Efficacy of primary treatment with immunoglobulin plus ciclosporin for prevention of coronary artery abnormalities in patients with Kawasaki disease predicted to be at increased risk of non-response to intravenous immunoglobulin (KAICA): a randomised controlled, open-label, blinded-endpoints, phase 3 trial


Summary
Background Genetic studies have indicated possible involvement of the upregulated calcium-nuclear factor of activated T cells pathway in the pathogenesis of Kawasaki disease. We aimed to assess safety and efficacy of ciclosporin, an immunosuppressant targeting this pathway, for protection of patients with Kawasaki disease against coronary artery abnormalities.

Methods We did a randomised, open-label, blinded endpoints trial involving 22 hospitals in Japan between May 29, 2014, and Dec 27, 2016. Eligible patients predicted to be at higher risk for intravenous immunoglobulin (IVIG) resistance were randomly assigned to IVIG plus ciclosporin (5 mg/kg per day for 5 days; study treatment) or IVIG (conventional treatment) groups, stratified by risk score, age, and sex. The primary endpoint was incidence of coronary artery abnormalities using Japanese criteria during the 12-week trial, assessed in participants who received at least one dose of study drug and who visited the study institution at least once during treatment. This trial is registered to Center for Clinical Trials, Japan Medical Association, number JMA-IIA00174.

Findings We enrolled 175 participants. One patient withdrew consent after enrolment and was excluded and one patient (in the study treatment group) was excluded from analysis because of lost echocardiography data. Incidence of coronary artery abnormalities was lower in the study treatment group than in the conventional treatment group (12 [14%] of 86 patients vs 27 [31%] of 87 patients; risk ratio 0·46; 95% CI 0·25–0·86; p=0·010). No difference was found in the incidence of adverse events between the groups (9% vs 7%; p=0·78).

Interpretation Combined primary therapy with IVIG and ciclosporin was safe and effective for favourable coronary artery outcomes in Kawasaki disease patients who were predicted to be unresponsive to IVIG.

Funding Japan Agency for Medical Research and Development (grant CCT-B-2503).

Introduction
Kawasaki disease is an acute vasculitis of unknown cause that predominantly affects infants and young children,¹ causes coronary artery abnormalities such as aneurysms and dilations in about 25% of untreated patients,² and is the leading cause of acquired heart disease in children in high-income countries.³ In the five decades that have passed since the initial recognition of Kawasaki disease, cardiologists have been increasingly involved in the management of adult patients with Kawasaki disease.⁴ Japan has the highest incidence of Kawasaki disease (265 cases per 100000 children <5 years of age) worldwide.⁵ In the USA, the national incidence in children younger than 5 years is 19 per 100000.⁶ An important genetic contribution to disease susceptibility is assumed because of the higher incidence among children of Japanese ancestry in Hawaii (210 per 100000) and of Asian or Pacific Islander descent in California (50·4 per 100000). USA.⁷ Intravenous immunoglobulin (IVIG) administered in the acute phase can reduce the incidence of coronary artery abnormalities.⁸ However, about 20% of patients develop persistent or recrudescent fever after standard therapy with IVIG and aspirin.⁹ Furthermore, IVIG resistance is a well-recognised risk
Evidence before this study
We searched PubMed for articles in English with a combination of the search terms “Kawasaki disease” and “Cyclosporine”. We excluded review articles and evaluated case reports, animal studies, retrospective comparisons, and clinical trials. We identified several reports worldwide about the use of calcineurin inhibitors for treatment-resistant Kawasaki disease. A report of case series in the USA indicated safety and effectiveness of using calcineurin inhibitors for refractory Kawasaki disease patients. A phase 2 trial of ciclosporin for Japanese patients with Kawasaki disease resistant to both initial and additional intravenous immunoglobulin treatment showed deferescence within 5 days in 79% of patients without serious adverse effects.

Added value of this study
Findings from our randomised study show that intravenous immunoglobulin combined with ciclosporin is better than intravenous immunoglobulin alone as the primary treatment in prevention of coronary artery abnormalities for Japanese patients with refractory Kawasaki disease. In this group, shorter duration of fever and smaller proportion of primary therapy nonresponders were also seen, but relapse increased and overall use of additional therapy was similar.

