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3 and Welfare, Japan (2008-2010).
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9
10 **Key words:** Kawasaki disease, intravenous immunoglobulin-resistant (IVIG-resistant),
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12 Cyclosporin A, T-cell activation
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19 **Abbreviated title:** CyA treatment for refractory Kawasaki disease
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22 **Running head title:** CyA treatment for refractory KD
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3 **Abstract**
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6 **Background:** There are still no definite treatments for refractory Kawasaki disease
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9 (KD). In this pilot study, we evaluated the use of CyA treatment in patients with
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11 refractory KD.
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15 **Methods:** We prospectively collected clinical data of CyA treatment (4-8mg/kg/day,
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17 oral administration) for refractory KD patients using a same protocol among several
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19 hospitals. Refractory KD is defined as the persistence or recurrence of fever (37.5 °C or
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21 more of an axillary temperature) at least 24hrs after second intravenous
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23 immunoglobulin (IVIG) (2g/kg) following the initial one.
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31 **Results:** Subjects were enrolled out of 329 KD patients who were admitted to our
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33 eight hospitals between January 2008 and June 2010. Among a total of twenty-eight
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35 patients of refractory KD treated with CyA, 18 (64.3%) responded promptly to be
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37 afebrile within three days and decreased C-reactive protein levels, the other 4 became
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39 afebrile within 4-5 days. However, 6 patients (21.4%) failed to become afebrile within 5
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41 days after the start of CyA and/or high fever returned after becoming afebrile within 5
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43 days. Although hyperkalemia developed in 9 patients at 3-7 days after the start of CyA
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45 treatment, there were no serious adverse effects such as arrhythmias. Four patients
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47 (1.2%), two before and the other two after the start of CyA treatment, developed
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3 coronary arterial lesions.
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6 **Conclusion:** CyA treatment is considered safe and well tolerated, and a promising
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9 option for patients with refractory KD. Further investigations will be needed to clarify
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13 optimal dose, safety, and timing of CyA treatment.
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INTRODUCTION

Kawasaki disease (KD)¹⁾ is an acute systemic vasculitis occurring in medium-sized arteries, especially coronary arteries. KD patients have been reported not only from East Asia including Japan but also USA and European countries.²⁻⁵⁾ Although many features of KD have been revealed by nationwide epidemiologic surveys in Japan, both its etiology and pathogenesis are still unclear. In the 19th nationwide survey conducted in Japan, more than ten thousand children with KD were reported annually in 2005 and 2006,⁶⁾ and KD is now a leading cause of acquired cardiac disease in childhood in the developed countries. Although the incidence of coronary arterial lesions (CAL) has been reduced to around 3-4% by standard therapy with intravenous immunoglobulin (IVIG) and aspirin⁷⁾, 10-20% of patients with KD who fail to respond to IVIG, so-called refractory KD, show a high prevalence of CAL. There have been a significant number of reports of new therapeutic options for refractory KD, such as steroid,^{8,9)} steroid pulse,^{10,11)} infliximab,^{12,13)} plasma exchange,¹⁴⁾ and immunosuppressants.¹⁵⁻¹⁶⁾ Several recent reports have described the use of an intensified therapy comprising steroid or steroid pulse with initial IVIG in the early acute phase of KD.¹⁷⁻²⁰⁾ However, the outcomes of such therapies are still controversial. With regard to infliximab, Burns et al.¹³⁾ compared the outcome of second IVIG infusion (2 g/kg) and infliximab (5 mg/kg)

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3 after initial IVIG therapy. They concluded that infliximab was a potentially useful
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6 alternative to an additional IVIG infusion or intravenous pulse methylprednisolone for
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9 patients with IVIG-resistant KD, at least until best clinical practice had been established
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12 by future clinical trials. Currently, therefore, there are still no definite treatment
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15 recommendations for refractory KD and development of an optimal alternative for these
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18 patients is now an urgent matter.
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22 We have reported that a functional polymorphism of *inositol 1,4,5-trisphosphate*
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25 *3-kinase C (ITPKC)* is associated with susceptibility to KD and formation of CAL.²¹⁾
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28 Since ITPKC acts as a negative regulator of T-cell activation by reducing amount of
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31 Ins(1,4,5)P3 (IP3), activated T cells may play a pivotal role in the pathogenesis of KD
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34 vasculitis. Several studies have already investigated the role of activated T cells in
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37 patients with KD.²²⁻²⁴⁾ From this viewpoint, cyclosporin A (CyA), which potently
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40 suppresses the activity of T cells by negative regulation of the NFAT pathway, may be a
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43 promising candidate for the treatment of acute KD, especially in patients resistant to
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Materials and Methods

