Elevated serum CRP levels before CyA treatment decreased rapidly after CyA treatment. Thus, serum CRP levels before CyA treatment significantly decreased two days after CyA treatment ($p<0.01$, Table 3).

After the start of CyA treatment, hyperkalemia developed (Table 3). The definition of hyperkalemia is $\geqq$6 mEq/L in infants aged less than 12 months, and $\geqq$5.5 mEq/L in children aged 12 months or over.[27] According to this definition, hyperkalemia developed in one of four infants and in nine of 24 children. The peak values appeared 3-13 (median 6.5) days after the start of CyA treatment. Although serum potassium levels increased after CyA treatment, both serum creatinine and eGFR did not change significantly (Table 3). In addition, no serious adverse effects such as ventricular arrhythmia occurred.

We examined the time course of the serum trough levels of CyA, which ranged between 60-200 ng/mL and were regarded as optimal. The level fluctuated in patients (nos. 3, 10 and 19 in Table 1 and 2) resistant to CyA therapy, because we increased and decreased the dose of CyA according to both clinical responses such as body temperature and the trough levels themselves.

Discussion

IVIG plus aspirin is now an initial standard therapy for KD, and has actually

reduced the incidences of CAL.[7] However, the precise mechanism by which IVIG suppresses KD vasculitis is still unclear. Furthermore, it has not been clarified why 10-20 % of KD patients are resistant to IVIG treatment. Thus, it is important to develop additional strategies for such IVIG-resistant patients.

In this study, CyA appeared to exert both antifebrile and anti-inflammatory effects in patients with refractory KD. Its effect was particularly clear in 18 of the 28 patients with resistance, because they became afebrile within 3 days after the start of CyA treatment. Although it took 4-5 days for 4 of the 28 patients to become afebrile, their body temperature fell close to the definition level of "afebrile" within 2 days after the start of CyA treatment. In addition, symptoms such as rash and swelling of the cervical lymph nodes also improved. On the other hand, 6 of the 28 patients failed to become afebrile within 5 days after the start of CyA and/or high fever returned after becoming afebrile within 5 days, despite having an adequate trough level of CyA. These facts suggest that certain subgroups of patients with refractory KD may be resistant to CyA. Two possible reasons for this can be suggested. First, the timing of CyA treatment might be too late. We used CyA to selectively treat KD patients who had been resistant to two courses of IVIG therapy. Because CyA was a new option for refractory KD and we had no data about its safety and efficacy for patients with KD, parents and guardians were

not expected to give their approval until the standard therapy for KD had proven ineffective. On the other hand, it is desirable to initiate any new treatment as rapidly as possible, as damage to the walls of coronary arteries might progress within the first ten days of illness unless the process of acute inflammation can be suppressed. Therefore, we set up a protocol in which CyA treatment was started immediately after completing the additional IVIG therapy. Second, the suppressive effect of CyA on the calcineurin or NFAT pathway might be insufficient to control the severe vasculitis. Further analyses of both the timing of CyA treatment and genetic background factors including the NFAT and other pathways will be needed to clarify these issues.

We did not have any information about whether oral administration or intravenous infusion of CyA would be more effective. However, we selected oral administration, because the oral route is easier and more tolerable for young children and infants, who need to be treated for two or three weeks. The volume of CyA was small, and therefore the patients were able to take it without major problems. By examining the trough values, it became clear that oral administration of CyA allowed a sufficient high serum concentration (60-200 ng/mL) to be obtained. Further analyses of trough values in more patients with refractory KD will be needed to assess the best therapeutic levels of CyA in KD.