Implications of all the available evidence
Further study to establish an intensified primary therapy protocol for this disease, in which the best option is appropriately selected for the individual patient, is warranted. Pharmacogenetics data in this study suggest the possibility of enhanced efficacy for ciclosporin in the carriers of ITPKC and CASP3 risk-associated alleles.

Methods
Study design and participants
The study protocol of the Kawasaki disease study to assess the efficacy of immunoglobulin plus ciclosporin A (KAICA trial) has been published previously. This trial was registered to the Center for Clinical Trials, Japan Medical Association on April 2, 2014, and done at 22 hospitals in Japan.

Patients were diagnosed as having Kawasaki disease according to the Japanese diagnostic guidelines. Patients who had at least five of the six major symptoms were diagnosed as having Kawasaki disease. Patients with only four of the six major symptoms can be diagnosed as having Kawasaki disease if they have coronary artery abnormalities. However, we excluded these patients to evaluate effects of Kawasaki disease therapy on prevention of coronary artery abnormalities. In the case of fever, the symptom was assigned as one major symptom if it occurred after 1 day or more of the other five major symptoms.

Evaluated endpoints were clinical reasons to introduce therapy (as the end point to prevent coronary abnormalities) and change in fever duration. Fever duration was calculated from the day fever started to the day when fever was no longer present or the day before admission to hospital for any reason. Fever duration was measured in days.

Results
Findings from our randomised study show that intravenous immunoglobulin combined with ciclosporin is better than intravenous immunoglobulin alone as the primary treatment in prevention of coronary artery abnormalities for Japanese patients with refractory Kawasaki disease. In this group, shorter duration of fever and smaller proportion of primary therapy nonresponders were also seen, but relapse increased and overall use of additional therapy was similar.
glomerular filtration rate of ≤50 mL/min per 1·73 m² or lower) dysfunction were also excluded. The full inclusion and exclusion criteria are listed in the appendix.

This trial was done in accordance with the Declarations of Helsinki and in compliance with Good Clinical Practice and other applicable regulatory requirements. The protocol was approved by the institutional review board at all participating institutions. All patients or their legal guardians received adequate information by use of an informed consent form approved by the institutional review board. We obtained signed consent forms from all guardians and assent if patients were aged 13 years or older; assent was obtained from five patients (aged between 95 and 135 months).

**Randomisation and masking**

We registered patients in a database on a cloud-based platform. After validation of eligibility, the patients were randomly allocated to 1:1 the study treatment group or conventional treatment group by the dynamic allocation method using risk score at enrolment (7 points or <6 points), age (12 months or <12 months), and sex as adjustment factors. Investigators were immediately notified of the group assignment by the allocation system. Patients and treating physicians were not masked to assignment. Echocardiography assessments were masked to treatment assignment.

**Procedures**

Patients in the conventional treatment group received initial treatment of IVIG 2·0 g/kg for 24 h and aspirin 30 mg/kg per day. Patients in the study treatment group received ciclosporin 5·0 mg/kg per day orally divided into two daily doses for 5 days in addition to IVIG and aspirin. Plasma ciclosporin concentrations were measured immediately before oral administration in the morning on treatment day 3 and 5. The dose of ciclosporin could be increased or decreased from 5 mg/kg per day for patients whose ciclosporin trough level was outside the effective concentration of 60–200 ng/mL. In the conventional treatment group, a matched placebo was not administered because it was not technically feasible. No enrolled patients in either groups received adjunctive steroid therapy.

An additional dose of IVIG 2·0 g/kg was administered to patients whose body temperature was more than 37·5°C at 48 h (±1 h) after initiation of the primary therapy, patients who were defined as non-responders, or patients who had Kawasaki disease relapse, defined as a return of fever (≥37·5°C) without another likely source after an afebrile period of 48 h or more from the initiation of primary therapy. Patients whose body temperature did not drop to below 37·5°C at 24 h after the initiation of the second dose of IVIG received third-line therapy according to the accepted treatment guidelines, including a third dose of IVIG and corticosteroids, intravenous meprednisolone, infliximab, ulinastatin, and plasmapheresis. Ciclosporin was available for patients who developed coronary artery abnormalities at that timepoint.