Patients: We prospectively collected clinical data of CyA treatment for refractory KD patients using a same protocol among eight hospitals in Japan: Tokyo Women's Medical University Yachiyo Medical Center in Chiba prefecture, Wakayama Medical University, Hashimoto Municipal Hospital, Naga Hospital, Wakayama Rosai Hospital, Hidaka General Hospital, Social Insurance Kinan Hospital in Wakayama prefecture, and Izumiotsu Municipal Hospital in Osaka prefecture. The study was approved by the ethics Committee of each institution. Study subjects aged 4 months or older were enrolled out of Japanese 329 patients who met the diagnostic criteria for KD²⁵⁾ and were admitted to our eight hospitals between January 2008 and June 2010. Written Informed consent was obtained from the parents of the patients investigated.

Protocol (Figure 1): All patients received initial IVIG infusion (2 g/kg for 24 hours) and aspirin (30-50 mg/kg/day) within 7 days after the onset of KD. The patients were considered afebrile when the axillary temperature remained below 37.5°C for more than 24 hours. The aspirin dose was decreased to 5 mg/kg/day after 2-3 days without fever. We defined patients who remained febrile (37.5 °C or more of an axillary temperature) within 24 hours after completion of initial IVIG therapy as being resistant to initial IVIG, and additional IVIG (2 g/kg for 24 hours) was administered. We defined

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3 patients who remained febrile at the end of second IVIG infusion as resistant to
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6 additional IVIG. These patients resistant to both initial and additional IVIG were treated
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9 with CyA by oral administration (Neoral[®], oral solution, Novartis Pharma Co. Ltd.,
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12 Tokyo, Japan). The initial dose of CyA was 4mg/kg/day, and patients received oral CyA
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15 divided into two equal daily doses every 12 hours. The dose of CyA was adjusted to
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18 between 4 and 8 mg/kg/day to maintain a trough level of 60-200 ng/ml by reference to
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21 clinical and laboratory data such as body temperature and C-reactive protein (CRP)
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24 level. Serum samples for measuring the trough levels of CyA were obtained just before
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27 oral intake of CyA in the morning (about 12 hours after receiving oral CyA last night).
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30 The trough levels of CyA were examined more than twice a week during CyA treatment.
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35 CyA treatment was continued until the patients became afebrile and their CRP level
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38 decreased to a negative value (<0.3mg/dL). In addition, the maximum duration of CyA
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41 treatment was decided on three weeks between January and December 2008, and on two
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44 weeks between January 2009 and June 2010. If patients remained febrile more than 5
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47 days after the start of CyA treatment, or if fever returned after becoming afebrile within
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50 5 days after the start of CyA treatment, CyA treatment was judged to be ineffective, and
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53 then the patients were given a third IVIG therapy. Patients resistant to both initial and
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56 additional IVIG, and who were less than 4 months of age, were also given a third of
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3 IVIG treatment. Laboratory assessments were performed before initial IVIG, before
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6 additional IVIG, before CyA, and sequentially thereafter every 2-3 days until CyA
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9 treatment was discontinued. Laboratory tests included the concentrations of CRP,
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12 electrolyte (potassium), creatinine. In order to evaluate renal function, we calculated
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15 estimated glomerular filtration rate (eGFR) before and after CyA treatment as follows:
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19 $0.55 \times \text{height (cm)} / \text{serum creatinine (enzyme method: mg/dL)} + 0.2.$
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22 **Evaluation of CAL:** In all patients with KD, two-dimensional echocardiography
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24 (2DE) was performed to evaluate CAL at least twice a week during hospitalization.
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29 Evaluation of the presence or absence of CAL was performed after one month of illness
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32 in accordance with the criteria of the Research Committee on Kawasaki disease.²⁶⁾ In
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35 addition, we performed coronary angiography within 3 months after illness onset in
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38 patients who were judged to have CAL on the basis of 2DE, in order to confirm the
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41 presence of CAL.
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43 44 45 **Statistical analysis**

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48 Statistical analysis was performed using Wilcoxon's signed rank test. Differences at a
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51 two-tailed p value of <0.05 were considered statistically significant.
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54 55 **Results**

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58 Of the 329 patients with KD, 245 (74.5%) became afebrile within 24 hours after
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3 completion of the initial IVIG therapy, and 84 (25.5%) continued to be febrile (Figure 2).