KD patients who were less than 4 months of age were excluded from the indication of CyA treatment, because there is insufficient information about the safety of CyA in infants and children with KD. However, CyA is known to be effective and safe for children with nephrotic syndrome resistant to steroid.[28,29] In the latter case, the dose of CyA was adjusted to maintain a trough level of 120-150 ng/ml during the initial 3 months of treatment, followed by 80-100 ng/ml during months 4-12.[28] Adverse events in children with nephrotic syndrome comprised CyA-related nephrotoxicity (3.8%), bacterial infections (2/38=5.3%), and posterior reversible encephalopathy syndrome (1/38=2.6%). As the duration of CyA treatment for KD was much shorter than that for nephrotic syndrome, it was expected that CyA treatment might be associated with few adverse events in this series. Indeed, the increase of hepatic enzymes and hypertension in these 28 patients did not develop. However, many of our patients treated with CyA showed hyperkalemia, a feature that was absent in nephrotic syndrome. Although the definition of hyperkalemia in infants and children is controversial,[30] we classified these patients according to the criteria of Japan.[27] Fortunately, no harmful events such as ventricular arrhythmia occurred. The levels of serum potassium were not correlated with serum CyA trough levels, serum creatinine levels, and eGFR. In addition, there have been a report in which pseudohyperkalemia was observed in the sera of KD despite the

normal plasma level.[31] This report indicates that pseudohyperkalemia should be considered in patients with KD whose platelet counts are markedly increased. Indeed, serum potassium levels were correlated closely with platelets counts in these 28 patients who were treated with CyA (data not shown). However, precise mechanism responsible for the hyperkalemia during CyA treatment in KD patients is still unclear. In this study, we did not examine the C2 levels of CyA, which might have been better correlated with the $AUC_{0\text{-}4}$ (area under the curve) than the trough level, because of the difficulty involved in taking frequent blood samples from infants and small children. We think that analyses for both C2 levels of CyA and potassium clearance rate will be needed in the future studies.

It is difficult to evaluate whether CyA inhibits the development of CAL, which is the most serious outcome of KD. Hashino K et al.[10] reported that there were 17 patients (17/262=6.5%) resistant to both initial (2g/kg) and additional (1g/kg) IVIG. They randomly divided these patients into two groups (third IVIG or steroid pulse therapy). After third additional option, there was no significant difference in the incidence of CAL between the two groups. In their study, 12 (70.6%) of 17 patients resistant to both initial (2g/kg) and additional (1g/kg) IVIG developed CAL. Thus, 12 (4.6%) of 262 patients developed CAL. Our present study was not a randomized control study but a

pilot study, in which 4 (13.3%) of 30 patients resistant to both initial (2g/kg) and additional (2g/kg) IVIG developed CAL. Thus, 4 (1.2%) of 329 patients developed CAL. All four patients were resistant to both initial and additional IVIG treatment, and were treated with CyA. However, coronary arterial dilatation occurred during additional IVIG (before CyA treatment) in two of the four patients, and CyA did not inhibit the progression of CAL in these patients. In the other two patients, CAL developed after the start of CyA treatment.

There were several limitations to this study. First, the sample size was small. We were unable to analyze the factors affecting the response to CyA because only six cases were resistant to CyA. Second, this was a pilot study and not a randomized control clinical trial. Therefore, we were unable to conclude whether CyA exerts preventive effects against CAL in patients with refractory KD.

In summary, CyA treatment is considered well tolerated and a safe and promising option for patients with refractory KD. Oral administration of CyA showed good compliance with treatments and has both antifebrile and anti-inflammatory effects in KD patients who are resistant to IVIG. Further investigations will be needed to clarify the dose, safety, optimum timing and duration of CyA treatment.

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Figure and Table legends

Figure 1: Study protocol:

KD: Kawasaki disease, IVIG: intravenous immunoglobulin, CyA: Cyclosporin A,

IC: informed consent.

*: Responders to each treatment. **: Patients resistant to initial IVIG or CyA.