Body temperatures were measured three times a day by the infra-axillary thermometry method using digital thermometers that had been provided and calibrated by the study committee. The highest value of the three measurements in each day was selected and used for the analyses. Patients were judged to be defervescent when they were continuously afebrile for 24 h. The defervescent timepoints were retrospectively defined as those 24 h before the judgment.

Any deviations from the protocol were recorded and discussed by the steering committee.

**Outcomes**

The primary endpoint was incidence of coronary artery abnormalities from treatment day 3 to week 12. Coronary
Coronary artery outcome

**Table 2:**

<table>
<thead>
<tr>
<th>Days of evaluation</th>
<th>IVIG plus ciclosporin (n=86)</th>
<th>IVIG (n=87)</th>
<th>p value</th>
<th>Risk ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 4</td>
<td>2 (2%)</td>
<td>1 (1%)</td>
<td>0.17</td>
<td>0.35 (0.07-1.67)</td>
</tr>
<tr>
<td>Week 1*</td>
<td>6 (7%)</td>
<td>14 (16%)</td>
<td>0.059</td>
<td>0.43 (0.17-1.08)</td>
</tr>
<tr>
<td>Week 2*</td>
<td>3 (4%)</td>
<td>14 (16%)</td>
<td>0.009</td>
<td>0.24 (0.07-0.81)</td>
</tr>
<tr>
<td>Week 4 (secondary endpoint)</td>
<td>2 (2%)</td>
<td>6 (7%)</td>
<td>0.17</td>
<td>0.35 (0.07-1.67)</td>
</tr>
<tr>
<td>Week 12*</td>
<td>2 (2%)</td>
<td>7 (8%)</td>
<td>0.11</td>
<td>0.30 (0.06-1.48)</td>
</tr>
</tbody>
</table>

**Table 1:** Demographic, laboratory, and echocardiographic baseline characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>IVIG plus ciclosporin (n=86)</th>
<th>IVIG (n=87)</th>
<th>p value</th>
<th>Risk ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, months</td>
<td>37 (13-54; 4-152)</td>
<td>37 (13-54; 4-146)</td>
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<tr>
<td>Age &lt;1 year</td>
<td>18 (21%)</td>
<td>18 (21%)</td>
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<td></td>
</tr>
<tr>
<td>Sex</td>
<td>Male 49 (57%) Female 37 (43%)</td>
<td>Male 50 (57%) Female 37 (43%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day of illness at enrolment</td>
<td>4.2 (1.2)</td>
<td>4.1 (1.1)</td>
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<td></td>
</tr>
<tr>
<td>White blood cell count, ×10^3 per μL</td>
<td>13.7 (10.8-17.3)</td>
<td>13.1 (10.3-17.6)</td>
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<td></td>
</tr>
<tr>
<td>Neutrophils, %</td>
<td>81.0 (69.7-85.5)</td>
<td>80.6 (67.3-87.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Haemoglobin, g/dL</td>
<td>11.3 (10.7-12.1)</td>
<td>11.5 (11.0-12.3)</td>
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<td></td>
</tr>
<tr>
<td>Platelet count, ×10^9 per mL</td>
<td>28.2 (23.5-32.8)</td>
<td>28.3 (24.0-34.7)</td>
<td></td>
<td></td>
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<tr>
<td>C-reactive protein, mg/dL</td>
<td>9.46 (x)</td>
<td>8.61 (5.60-12.8)</td>
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<td></td>
</tr>
<tr>
<td>Aspartate aminotransferase, U/L</td>
<td>79 (37-156)</td>
<td>105 (41-215)</td>
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</tr>
<tr>
<td>Alanine aminotransferase, U/L</td>
<td>82 (2-178)</td>
<td>119 (29-382)</td>
<td></td>
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</tr>
<tr>
<td>Total bilirubin, mg/dL</td>
<td>0.70 (0.50-1.50)</td>
<td>0.70 (0.50-1.50)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sodium, mEq/L</td>
<td>132 (131-133)</td>
<td>132 (130-134)</td>
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<td></td>
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<tr>
<td>Magnesium, mg/dL</td>
<td>2.20 (2.07-2.31)</td>
<td>2.20 (2.10-2.31)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Risk score</td>
<td>6 (range 3-10)</td>
<td>6 (range 5-11)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Frequency of rs28493229 C allele, %</td>
<td>16</td>
<td>16</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Frequency of rs113420705 A allele, %</td>
<td>47</td>
<td>47</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Z score of proximal right coronary artery</td>
<td>0.77 (0.83)</td>
<td>0.91 (1.03)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Z score of left main coronary arteries</td>
<td>1.24 (0.83)</td>
<td>1.05 (0.83)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Z score of proximal left anterior descending artery</td>
<td>0.93 (0.83)</td>
<td>0.77 (0.92)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients with coronary artery abnormalities at enrolment</td>
<td>7 (8%)</td>
<td>7 (8%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Data are median (IQR; range), n (%), mean (SD), or median (IQR), unless otherwise stated. IVIG=intravenous immunoglobulin. *One patient with a risk score of 3 was enrolled by an investigator who miscalculated the score to be 5. †Three independent paediatric cardiologists blinded to the patients’ identity and allocation groups retrospectively evaluated the coronary artery status.