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6 The latter 84 patients received additional IVIG, and 54 (64.3%) of them became afebrile

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9 before completion of the additional IVIG course. The other 30 (35.7%) failed to become

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12 afebrile, and 28 of them who were more than 4 months of age were treated with CyA.

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15 The remaining two patients, who were less than four months of age, received a third

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18 course of IVIG (2 g/kg), and subsequently became afebrile.

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21 The characteristics of the 28 patients treated with CyA are summarized in Tables

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24 1-3. They received the initial IVIG course on illness days 3-6 (median; 4.5) and the

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27 additional IVIG on illness days 5-10 (median; 7). CyA treatment was initiated on days

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30 7-12 of illness (median; 8). The dose of CyA was 4-8 mg/kg/day, and the duration of

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33 treatment was 5-50 (median; 14) days.

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36 The duration until afebrile after the start of CyA treatment was 1-13 (median; 2)

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39 days. Eighteen of the 28 patients responded promptly to be afebrile within three days,

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42 and the other 4 became afebrile within 4-5 days after the start of CyA treatment.

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45 Axillary temperature (°C) of 2 days after the start of CyA treatment was significantly

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48 lower than that of the day of the start of CyA treatment ($p < 0.01$, Table 3). However, 6

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51 patients (nos. 3, 8, 10, 19, 26, and 28 in Table 1 and 2) failed to become afebrile within

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54 5 days after the start of CyA and/or high fever returned after becoming afebrile within 5

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3 days. Four patients (nos. 3, 10, 26 and 28 in Table 1 and 2) received a third IVIG
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6 infusion. Patient no. 3 received the third IVIG infusion on the 10th day after the start of
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9 CyA treatment. However, low-grade fever (37.5-38.5°C) continued, and therefore she
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12 received CyA for 50 days until she became completely afebrile. Patient no. 10 became
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15 afebrile on the 4th day after CyA treatment, but high fever returned on the 13th day,
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18 despite CyA continuation. He received the third IVIG infusion on the 15th day after CyA,
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21 and then he became afebrile. Both patient no.26 and 28 became afebrile on the 7th after
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24 CyA treatment, but high fever returned after CyA treatment for 14 days. They received
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27 the third IVIG infusion on the next day or three days after CyA, and then they became
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30 afebrile. The other two patients (nos. 8, and 19) did not receive any other therapy,
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33 because high fever (more than 38.0°C) was absent, and they gradually became afebrile
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38 with continued CyA therapy.
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41 Although 4 patients (nos. 3, 8, 10, and 19) developed CAL, the coronary arteries
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44 had already dilated (more than 4mm by 2DE) in 2 of them (no. 10 and 19) before CyA
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47 treatment. In addition, patient no. 10 became afebrile within 24 hours after CyA
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50 treatment, but the diameter of the right coronary artery (C1-C2) was found to be
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53 increasing on a daily basis, reaching around 10 mm in diameter (giant coronary arterial
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57 aneurysm) in spite of continuation of CyA for 2 weeks.
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3 Elevated serum CRP levels before CyA treatment decreased rapidly after CyA
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6 treatment. Thus, serum CRP levels before CyA treatment significantly decreased two
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9 days after CyA treatment ($p < 0.01$, Table 3).
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12 After the start of CyA treatment, hyperkalemia developed (Table 3). The definition
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14 of hyperkalemia is ≥ 6 mEq/L in infants aged less than 12 months, and ≥ 5.5 mEq/L
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16 in children aged 12 months or over.²⁷⁾ According to this definition, hyperkalemia
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18 developed in one of four infants and in nine of 24 children. The peak values appeared
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20 3-13 (median 6.5) days after the start of CyA treatment. Although serum potassium
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22 levels increased after CyA treatment, both serum creatinine and eGFR did not change
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24 significantly (Table 3). In addition, no serious adverse effects such as ventricular
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26 arrhythmia occurred.
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38 We examined the time course of the serum trough levels of CyA, which ranged
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40 between 60-200 ng/mL and were regarded as optimal. The level fluctuated in patients
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42 (nos. 3, 10 and 19 in Table 1 and 2) resistant to CyA therapy, because we increased and
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44 decreased the dose of CyA according to both clinical responses such as body
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46 temperature and the trough levels themselves.
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54 Discussion