***: Patients resistant to additional IVIG. IC: informed consent.

All patients with KD received initial IVIG infusion (2 g/kg) and aspirin (30-50 mg/kg/day). Patients resistant to initial IVIG received additional IVIG (2 g/kg). In addition, patients who were resistant to additional IVIG and were 4 months old or more, were treated with CyA. Patients who were resistant to additional IVIG and aged less than 4 months were treated with a 3rd course of IVIG.

Figure 2: Protocol outcomes.

KD: Kawasaki disease, IVIG: intravenous immunoglobulin, CyA: Cyclosporin A,

CAL: coronary arterial lesions.

Of 329 patients with KD, 245 (74.5%) became afebrile after initial IVIG. Eighty-four patients resistant to initial IVIG received additional IVIG, of whom 30 failed to become afebrile within the treatment completion time. Among these 30 patients,

28 who were 4 months old or more, were treated with CyA, and the other two patients, who were less than four months of age, received a third course of IVIG (2 g/kg).

*: CAL developed in these two patients (no. 11 and no. 19 in Table 2) before CyA treatment (during additional IVIG).

Table 1: Characteristics of 8 patients treated with CyA between January and December 2008.

CyA: Cyclosporin A, IVIG: intravenous immunoglobulin, An: Aneurysm, ID: illness day, CAL: coronary arterial lesions.

These 8 patients ranged in age from 5 to 39 months. The male to female ratio was 6:2. CyA treatment was started in days 7-12 of illness, and the dose of CyA was 4-8 mg/kg/day. We increased and decreased the dose of CyA according to both clinical responses such as fever and the trough levels themselves. One patient (no.3) received a 3rd IVIG infusion. Two patients (nos. 3 and 8) developed CAL.

Table 2. Characteristics of 20 patients treated with CyA between January 2009 and June 2010.

CyA: Cyclosporin A, IVIG: intravenous immunoglobulin, An: Aneurysm, AnG:

giant Aneurysm, ID: illness day, CAL: coronary arterial lesions

These 20 patients ranged in age from 4 to 93 months. The male to female ratio was 14:6. CyA treatment was started in days 7-11 of illness, and the dose of CyA was 4-8 mg/kg/day. 4 patients (nos. 10, 19, 26, and 28) failed to become afebrile within 5 days after the start of CyA and/or high fever returned after becoming afebrile within 5 days. Three patients (nos. 10, 26 and 28) received a third course of IVIG infusion. Two patients (nos. 11 and 19) developed CAL before CyA treatment (during additional IVIG).

Table 3. Summary of clinical parameters in 28 KD patients treated with CyA.

CyA: Cyclosporin A , IVIG: intravenous immunoglobulin

Values are ranges and (medians). P values* were calculated by Wilcoxon's signed rank test.

Table 1. Characteristics of 8 patients treated with CyA between January and December 2008.

Case No.	age	Sex	Initial IVIG (illness day of IVIG)	additional IVIG (illness day of IVIG)	CyA (illness day of CyA)	CyA dose (mg/kg/day)	CyA duration (days)	duration (days) until afebrile after CyA	CAL
1)	3y 3 m	M	4	6	9	4	21	1	(-)
2)	2y 0 m	M	5	8	12	4	21	1	(-)
3)	1y 11m	F	6	9	11	4 - 8	50	13	An (5mm)
								3rd-IVIG (21th ID)	
4)	1y 10m	M	4	6	9	4	21	3	(-)
5)	3y 0 m	M	5	7	9	4	21	2	(-)
6)	1y 3 m	M	4	7	8	4 - 6	13	5	(-)
7)	5 m	F	6	8	9	4	21	3	(-)
8)	1y 2m	M	3	5	7	4 - 8	21	13	An (4mm)

Table 2. Characteristics of 20 patients treated with CyA between January 2009 and June 2010.