**Table 2:** Coronary artery outcome

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IVIG=intravenous immunoglobulin. *Post-hoc analysis.

artery abnormalities were detected by echocardiography. Echocardiography was done at each institution once before the primary treatment started and five times after (at day 3, week 1, week 2, week 4, and week 12), and the video data were recorded on DVD-R. Video data were masked for clinical information, analysed by the event evaluation committee (comprising three independent paediatric cardiologists), and centrally reviewed. At each timepoint, absolute diameters of the proximal right coronary artery, left main coronary artery, proximal left anterior descending artery, and left circumflex artery were measured. Coronary artery abnormalities were diagnosed according to the criteria defined by the Japanese Ministry of Health, Labour, and Welfare, which was based on absolute values (≥3 mm in children <5 years old and ≥4 mm in children ≥5 years old) or relative increase (≥1.5 times adjacent segments or baseline values) of internal diameter of coronary arteries.

The secondary endpoints were incidence of coronary artery abnormalities at week 4, and Z scores (echocardiographic measurements of the internal diameter normalised for body surface area) of coronary artery dimensions for three segments: proximal right coronary artery, left main coronary artery, and proximal left anterior descending artery. The maximum Z score was defined by the largest Z score in the three segments between treatment day 3 and week 12. Coronary artery abnormalities were classified by Z scores according to 2017 American Heart Association guidelines. Other secondary endpoints were duration of fever after initiation of primary treatment, the proportion of patients who were afebrile at each treatment day, use of additional or third-line therapy, and laboratory data. We obtained laboratory data at baseline, treatment day 3, day 5, week 1, week 4, and week 12. Changes in the C-reactive protein concentration were assessed as a ratio to baseline data. The effects of the risk alleles of ITPKC (rs28493229) and CASP3 (rs113420705) on patients’ outcome in the two treatment groups were also investigated.

In a post-hoc analysis, we present the incidence of coronary artery abnormalities at other timepoints (other than week 4) to help understand this secondary endpoint.

An adverse event was defined as any unfavourable or unintended disease or clinical sign, including abnormal laboratory values, that developed in patients after obtaining consent regardless of its causal relationship to the investigational drug. The efficacy and safety assessment committee reviewed safety data on March 30, 2015; Nov 30, 2015; June 11, 2016; and Jan 19, 2017.

**Statistical analysis**

We analysed primary and secondary endpoints in the full analysis set, which was defined as all participants with efficacy data who were enrolled in the clinical study, received at least one dose of the investigational drug after randomisation, and visited the study institution at least once during treatment. For the primary endpoint, we
also analysed a per-protocol set, which included all patients in full analysis set but excluded those who met any of the exclusion criteria (eg, unnoticed coronary artery abnormality at enrolment) or received prohibited concomitant drugs or therapies.

