Ⅳ.研究成果の刊行物・別刷

Efficacy of immunoglobulin plus prednisolone for prevention of coronary artery abnormalities in severe Kawasaki disease (RAISE study): a randomised, open-label, blinded-endpoints trial

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Summary

Background Evidence indicates that corticosteroid therapy might be beneficial for the primary treatment of severe Kawasaki disease. We assessed whether addition of prednisolone to intravenous immunoglobulin with aspirin would reduce the incidence of coronary artery abnormalities in patients with severe Kawasaki disease.

Methods We did a multicentre, prospective, randomised, open-label, blinded-endpoints trial at 74 hospitals in Japan between Sept 29, 2008, and Dec 2, 2010. Patients with severe Kawasaki disease were randomly assigned by a minimisation method to receive either intravenous immunoglobulin (2 g/kg for 24 h and aspirin 30 mg/kg per day) or intravenous immunoglobulin plus prednisolone (the same intravenous immunoglobulin regimen as the intravenous immunoglobulin group plus prednisolone 2 mg/kg per day given over 15 days after concentrations of C-reactive protein normalised). Patients and treating physicians were unmasked to group allocation. The primary endpoint was incidence of coronary artery abnormalities during the study period. Analysis was by intention to treat. This trial is registered with the University Hospital Medical Information Network clinical trials registry, number UMIN000000940.

Findings We randomly assigned 125 patients to the intravenous immunoglobulin plus prednisolone group and 123 to the intravenous immunoglobulin group. Incidence of coronary artery abnormalities was significantly lower in the intravenous immunoglobulin plus prednisolone group than in the intravenous immunoglobulin group during the study period (four patients [3%] *vs* 28 patients [23%]; risk difference 0·20, 95% CI 0·12–0·28, p<0·0001). Serious adverse events were similar between both groups: two patients had high total cholesterol and one neutropenia in the intravenous immunoglobulin plus prednisolone group, and one had high total cholesterol and another non-occlusive thrombus in the intravenous immunoglobulin group.

Interpretation Addition of prednisolone to the standard regimen of intravenous immunoglobulin improves coronary artery outcomes in patients with severe Kawasaki disease in Japan. Further study of intensified primary treatment for this disease in a mixed ethnic population is warranted.

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Introduction

Kawasaki disease is an acute systemic vasculitis of unknown cause that affects mainly infants and children and is a major cause of acquired heart disease in developed countries.[1] Treatment with high-dose intravenous immunoglobulin plus aspirin resolves inflammation and reduces the occurrence of coronary artery abnormalities.[2–4] However, about 20% of patients have persistent or recurrent fever after completion of intravenous immunoglobulin[5] and these patients have a particularly high risk of developing coronary artery abnormalities.[6–8]

Although corticosteroids are a useful treatment option for various forms of vasculitis, many physicians have hesitated to use them because a report[9] showed a high incidence of coronary artery abnormalities in patients who received a prolonged course of oral prednisolone alone. However, findings from a subsequent retrospective study[10] of the effects of corticosteroids in Kawasaki disease showed possible benefits. In a meta-analysis,[11] inclusion of corticosteroids in regimens containing aspirin for primary treatment of Kawasaki disease reduced the incidence of coronary artery abnormalities. In 2007, findings from a randomised, placebo-controlled trial[12] of the efficacy of a single dose of pulsed intravenous methylprednisolone added to conventional therapy showed that pulsed corticosteroid treatment did not improve coronary artery outcomes. In a randomised, open-label, non-blinded trial,[13] intravenous immunoglobulin plus prednisolone decreased the incidence of coronary artery abnormalities and treatment failure; however, the trial had potential methodological flaws.[14] We subsequently noted in a retrospective analysis[15] that primary treatment with intravenous immunoglobulin plus prednisolone improved

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coronary and clinical outcomes in patients at high risk for no response to primary intravenous immunoglobulin. Thus, the addition of corticosteroids to intravenous immunoglobulin as primary treatment might offer important therapeutic benefits to such patients with Kawasaki disease at high risk for non-response to primary treatment with intravenous immunoglobulin.