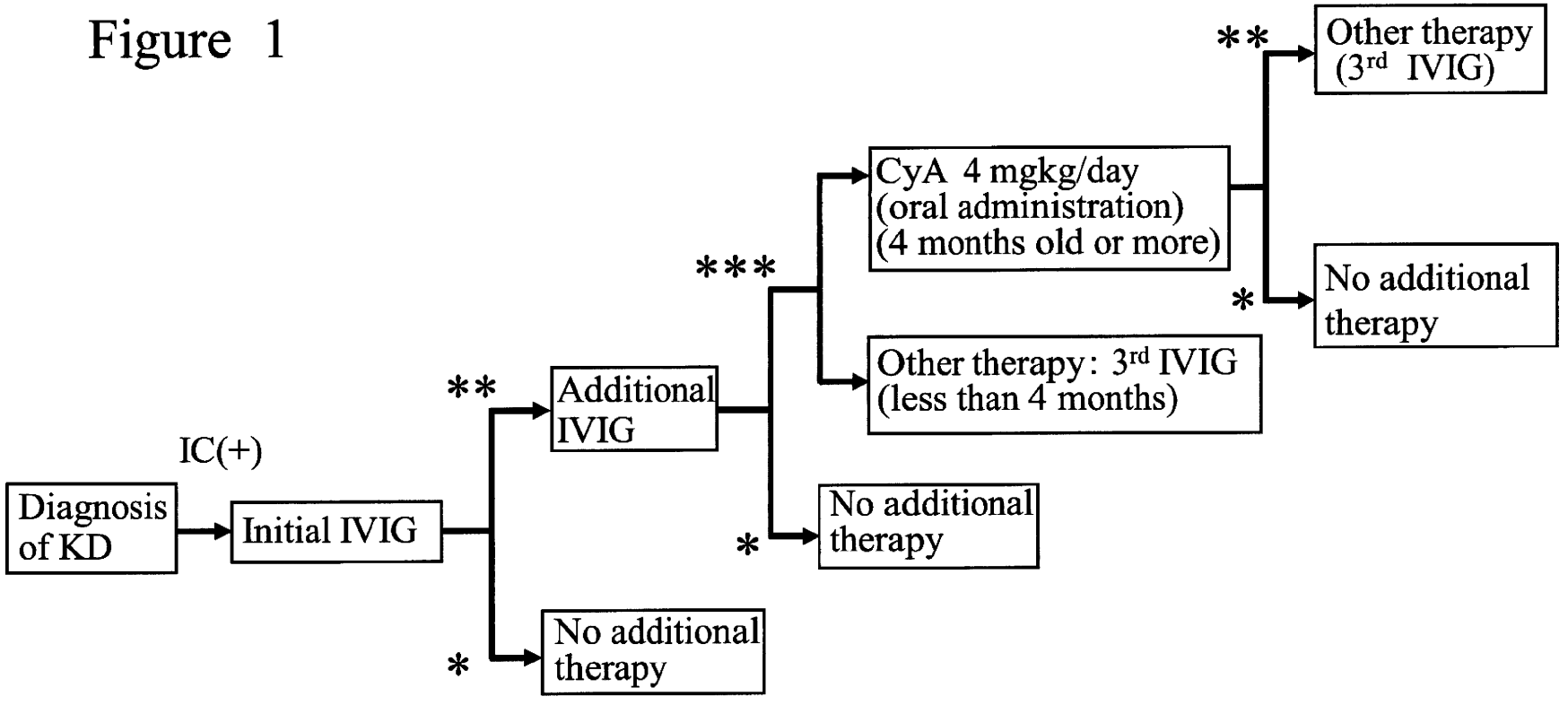
Case No.	age	Sex	Initial IVIG (illness day of IVIG)	additional IVIG (illness day of IVIG)	CyA (illness day of CyA)	CyA dose (mg/kg/day)	CyA duration (days)	duration (days) until afebrile after CyA	CAL
9)	1y 5m	F	5	10	11	4 - 6	14	1	(-)
10)	1y 4m	M	4	6	7	4 - 7	14	4 3rd-IVIG (22th ID)	(-)
11)	5y 3 m	F	5	8	9	4	14	1	AnG(10mm)
12)	6 m	M	4	6	8	4	14	2	(-)
13)	4y10m	M	4	7	8	4	14	1	(-)
14)	1y 3 m	M	4	6	8	4 - 6	13	5	(-)
15)	2y11m	M	5	7	8	4 - 6	14	4	(-)
16)	4y 3 m	M	4	7	8	4	10	1	(-)
17)	2y 6m	F	5	7	8	4 - 6	11	1	(-)
18)	1y 4 m	M	3	6	7	4 - 5	13	5	(-)
19)	5y 4 m	M	5	7	8	4 - 5	14	6	An (6mm)
20)	2y 7 m	M	5	7	8	4	14	3	(-)
21)	1y11m	F	4	7	8	4	5	1	(-)
22)	4 m	M	4	6	7	4	14	1	(-)
23)	7y9m	M	4	7	8	4	14	1	(-)
24)	2y6m	M	4	6	7	4	14	3	(-)
25)	5m	F	5	8	9	4	14	1	(-)
26)	1y1m	F	4	6	8	4 - 8	14	7 3rd-IVIG(22th ID)	(-)
27)	1y8m	M	5	7	8	4	8	1	(-)
28)	1y1m	M	5	7	9	4 - 8	14	7 3rd-IVIG(26th ID)	(-)