Assuming combined treatment with IVIG plus ciclosporin would have efficacy in preventing coronary artery abnormalities comparable with IVIG plus prednisolone,4 we predicted that the incidence of coronary artery abnormalities would be 5% in the study treatment group and 20% in the conventional treatment group. 82 patients per group were estimated to be required, assuming 80% power and a two-sided significance level of 0.05 to account for withdrawals, we aimed to enrol 86 patients per group.

The incidence of coronary artery abnormalities and additional treatments in both groups were compared using Mantel-Haenszel stratified analysis adjusting for randomisation factors (age, sex, and risk scores). Means of Z scores and laboratory data were estimated and compared by using mixed-effects models with time, group, and group by time interaction as fixed effects, and patients as random effects. To compare the duration of fever after treatment initiation, a log-rank test was done. The incidence of adverse events, as the endpoint of safety, was assessed by use of Fisher’s exact test. All analyses were done using SAS version 9.4.

Role of the funding source
Novartis, the manufacturer of ciclosporin, provided a good manufacturing practice-grade drug for this study. The sponsors of this study had no role in the study design, data collection and analysis, or decision to submit for publication. The only person who was able to access the raw clinical data was the data manager at Chiba University, and no co-author could access all these data. The final decision on content was retained exclusively by all authors.

Results
We screened 1815 patients with Kawasaki disease, of whom 1640 (90%) were ineligible (figure 1, table 1). The first participant was enrolled on May 29, 2014, and the last patient had their last follow-up visit on Dec 27, 2016. Data were frozen on June 7, 2017. 14 patients with coronary artery abnormalities at enrolment evaluated by IVIG plus ciclosporin (n=86) IVIG (n=87) p value

Proximal right coronary artery
Day 3 0.68 (0.47–0.88) 0.94 (0.74–1.18) 0.072
Week 1 0.78 (0.56–1.00) 0.98 (0.74–1.11) 0.50
Week 2 0.70 (0.49–0.91) 0.82 (0.61–1.03) 0.40
Week 4 0.47 (0.28–0.66) 0.61 (0.42–0.80) 0.31
Week 12 0.39 (0.20–0.57) 0.50 (0.31–0.69) 0.39

Left main coronary artery
Day 3 1.39 (1.20–1.58) 1.31 (1.12–1.50) 0.54
Week 1 1.47 (1.27–1.66) 1.42 (1.23–1.61) 0.71
Week 2 1.37 (1.16–1.58) 1.15 (0.94–1.36) 0.11
Week 4 1.21 (1.00–1.41) 1.03 (0.82–1.24) 0.19
Week 12 1.10 (0.90–1.30) 0.88 (0.69–1.08) 0.09

Proximal left anterior descending artery
Day 3 0.92 (0.75–1.09) 0.93 (0.75–1.10) 0.95
Week 1 0.98 (0.79–1.18) 0.95 (0.75–1.15) 0.81
Week 2 0.96 (0.78–1.15) 0.76 (0.57–0.95) 0.10
Week 4 0.90 (0.72–1.08) 0.60 (0.42–0.79) 0.014
Week 12 0.65 (0.47–0.82) 0.45 (0.28–0.63) 0.10

Values of Z scores are median estimated by mixed-effects model (95% CI).
IVIG=intravenous immunoglobulin.

Table 3: Coronary artery Z scores

Figure 2: Maximum values and time-course changes of coronary artery Z scores
(A) Maximum Z scores; red circles show patients considered positive based on the absolute diameter criteria in Japan. (B) Change of Z score at each coronary artery segment as mean (95% CI). IVIG=intravenous immunoglobulin.
of 175 enrolled patients, one patient withdrew consent just after enrolment and was excluded. Consequently, 87 patients each were randomly assigned to the study treatment or conventional treatment group. One patient in the study treatment group was excluded from analysis because of loss of echocardiographic data due to a technical error (figure 1).

The incidence of coronary artery abnormalities during the trial was significantly lower in the study treatment group than in the conventional treatment group (12 [14%] of 86 vs 27 [31%] of 87; risk ratio 0·46; 95% CI 0·25–0·86; p=0·010; table 2). This result was consistent in the per-protocol set, in which 14 patients with coronary artery abnormalities at enrolment were excluded (seven [9%] of 78 vs 2 [27%] of 79; 0·35; 0·15–0·79; p=0·0063). Incidence of coronary artery abnormalities in both groups was different at week 2 (three [4%] of 86 vs 14 [16%] of 87; 0·24; 0·07–0·81; p=0·0093), whereas they were not at day 3, week 1, week 4, and week 12 (table 2). Information on the patients who had coronary artery abnormalities is detailed in the appendix.