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57 IVIG plus aspirin is now an initial standard therapy for KD, and has actually
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3 reduced the incidences of CAL.⁷⁾ However, the precise mechanism by which IVIG
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6 suppresses KD vasculitis is still unclear. Furthermore, it has not been clarified why
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9 10-20 % of KD patients are resistant to IVIG treatment. Thus, it is important to develop
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12 additional strategies for such IVIG-resistant patients.
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16 In this study, CyA appeared to exert both antifebrile and anti-inflammatory effects
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18 in patients with refractory KD. Its effect was particularly clear in 18 of the 28 patients
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20 with resistance, because they became afebrile within 3 days after the start of CyA
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22 treatment. Although it took 4-5 days for 4 of the 28 patients to become afebrile, their
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24 body temperature fell close to the definition level of “afebrile” within 2 days after the
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26 start of CyA treatment. In addition, symptoms such as rash and swelling of the cervical
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28 lymph nodes also improved. On the other hand, 6 of the 28 patients failed to become
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30 afebrile within 5 days after the start of CyA and/or high fever returned after becoming
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32 afebrile within 5 days, despite having an adequate trough level of CyA. These facts
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34 suggest that certain subgroups of patients with refractory KD may be resistant to CyA.
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38 Two possible reasons for this can be suggested. First, the timing of CyA treatment might
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40 be too late. We used CyA to selectively treat KD patients who had been resistant to two
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42 courses of IVIG therapy. Because CyA was a new option for refractory KD and we had
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44 no data about its safety and efficacy for patients with KD, parents and guardians were
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3 not expected to give their approval until the standard therapy for KD had proven
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6 ineffective. On the other hand, it is desirable to initiate any new treatment as rapidly as
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9 possible, as damage to the walls of coronary arteries might progress within the first ten
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12 days of illness unless the process of acute inflammation can be suppressed. Therefore,
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15 we set up a protocol in which CyA treatment was started immediately after completing
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18 the additional IVIG therapy. Second, the suppressive effect of CyA on the calcineurin or
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21 NFAT pathway might be insufficient to control the severe vasculitis. Further analyses of
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24 both the timing of CyA treatment and genetic background factors including the NFAT
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27 and other pathways will be needed to clarify these issues.
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32 We did not have any information about whether oral administration or intravenous
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35 infusion of CyA would be more effective. However, we selected oral administration,
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38 because the oral route is easier and more tolerable for young children and infants, who
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41 need to be treated for two or three weeks. The volume of CyA was small, and therefore
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44 the patients were able to take it without major problems. By examining the trough
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47 values, it became clear that oral administration of CyA allowed a sufficient high serum
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50 concentration (60-200 ng/mL) to be obtained. Further analyses of trough values in more
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53 patients with refractory KD will be needed to assess the best therapeutic levels of CyA
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57 in KD.
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3 KD patients who were less than 4 months of age were excluded from the indication
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6 of CyA treatment, because there is insufficient information about the safety of CyA in
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9 infants and children with KD. However, CyA is known to be effective and safe for
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12 children with nephrotic syndrome resistant to steroid.^{28,29)} In the latter case, the dose of
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15 CyA was adjusted to maintain a trough level of 120-150 ng/ml during the initial 3
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18 months of treatment, followed by 80-100 ng/ml during months 4-12.²⁸⁾ Adverse events
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21 in children with nephrotic syndrome comprised CyA-related nephrotoxicity (3.8%),
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24 bacterial infections (2/38=5.3%), and posterior reversible encephalopathy syndrome
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27 (1/38=2.6%). As the duration of CyA treatment for KD was much shorter than that for
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30 nephrotic syndrome, it was expected that CyA treatment might be associated with few
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33 adverse events in this series. Indeed, the increase of hepatic enzymes and hypertension
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36 in these 28 patients did not develop. However, many of our patients treated with CyA
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39 showed hyperkalemia, a feature that was absent in nephrotic syndrome. Although the
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42 definition of hyperkalemia in infants and children is controversial,³⁰⁾ we classified these
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45 patients according to the criteria of Japan.²⁷⁾ Fortunately, no harmful events such as
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48 ventricular arrhythmia occurred. The levels of serum potassium were not correlated with
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51 serum CyA trough levels, serum creatinine levels, and eGFR. In addition, there have
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65 been a report in which pseudohyperkalemia was observed in the sera of KD despite the