We aimed to assess the efficacy of primary prednisolone treatment as an addition to conventional treatment with intravenous immunoglobulin.

Methods

Study design and patients

We did the Randomized controlled trial to Assess Immunoglobulin plus Steroid Efficacy for Kawasaki disease (RAISE study)—a multicentre, prospective, randomised, open-label, blinded-endpoints, parallel-group study—at 74 hospitals in Japan between Sept 29, 2008, and Dec 2, 2010. We diagnosed Kawasaki disease with the Japanese diagnostic guidelines for Kawasaki disease.[16] Eligible participants had a risk score[17] of five points or higher, which emphasises the positive predictive value of no response to initial treatment with intravenous immunoglobulin. Scoring and cutoff values of the risk score were as follows: two points each for serum sodium concentration of 133 mmol/L or less, 4 days or fewer of illness at diagnosis, aspartate aminotransferase concentration of 100 U/L or more, white blood cells representing neutrophils of 80% or greater; and one point each for platelet count 30×10^4/μL or less, C-reactive protein concentration of 100 mg/L or more, and age 12 months or younger. If laboratory tests were done more than once before primary treatment, we used the highest value for percentage of neutrophils, aspartate aminotransferase, and C-reactive protein, and the lowest value for platelet count and sodium.

We excluded patients with a history of Kawasaki disease, those diagnosed on or after day 9 of illness (the first illness day was defined as the day of fever onset), those with coronary artery abnormalities before enrolment, those who were afebrile before enrolment, those who had received steroids (oral, intravenous, intramuscular, or subcutaneous) in the 30 days before the study or intravenous immunoglobulin in the previous 180 days, those with concomitant severe medical disorders (eg, immunodeficiency, chromosomal anomalies, congenital heart diseases, metabolic diseases, nephritis, collagen diseases), and those with suspected infectious disease, including sepsis, septic meningitis, peritonitis, bacterial pneumonia, varicella, and influenza. The study was approved by an independent ethics committee or institutional review board at all participating institutions and was done in accordance with International Conference on Harmonisation guidelines on Good Clinical Practice and the Declaration of Helsinki. Before enrolment, all patients or their guardians provided written informed consent.

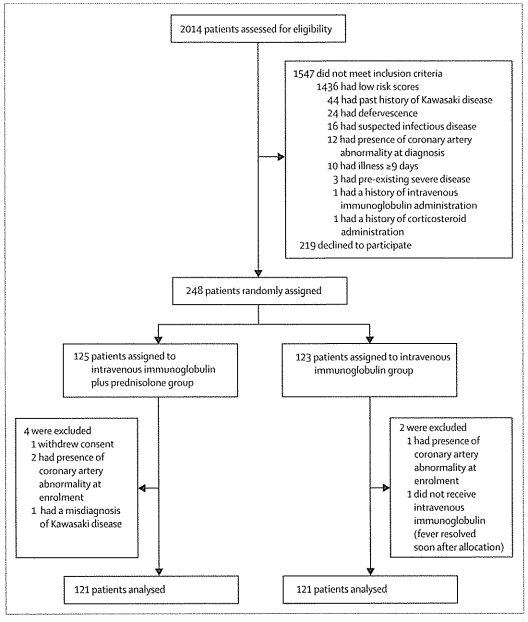

Figure 1: **Trial profile**
Three patients were excluded after randomisation because echocardiograms of the coronary artery at enrolment were classified as abnormal in a centralised review of echocardiography data.

Randomisation and masking

We used a randomisation sequence that was computer generated by the Internet Data and Information Center for Medical Research (INDICE) at the University Hospital Medical Information Network. We used a web-based system to register patients in a database at INDICE in Tokyo, Japan, and after validation of eligibility criteria, we used dynamic (minimisation) allocation to randomly assign patients to either the intravenous immunoglobulin plus prednisolone group or the intravenous immunoglobulin group, in a 1:1 ratio within strata according to age (≤12 months or ≥13 months), sex, and institution. Group assignment was immediately communicated by INDICE to the investigator via the web-based registration system. Patients and treating physicians were not masked to assignment.