Table 3. Summary of clinical parameters in 28 KD patients treated with CyA.

1) age (months)	4-93 (23)	
2) male:female	20 : 8	
3) illness day of initial IVIG	3 - 6 (4.5)	
4) illness day of additional IVIG	5 -10 (7)	
5) illness day of the start of CyA treatment	7 -12 (8)	
6) duration (days) of CyA treatment	5 -50 (14)	
7) duration (days) until afebrile after CyA treatment	1 -13 (2)	
8) axillary temperature (centigrade)		
on the day of the start of CyA treatment	38.0-40.3 (38.9)	}
2 days after the start of CyA treatment	36.1-40.4 (37.6)	} p<0.01*
9) CRP (mg/dL)		
on the day of the start of CyA treatment	1.2-16.8 (9.3)	}
2 days after the start of CyA treatment	0.4-16.1 (5.2)	} p<0.01*
10) serum potassium levels		
on the day of the start of CyA treatment	2.9-5.1 (4.1)	}
maximum potassium levels	4.9-6.1 (5.4)	} p<0.01*
duration (days) until maximum potassium levels	3 -13 (6.5)	
11) serum creatinine levels		
on the day of the start of CyA treatment	0.1-0.33 (0.23)	}
on the day of maximum potassium levels	0.12-0.33 (0.24)	} p=0.156*
12) estimated GFR:		
on the day of the start of CyA treatment	85.5-152.3 (109.9)	}
on the day of maximum potassium levels	83.4-135 (103.9)	} p=0.123*

ranges (median)
*: Wilcoxon's signed rank test

Figure 1


Diagnosis of KD
IC(+)
Initial IVIG
**
Additional IVIG
*
No additional therapy
***
CyA 4 mgkg/day (oral administration) (4 months old or more)
Other therapy: 3rd IVIG (less than 4 months)
*
No additional therapy
**
Other therapy (3rd IVIG)
Aspirin (30-50mg/kg/day, p.o.) <After afebrile, 5mg/kg/day, p.o.>
Initial therapy, for 48 hours
Additional therapy, for 24 hours
CyA therapy, for 2-3 weeks
observation
Initial IVIG 2 g/kg (24 hours) + observation (24 hours)
Additional IVIG 2 g/kg (24 hours)
4 - 8 mg/kg/day trough level (60-200 ng/ml)
Total periods: 4 weeks after initial IVIG therapy

