<td>134 ± 2.5</td>
<td>133 ± 2.6</td>
<td>NS</td>
</tr>
<tr>
<td>Albumin (mg/dl)</td>
<td>4 ± 2.4</td>
<td>3.9 ± 0.4</td>
<td>NS</td>
</tr>
</tbody>
</table>

Data are the mean ± S.D. WBC, white blood cells; Ht, hematocrit; CRP, C-reactive protein; AST, aspartate aminotransferase; ALT, alanine aminotransferase.

Group 1, steroid pulse therapy group; group 2, IVIG treatment group.
neutrophils, no significant difference was found between the 2 groups with regard to laboratory data on admission (Table 3). In the 36—48 h after initial treatment, except for platelet count, no significant difference was found in laboratory data between the 2 groups (Table 2). However, 36—48 h after additional treatment, the CRP level in group 1 patients (0.6 ± 1.4 mg/dl) was significantly lower than that in group 2 patients (1.7 ± 4.9 mg/dl; P < 0.05).

### Medical cost and duration of hospital stays

The medical costs for the 2 therapies were calculated to be 290,610 ± 57,477 yen (group 1) and 918,300 ± 61,405 yen (group 2), respectively. The medical costs of patients treated with steroid pulse therapy were significantly lower than those of patients treated with additional IVIG treatment (P < 0.05). There was no significant difference in hospital stay in patients treated with steroid pulse therapy and that in patients treated with additional IVIG (14.5 ± 2.0 days group 1 versus 12 ± 2.1 days group 2).

### Discussion

#### CAA

There was no statistically significant difference in the incidence of CAA between the 2 groups. In the present study, 3 patients who were treated with additional IVIG therapy developed a CAA. However, no patients treated with steroid pulse therapy had a CAA. Steroid pulse therapy, which has various anti-inflammatory effects, is widely used for the clinical treatment of inflammatory and autoimmune disorders [3—6,15,16]. Both IVIG treatment and steroid pulse therapy may inhibit the production of cytokines that act in the reconstruction of the inflamed coronary artery wall. Makata et al. previously reported that steroid therapy resulted in a more wide inhibition of inflammatory cells compared with immunoglobulin treatment in cultured cells setting [17]. However, it remains unclear whether steroid pulse therapy affects the coronary artery wall, particularly in the long-term [18—20]. The long-term effect of steroid pulse therapy on the coronary arteries (i.e., the incidence of regression, the occurrence of stenosis or obstruction, the development of aneurysms, and endothelial function) has not been clarified. Further investigation of the long-term outcome of the coronary arteries in KD patients treated with steroid pulse therapy and estimation of the endothelial function of coronary arteries in KD patients is needed. In addition, prospective studies will be needed to assess the long-term benefits or disadvantages to patients who receive steroid pulse therapy or additional IVIG treatment.

### Clinical implications

A previous meta-analysis reported on the effectiveness of steroids in KD treatment [21]. However, Newburger et al. reported that the effectiveness of steroid pulse therapy in initial treatment is not recognized [22]. In the present study, we first demonstrated the clinical utility of steroid pulse therapy as a second treatment in IVIG treatment-resistant KD patients. The duration of fever after additional treatment in the steroid pulse therapy group was significantly shorter than that in the additional IVIG treatment group. In addition, the medical costs were lower in the steroid pulse therapy group. It should be noted, however, that this study employed only a small number of patients and was not randomized. In the future, a randomized prospective study involving multiple treatment centers may be necessary to examine the clinical utility of additional therapy for KD patients resistant to initial IVIG treatment.

<table>
<thead>
<tr>
<th>Table 3</th>
<th>Laboratory data on admission</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Group 1</td>
</tr>
<tr>
<td>WBC (μl)</td>
<td>14,200 ± 5,435</td>
</tr>
<tr>
<td>Neutrophils (%)</td>
<td>77 ± 24</td>
</tr>
<tr>
<td>Ht (%)</td>
<td>32 ± 2</td>
</tr>
<tr>
<td>Platelets (×10^4)</td>
<td>31 ± 11</td>
</tr>
<tr>
<td>CRP (mg/dl)</td>
<td>7.3 ± 9.8</td>
</tr>
<tr>
<td>AST (IU)</td>
<td>40 ± 533</td>
</tr>
<tr>
<td>ALT (IU)</td>
<td>26 ± 207</td>
</tr>
<tr>
<td>Na (mequiv./l)</td>
<td>133 ± 1.9</td>
</tr>
<tr>
<td>Albumin (mg/dl)</td>
<td>3.8 ± 0.4</td>
</tr>
</tbody>
</table>

Data are the mean ± S.D. WBC, white blood cells; Ht, hematocrit; CRP, C-reactive protein; AST, aspartate aminotransferase; ALT, alanine aminotransferase. Group 1, steroid pulse therapy group; group 2, IVIG treatment group.
Conclusions

Steroid pulse therapy was useful to reduce the fever duration and medical costs in KD patients. Steroid pulse therapy may be as effective as additional IVIG treatment to prevent the development of CAA.

References