Procedures

Patients in the intravenous immunoglobulin group received immunoglobulin 2 g/kg given over 24 h and aspirin 30 mg/kg per day until they were afebrile, followed by aspirin 3–5 mg/kg per day for at least 28 days after fever onset. Patients in the intravenous immunoglobulin plus prednisolone group received the same immunoglobulin regimen as the monotherapy group plus prednisolone 2 mg/kg per day in three divided doses given by intravenous injection in 5 days. If fever resolved 5 days after prednisolone administration, the drug was given orally. When concentration of C-reactive protein normalised (≤5 mg/L), we tapered the prednisolone dose over 15 days in 5-day steps, from 2 mg/kg per day to 1 mg/kg per day to 0·5 mg/kg per day. We did laboratory testing two to three times per week until concentration of C-reactive protein had decreased to 5 mg/L or less.

The maximum dose of prednisolone is 60 mg per day; thus, we tapered patients weighing more than 30 kg from prednisolone 60 mg per day to 30 mg per day to 15 mg/day. 0·5 mg/kg per day of H2-blocker famotidine was given during prednisolone administration. We allowed additional treatment for any patient with fever lasting more than 24 h (ie, no response to primary treatment) or recrudescent fever associated with other symptoms of Kawasaki disease after an afebrile period (relapse), according to the guidelines for acute phase therapy for Kawasaki disease by the Japanese Society of Paediatric Cardiology and Cardiac Surgery.[18] The appendix shows details of additional rescue treatments. We considered patients with an axillary temperature of less than 37·5°C for more than 24 h as afebrile. We obtained an echocardiogram and laboratory data at baseline and at weeks 1 (6–8 days after enrolment), 2 (12–16 days after enrolment), and 4 (24–32 days after enrolment).

Two-dimensional echocardiograms were digitally recorded at institutes and interpreted at a core laboratory by two paediatric cardiologists who were masked to patient identity and group assignment (interobserver reliability κ 0·92; intraobserver reliability κ 0·95 and 0·97). We defined a coronary artery as abnormal when the luminal diameter was more than 3·0 mm in a child aged younger than 5 years or more than 4·0 mm in those aged 5 years and older, respectively, when the internal diameter of a segment was 1·5 times or greater than that of an adjacent segment, or when the luminal contour was clearly irregular.[19] We estimated *Z* score of the proximal right coronary artery, the left main coronary artery, and the proximal left anterior descending artery,[20] and the maximum *Z* score of coronary arteries at weeks 1, 2, and 4.

We clinically monitored patients for adverse events during administration of study treatment and in the subsequent 4 weeks. Safety assessments included recording of all severe adverse events, undertaking of physical examinations (including monitoring of vital signs) and laboratory assessments (including haematology, urinalysis, and serum chemistry screening). The appendix shows definitions of adverse events.

The primary endpoint was incidence of coronary artery abnormalities during the study period, which we identified with two-dimensional echocardiography. We classified patients as having an abnormality if they fulfilled the criterion for the primary endpoint at any timepoint—ie, at week 1, 2, or 4. Secondary endpoints were incidence of coronary artery abnormalities at week 4 after enrolment, *Z* scores of coronary arteries, incidence of need for additional rescue treatment, duration of fever after enrolment, serum concentrations of C-reactive protein at 1 and 2 weeks after enrolment, and serious adverse events. If concentration of C-reactive protein was undetectable, we imputed it as 50% of the lower limit of the assay.

Statistical analyses

We calculated the required sample size on the basis of the assumption that intravenous immunoglobulin plus prednisolone would reduce the percentage of patients with coronary artery abnormalities from 18% to 8%. With a two-sided test, an α of 0·05, a power of 80%, and the assumption that 10% of patients would not complete the study, a total sample of 392 patients would be needed. We did analyses by intention to treat. We planned one interim analysis to analyse the primary endpoint (p=0·0034). We used the Lan-DeMets α-spending function[21] with the O'Brien-Fleming monitoring boundaries to adjust for several comparisons.