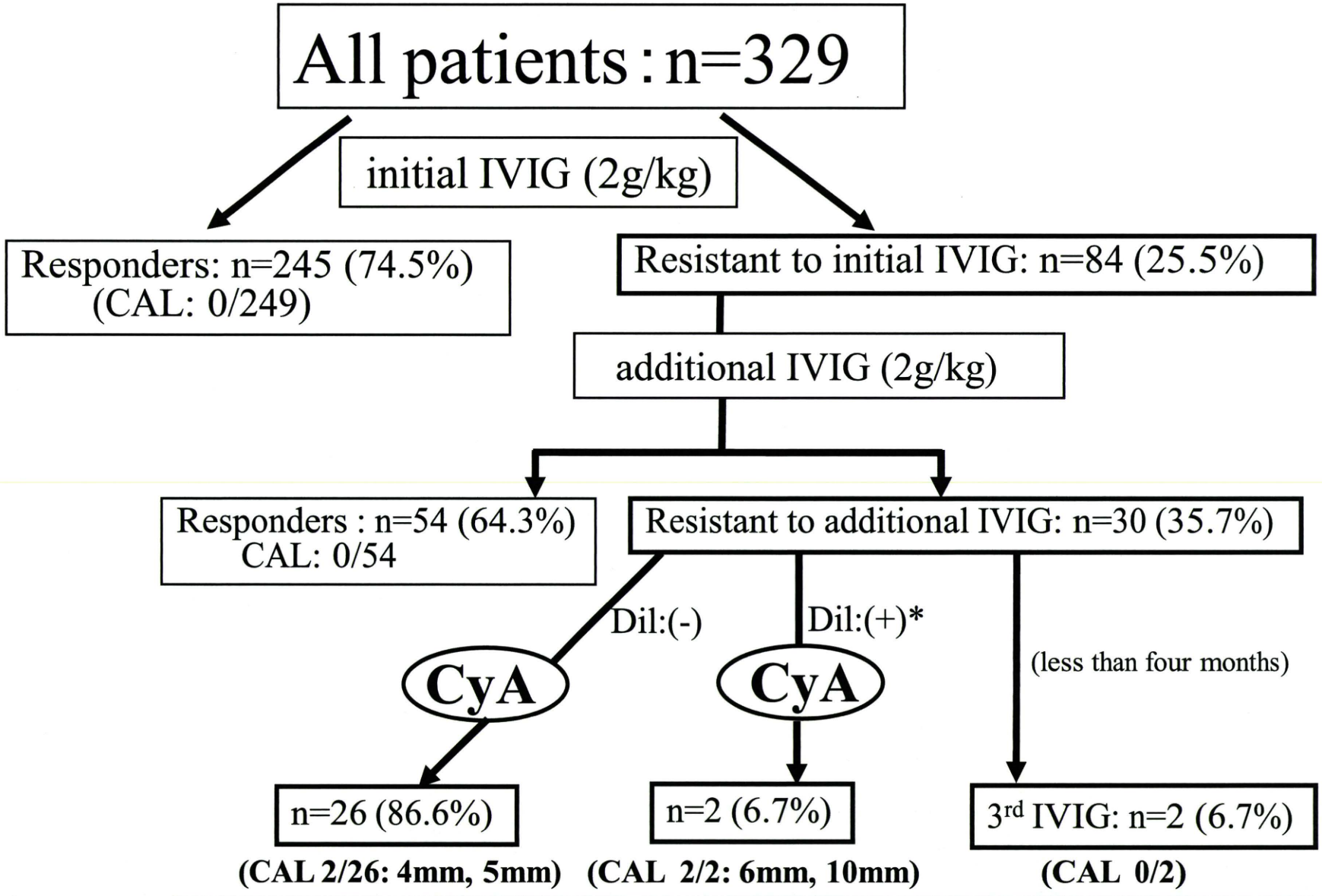

All patients : n=329
initial IVIG (2g/kg)
Responders: n=245 (74.5%)
(CAL: 0/249)
Resistant to initial IVIG: n=84 (25.5%)
additional IVIG (2g/kg)
Responders : n=54 (64.3%)
CAL: 0/54
Resistant to additional IVIG: n=30 (35.7%)
Dil:(-)
Dil:(+)*
(less than four months)
CyA
CyA
n=26 (86.6%)
n=2 (6.7%)
3rd IVIG: n=2 (6.7%)
(CAL 2/26: 4mm, 5mm)
(CAL 2/2: 6mm, 10mm)
(CAL 0/2)
CAL= 4 / 329 (1.2%)

Figure 2

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ORIGINAL ARTICLE

Matrix metalloproteinase haplotypes associated with coronary artery aneurysm formation in patients with Kawasaki disease

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Aneurysms of the vascular wall represent a final common pathway for a number of inflammatory processes, including atherosclerosis and idiopathic vasculitis syndromes. Kawasaki disease (KD) is an acute, self-limited vasculitis in children and the leading cause of acquired coronary artery aneurysms. We sought to identify shared molecular mechanisms of aneurysm formation by genotyping eight polymorphisms in *matrix metalloproteinase (MMP)-1, 3, 7, 12* and *13* in the gene cluster on Chr.11q22, whose gene products have been implicated in aneurysm formation or are known to have elastase activity. We genotyped 482 US–UK KD patients (aneurysm+: n=111, aneurysm−: n=371) and tested our findings in an independent cohort of 200 Japanese KD patients (aneurysm+: n=58, aneurysm−: n=142). Analysis of the five MMP genes identified modest trends in allele and genotype frequencies for *MMP-3* rs3025058 (−/T) and haplotypes containing *MMP-3* rs3025058 (−/T) and *MMP-12* rs2276109 (A/G) (nominal P=2 to 4×10^{-5}) that conferred increased risk of aneurysm formation in US–UK subjects. This finding was validated in Japanese subjects and suggests the importance of this locus in aneurysm formation in children with KD. The region encompassing these risk haplotypes is a prime candidate for resequencing to look for rare genetic variation that may influence aneurysm formation.