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3 normal plasma level.³¹⁾ This report indicates that pseudohyperkalemia should be
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6 considered in patients with KD whose platelet counts are markedly increased. Indeed,
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9 serum potassium levels were correlated closely with platelets counts in these 28 patients
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12 who were treated with CyA (data not shown). However, precise mechanism responsible
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15 for the hyperkalemia during CyA treatment in KD patients is still unclear. In this study,
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18 we did not examine the C2 levels of CyA, which might have been better correlated with
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21 the AUC₀₋₄ (area under the curve) than the trough level, because of the difficulty
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24 involved in taking frequent blood samples from infants and small children. We think
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27 that analyses for both C2 levels of CyA and potassium clearance rate will be needed in
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30 the future studies.
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35 It is difficult to evaluate whether CyA inhibits the development of CAL, which is
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38 the most serious outcome of KD. Hashino K et al.¹⁰⁾ reported that there were 17 patients
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41 (17/262=6.5%) resistant to both initial (2g/kg) and additional (1g/kg) IVIG. They
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44 randomly divided these patients into two groups (third IVIG or steroid pulse therapy).
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47 After third additional option, there was no significant difference in the incidence of
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50 CAL between the two groups. In their study, 12 (70.6%) of 17 patients resistant to both
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53 initial (2g/kg) and additional (1g/kg) IVIG developed CAL. Thus, 12 (4.6%) of 262
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56 patients developed CAL. Our present study was not a randomized control study but a
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3 pilot study, in which 4 (13.3%) of 30 patients resistant to both initial (2g/kg) and
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6 additional (2g/kg) IVIG developed CAL. Thus, 4 (1.2%) of 329 patients developed
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9 CAL. All four patients were resistant to both initial and additional IVIG treatment, and
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12 were treated with CyA. However, coronary arterial dilatation occurred during additional
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15 IVIG (before CyA treatment) in two of the four patients, and CyA did not inhibit the
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18 progression of CAL in these patients. In the other two patients, CAL developed after the
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21 start of CyA treatment.
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25 There were several limitations to this study. First, the sample size was small. We were
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28 unable to analyze the factors affecting the response to CyA because only six cases were
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31 resistant to CyA. Second, this was a pilot study and not a randomized control clinical
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34 trial. Therefore, we were unable to conclude whether CyA exerts preventive effects
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37 against CAL in patients with refractory KD.
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41 In summary, CyA treatment is considered well tolerated and a safe and promising
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44 option for patients with refractory KD. Oral administration of CyA showed good
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47 compliance with treatments and has both antifebrile and anti-inflammatory effects in
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50 KD patients who are resistant to IVIG. Further investigations will be needed to clarify
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53 the dose, safety, optimum timing and duration of CyA treatment.
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References

1. Kawasaki T. Acute febrile mucocutaneous syndrome with lymphoid involvement with specific desquamation of fingers and toes in children: clinical observation of 50 cases. *Jpn J Allergol* 1967 ; 16:178-222.
2. Park YW, Han JW, Park IS, et al.: Kawasaki disease in Korea, 2003-2005. *Pediatr Infect Dis J* 2007; 26(9):821-823.
3. Huang WC, Huang LM, Chang IS, et al.: Epidemiologic features of Kawasaki disease in Taiwan, 2003-2006. *Pediatrics* 2009; 123(3):e401-405.
4. Holman RC, Belay ED, Christensen KY, Folkema AM, Steiner CA, Schonberger LB.: Hospitalizations for Kawasaki syndrome among children in the United States, 1997-2007. *Pediatr Infect Dis J* 2010; 29(6):483-488.
5. Harnden A, Mayon-White R, Perera R, Yeates D, Goldacre M, Burgner D.: Kawasaki disease in England: ethnicity, deprivation, and respiratory pathogens. *Pediatr Infect Dis J* 2009; 28(1):21-24.
6. Nakamura Y, Yashiro M, Uehara R, Oki I, Kayaba K, Yanagawa H.: Epidemiologic features of Kawasaki disease in Japan: Results from the nationwide survey in 2005- 2006. *J Epidemiol* 2008; 18(4):167-172.
7. Newburger JW, Takahashi M, Beiser AS, et al.: A single intravenous infusion of