The mean Z scores for each coronary artery segment did not differ between groups (table 3). The incidence of patients with coronary artery abnormalities with Z score of 2·5 or more during the trial did not differ between groups, but more patients in the conventional treatment group seemed to have coronary artery Z score of 3·0 or more (figure 2A). The incidence of patients with coronary arteries meeting another criterion in the Japan guidelines and aneurysmal changes of 1·5 times larger diameter or more compared with adjacent segments, was lower in the study treatment group (six [7%] of 86 vs 16 [18%] of 87; risk ratio 0·38; 95% CI 0·16–0·92; p=0·029). The combined incidence of coronary arteries with Z score 3·0 or more or a 1·5 times or more diameter increase compared with adjacent segments was also different between the groups (nine [10%] of 86 vs 21 [24%] of 87, 0·44; 0·21–0·92; p=0·021). Z scores of each coronary artery showed similar shifting patterns—peaking at day 0 to week 1 and then gradually reduced—during the trial period and those at week 12 were 0·2–0·35 points smaller than their baseline values in both treatment groups (figure 2B). The transient increase in Z scores after treatment initiation in both treatment groups seemed to be more modest in the study treatment group.

One patient in the conventional treatment group had a medium-sized aneurysm (Z score 5–9) and giant aneurysm (Z score ≥10 or internal dimension ≥8 mm) was seen in neither of the groups (table 3).
on day 3 (0·46 vs 0·64; ratio 0·72; 95% CI 0·62–0·82; p=0·0001) and day 5 (0·20 vs 0·28; 0·73; 0·59–0·91; p=0·0051; figure 3B).

The proportion of initial therapy non-responders—who were diagnosed at 48 h after the initiation of IVIG and received additional IVIG—was lower in the study treatment group than in the conventional treatment group (15 [17%] of 86 vs 32 [37%] of 87; risk ratio 0·49; 95% CI 0·29–0·82; p=0·0040; table 4). However, relapse occurred in more patients in the study treatment group (23 patients) than the conventional treatment group (seven patients), and these patients also received additional therapy. As a result, the overall incidence of additional therapy was comparable between groups and the timepoints of administration seemed to be later in the study treatment group (table 4, appendix). Incidence of coronary artery abnormalities among the patients with relapsed Kawasaki disease was comparable in both treatment groups (six of 23 patients in the study treatment group and two of seven patients in the conventional treatment group; appendix). The incidence of third-line therapy was also equivalent between the groups (table 4).

Median trough concentrations of ciclosporin were 122 ng/mL (95% CI 111–134) at treatment day 3 and 112 ng/mL (103–122) at day 5. No patient discontinued ciclosporin during primary therapy.

The risk allele frequencies of ITPKC and CASP3 single nucleotide polymorphisms did not differ between groups (table 1). Consistent with our previous findings,6 risk allele carriers of either one or both single nucleotide polymorphisms tended not to respond to the conventional IVIG treatment and the same trend was seen in those that received the study treatment (appendix). Although not significant, the preventive effect of IVIG plus ciclosporin for coronary artery abnormalities seemed stronger when the patients had the risk alleles and the trend of different efficacy was not seen in the subgroups of patients who received the conventional treatment (appendix).

Except for the increased incidence of extended hospital stay due to Kawasaki disease relapse in the study treatment group (22 [25%] of 87 vs 9 [10%] of 87; p=0·017), the incidence of adverse events and serious adverse events did not differ between the groups (table 5; appendix). Three patients in the conventional treatment group had cardiovascular collapse because of Kawasaki disease shock syndrome, one of the most severe forms of Kawasaki disease.23 No deaths occurred in either group.