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Keywords: coronary artery aneurysm; haplotype; Kawasaki disease; matrix metalloproteinase

INTRODUCTION

Aneurysms of the vascular wall complicate many different diseases that involve vessel wall inflammation and destruction of extracellular matrix and elastic fibers. In children with Kawasaki disease (KD), coronary artery aneurysms (CAA) form in 25% of untreated patients and in 5% of patients treated with intravenous immunoglobulin within the first 10 days after fever onset. A hallmark of CAA is focal destruction of the internal elastic lamina with early neutrophil infiltration followed by macrophages and cytotoxic T lymphocytes.[1] For this reason, enzymes that cleave elastin have been implicated in the pathogenesis of KD.[2,3] Proteases capable of degrading elastin include neutrophil elastase and the matrix metalloproteinases (MMPs)-2, 3, 7, 9 and 12.[4] MMPs are zinc-dependent endopeptidases produced by a wide variety of cell types. In addition to the degradation of extracellular matrix, MMPs also cleave cytokines and chemokines[5] and influence recruitment of inflammatory cells. Therefore, MMPs have important roles in both inflammation and tissue remodeling.

According to a current paradigm, KD is triggered by an infectious agent that elicits an inflammatory response directed at cardiovascular tissues in genetically susceptible hosts.[6] A genetic influence on disease susceptibility in KD has been explored in candidate gene association studies, a genome-wide linkage analysis of siblings concordant for KD followed by linkage disequilibrium mapping, and a genome-wide association study.[7–11] However, fewer studies have explored the impact of genetic variation on aneurysm formation because of the difficulty in collecting a sufficient sample size of patients with this phenotype for genotyping. To bridge this gap in knowledge, we collaborated with groups in the United Kingdom and Japan to collect DNA from KD

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