- 1
2
3 gamma globulin as compared with four infusions in the treatment of acute
4
5
6 Kawasaki syndrome. *N Engl J Med* 1991;324:1633-1639
7
8
9
10 8. Takeshita S, Kawamura Y, Nakatani K, Tujimoto H, Tokutomi T.: Standard-dose
11
12 and short-term corticosteroid therapy in immunoglobulin-resistant Kawasaki
13
14 disease. *Clin Pediatr (Phila)* 2005; 44(5): 423-426.
15
16
17
18 9. Lang BA, Yeung ES, Oen KG, Malleson PN, Huber AM, Riley M, et al.:
19
20 Corticosteroid treatment of refractory Kawasaki disease. *J Rheumatol.*2006;
21
22 33(4):803-809.
23
24
25
26
27
28 10. Hashino K, Ishii M, Iemura M, Akagi T, Kato H.: Re-treatment for immuno
29
30 globulin-resistant Kawasaki disease: a comparative study of additional immune
31
32 globulin and steroid pulse therapy. *Pediatr Int.* 2001; 43(3):211-217.
33
34
35
36
37
38 11. Furukawa T, Kishiro M, Akimoto K, Nagata S, Shimizu T, Yamashiro Y.:
39
40 Effects of steroid pulse therapy on immunoglobulin-resistant Kawasaki disease.
41
42
43
44
45 Arch Dis Child 2008; 93(2): 142-146.
46
47
48 12. Burns JC, Mason WH, Hauger SB, Janai H, Bastian JF, W Ehrley JD, et al.:
49
50
51
52
53
54
55
56
57
58
59
60
61
62
63
64
65

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2
3 treatment of intravenous immunoglobulin-resistant Kawasaki disease. *J Pediatr.*
4
5
6 2008;153(6):833-836.
7
8
9
10 14. Mori M, Imagawa T, Katakura S, Miyamae T, Okuyama K, Ito S, et al.: Efficacy
11
12 of plasma exchange therapy for Kawasaki disease intractable to intravenous
13
14 gamma-globulin. *Mod Rheumatol.* 2004; 14(1):43-47.
15
16
17
18
19 15. Raman V, Kim J, Sharkey A, Chatila T.: Response of refractory Kawasaki
20
21 disease to pulse steroid and cyclosporine A therapy. *Pediatr Infect Dis J* 2001;
22
23 20(6):635-637.
24
25
26
27
28
29 16. Lee TJ, Kim KH, Chun JK, Kim DS.: Low-dose methotrexate therapy for
30
31 intravenous immunoglobulin-resistant Kawasaki disease. *Yonsei Med J* 2008;
32
33 49(5):714-718.
34
35
36
37
38
39 17. Inoue Y, Okada Y, Shinohara M, Kobayashi T, Kobayashi T, Tomomasa T, et al.:
40
41 A multicenter prospective randomized trial of corticosteroids in primary therapy
42
43 for Kawasaki disease: clinical course and coronary artery outcome. *J*
44
45 *Pediatr.*2006; 149(3):336-341.
46
47
48
49
50
51 18. Kobayashi T, Inoue Y, Otani Y, Morikawa A, Kobayashi T, Takeuchi K, et al.:
52
53 Risk stratification in the decision to include prednisolone with intravenous
54
55
56
57
58
59
60
61
62
63
64
65

- 1
2
3 immunoglobulin in primary therapy of Kawasaki disease. *Pediatr Infect Dis J*
4
5
6 2009; 28(6):496-502.
7
8
9
- 10 19. Newburger JW, Sleeper LA, McCrindle BW, Minich LL, Gersony W, Vetter VL,
11
12 et al.: Randomized trial of pulsed corticosteroid therapy for primary treatment of
13
14
15
16
17
18
19
20 20. Okada K, Hara J, Maki I, Miki K, Matsuzaki K, Matsuoka T, et al.: Pulse
21
22
23
24
25
26
27
28
29
30
31
32
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36
37
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53
54
55
56
57
58
59
60
61
62
63
64
65
21. Onouchi Y, Gunji T, Burns JC, Shimizu C, Newburger JW, Yashiro M, et al.:
ITPKC functional polymorphism associated with Kawasaki disease susceptibility
and formation of coronary artery aneurysms. *Nat Genet.* 2008 ; 40(1): 35-42.
22. de Inocencio J, Hirsch R.: The role of T cells in Kawasaki disease.
Crit Rev Immunol. 1995; 15(3-4):349-357.
23. Brogan PA, Shah V, Clarke LA, Dillon MJ, Klein N.: T cell activation profiles in
Kawasaki syndrome. *Clin Exp Immunol.* 2008 ;151(2):267-74.
24. Suzuki H, Suenaga T, Takeuchi T, Shibuta S, Yoshikawa N: Marker of T-cell
activation is elevated in refractory Kawasaki disease. *Pediatr Int.* 2010;
52:785-789