Discussion

In our study, coronary artery abnormality defined according to the Japanese criteria was more efficiently prevented by ciclosporin combined with IVIG than conventional IVIG treatment alone. Several patients enrolled into this trial and assessed in the primary analysis had coronary artery abnormalities at enrolment, which were not identified on echocardiographic screening but were identified in the central event evaluation (table 1).

The difference we noted was still significant even when these patients were excluded. The number of such patients was similar in the two treatment groups and this similarity, in accordance with the similarity of demographic characteristics, supports the adequacy of the assignment of patients into each group.

Although Kawasaki disease is self-limiting in many cases and several efficient treatment measures have been established, complete prevention of coronary artery abnormalities has not been achieved, and this is the most important clinical issue. Because no good risk scoring system exists for coronary artery abnormality prediction and patients who do not respond to IVIG treatment are known to be prone to coronary artery abnormalities, in this study, patients at high risk of IVIG resistance were recruited.

The mean Z scores for each coronary artery segment did not differ between the two groups. Z scores have become the standard for assessing coronary artery abnormalities. In the 2017 American Heart Association guidelines for Kawasaki disease, dilated coronary arteries with Z scores...
of 2·5 or more were defined as small aneurysms with the recommendation for careful follow up.\textsuperscript{22} Most of the coronary arteries that fulfilled the absolute dimension criteria in this trial had Z scores of 2·5 or more; however, a substantial proportion of coronary arteries with this score did not meet the Japanese criteria. Thus, it is possible that some coronary artery abnormalities were underdiagnosed, and the coronary artery abnormalities with more severe manifestations were targeted in this study. In fact, the proportion of coronary artery abnormalities with Z scores 3·0 or more seemed to be lower in the study treatment group (figure 2A). The proportion of abnormalities with at least 1·5 times diameter increase from adjacent segments, a criterion stated to be useful in the American Heart Association guideline, was also reduced. Given these findings, the current protocol of combined treatment probably had no superiority over conventional IVIG treatment in keeping the coronary arteries within a Z score of less than 2·5; instead, it prevented coronary artery abnormalities developing beyond Z score of 3·0 or larger more efficiently than the conventional treatment.

The percentage of coronary artery abnormalities in the conventional treatment groups (31%) was higher than in the previous randomised trial in Japan (23% in IVIG group),\textsuperscript{8} in which echocardiography was performed at week 1, week 2, and week 4. Our trial included data at treatment day 3 and week 12 in addition to week 1, week 2, and week 4. When we excluded day 3 and week 12 data, the incidence of patients with coronary artery abnormalities in the conventional treatment groups was 22%, which was similar to that in the previous study. In terms of percent reduction, combination therapy with IVIG plus ciclosporin (17%) seemed to have a preventive effect on coronary artery abnormality development comparable with that with IVIG plus prednisolone (20%).\textsuperscript{8}

In this study, 14 patients (8%) already had coronary artery abnormalities at enrolment and 79% (33 of 42) of coronary artery abnormalities developed by 1 week after treatment initiation (appendix). Histopathological changes in the coronary media of patients with Kawasaki disease have been reported to take place as early as days 6–8 of illness.\textsuperscript{23} A nationwide survey in Japan\textsuperscript{4} showed disease have been reported to take place as early as days changes in the coronary media of patients with Kawasaki group),\textsuperscript{8} in which echocardiography was performed at the previous randomised trial in Japan (23% in IVIG conventional treatment groups (31%) was higher than in developing beyond Z score of 3·0 or larger more efficiently could reduce relapse rates and incidence of coronary artery abnormalities remains to be explored.

On the basis that pathogenic mechanisms of severe manifestations and unresponsiveness to therapy are complex and heterogeneous, coronary artery abnormalities in these patients could possibly have been prevented by the other established options.\textsuperscript{8,13} Further development of new therapeutic options and measures to determine the best option for each high-risk patient in the earliest days of illness after hospitalisation would be required. Although validation in a larger cohort is needed, the suggestion of enhanced efficacy of ciclosporin in preventing coronary artery abnormalities in carriers of risk-associated ITPKC and CASP3 alleles suggests that ciclosporin in combination with IVIG could be considered as the drug of first choice for these patients, as well as those patients that are at higher risk of hyperactivation of the calcium-NFAT pathway. ITPKC has been shown to regulate NLR family, pyrin domain-containing 3 inflammasome activation.\textsuperscript{27} Furthermore, accumulating evidence suggests that interleukin-1 (IL-1) receptor blockade is effective in recalcitrant Kawasaki disease. Determination of whether IL-1 receptor blockade is similarly affected by ITPKC genotype, given that IL-1β is produced by activation of the inflammasomes, would be of interest.

Serious adverse events were no more common in the study treatment group than in the conventional treatment group. Elevated potassium concentrations and decreased magnesium concentrations in response to additional ciclosporin rescue treatment have been reported;\textsuperscript{25,26} however, they were not observed in this trial.

We have already noted several weaknesses of our trial, such as the discrepancy between coronary artery
abnormality results defined by Japanese and international criteria, and the greater number of relapsed patients in the study treatment group. The trial was designed to enrol the minimum number of patients that would be sufficient to detect superiority of the study treatment in the primary outcome. Considering that in many of the secondary outcomes, a pattern of improvement could be seen but the p values were not statistically significant, the sample size and statistical power might have been too small for these secondary outcomes. Additionally, even though sensitivity was 86% and specificity 68% in the original report in a Japanese population,36 the risk scoring system employed in this trial had adequate specificity (87%) but poor sensitivity (33%) for predicting IVIG non-responders in a European population.37 Current findings were restricted to Japanese patients defined as high risk by the risk score. It is also true that patients with Kawasaki disease who are appropriately treated and favourably respond to the primary treatment can still develop coronary artery abnormalities. Hence, further studies are needed to determine which patients are most likely to benefit from ciclosporin treatment.

In conclusion, combined treatment with IVIG and ciclosporin had efficacy for favourable coronary artery outcomes in children with Kawasaki disease who are predicted to be unresponsive to IVIG. It had no superiority in suppressing coronary artery abnormalities with Z score less than 2.5, but it might suppress enlargement of coronary artery abnormalities beyond Z score of 3-0 or of a 1-5 times relative increase in diameter from adjacent segments more efficiently than the conventional IVIG treatment. Further investigation is warranted to optimise the use of IVIG plus ciclosporin and determine which Kawasaki disease patients will most benefit from this combination as an initial therapy.

Contributors
HHam, HS, and YOno contributed equally to this work. They wrote the manuscript, prepared the figures, and served on the steering committee, which designed and controlled the study. HHam and HS were principal investigators in each institute and enrolled the patients. RE, MaT, MoT, RA, Tsa, YF, and TF worked as members of the steering committee. KHIRAI, TSO, YOKU, NT, MY, JS, MA, HE, YNO, YH, KO, HM, ST, KHIRONO, TA, TH, and AO were principal investigators in each participating institute and enrolled the patients. HHam verified the study design and ethical matters. AH is responsible for this work, submitted the grant application for this project, and oversaw the project.

Declaration of interests
HHam, RE, and YF report grants from Novartis Pharma, outside the submitted work. HHam and RE report grants from Teijin Pharma, outside the submitted work. RE reports grants from Nihon Pharmaceutical, outside the submitted work. RE and HM report grants from Japan Blood Products Organization, outside the submitted work. KO reports grants and personal fees from MSD, Pfizer, Taisyo-Toyama, Daichi-Sankyo, and Shionogi, outside the submitted work. All other authors declare no competing interests.

Data sharing
After the publication of this paper, individual participant data will be shared with the co-authors, and the chief investigator (with approval from the coordinating investigator) will share individual participant data through email. The clinical study was done as an investigator-initiated clinical study as a part of the Project Promoting Clinical Trials for Development of New Drugs and Medical Devices, with research expenses paid by the Japan Agency for Medical Research and Development, mainly done by the Center for Clinical Trials, Japan Medical Association (JMA). Publishing or presentation of results or methods of the Project Promoting Clinical Trials for Development of New Drugs and Medical Devices, either in part or in entirety, must be notified to the Center for Clinical Trials, JMA using the Notice of Research Results, according to the requirements of the Project Promoting Clinical Trials for Development of New Drugs and Medical Devices. Ultimately, the publication of study results and other information will be provided in JMA Clinical Trial Registry.

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References