All reported p values are two-sided. To compare the distributions of data between the two study groups, we

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See Online for appendix

	IVIG+PSL (N=121)	IVIG (N=121)
Age (months)	31 (12–50)	30 (13–47)
≤6 months	17 (14%)	15 (12%)
Male sex	67 (55%)	68 (56%)
Days of illness at enrolment	4 (4–5)	4 (3–5)
White-cell count ($\times10^3$/μL)	15·4 (4·9; 121)	15·6 (4·7; 121)
Neutrophils (%)	82·0% (71·2–87·0; 121)	80·5% (69·6–87·0; 120)
Haematocrit (%)	33·7% (3·0; 121)	34·0% (2·9; 121)
Platelet count ($\times10^4$/μL)	27·4 (23·7–34·6; 121)	28·9 (24·3–36·3; 121)
Aspartate aminotransferase (U/L)	90 (42–211; 121)	120 (47–319; 121)
Sodium (mmol/L)	132 (130–133; 121)	133 (130–134; 121)
Blood glucose (mmol/L)	6·2 (1·3; 110)	6·3 (1·3; 107)
Total cholesterol (mmol/L)	3·6 (0·7; 113)	3·6 (0·8; 109)
C-reactive protein (mg/L)	93 (57–130; 121)	88 (57–114; 121)
Risk score	6 (5–7; 121)	6 (5–7; 121)
Absolute diameter of coronary artery*	n=121	n=121
Proximal right coronary artery	1·94 (0·37)	1·94 (0·33)
Left main coronary artery	2·35 (0·38)	2·35 (0·37)
Proximal left anterior descending artery	1·96 (0·35)	1·93 (0·29)
Z score of coronary artery diameters†	n=119	n=119
Proximal right coronary artery	1·39 (0·89–2·06)	1·61 (1·06–2·28)
Left main coronary artery	1·57 (1·20–1·97)	1·70 (1·30–2·13)
Proximal left anterior descending artery	1·57 (1·07–2·15)	1·67 (1·20–2·04)

Data are median (IQR), n (%), mean (SD; n), or median (IQR; n), unless otherwise indicated. IVIG=intravenous immunoglobulin. PSL=prednisolone.

Table 1: **Demographic, laboratory, and echocardiographic characteristics of patients at enrolment**

used the *t* test for continuous variables if the data were normally distributed, and the Mann-Whitney U test for data that were not normally distributed. We used the Kolmogorov-Smirnov algorithm to identify whether variables had a normal distribution. We assessed duration of fever after enrolment with the log-rank test, and assessed categorical variables with Fisher's exact test. We did statistical analyses related to the interim analysis with programs for computing group sequential boundaries using the Lan-DeMets method (version 2.1). We did other analyses with the IBM SPSS statistical software (version 19.0). This trial is registered with the University Hospital Medical Information Network clinical trials registry, number UMIN000000940.

	IVIG+PSL (N=121)	IVIG (N=121)	p value
Coronary artery abnormality			
During study period	4/121 (3%)	28/121 (23%)	<0·0001
At week 4	4/120 (3%)	15/120 (13%)	0·014
Absolute diameter of coronary artery			
Week 1	n=120	n=120	..
Proximal right coronary artery	1·94 (0·50)	2·09 (0·68)	0·013
Left main coronary artery	2·34 (0·38)	2·51 (0·45)	0·0025
Proximal left anterior descending artery	1·97 (0·34)	2·05 (0·39)	0·10
Week 2	n=120	n=120	..
Proximal right coronary artery	1·91 (0·37)	2·11 (0·68)	0·030
Left main coronary artery	2·36 (0·49)	2·53 (0·46)	0·0046
Proximal left anterior descending artery	1·97 (0·46)	2·14 (0·88)	0·052
Week 4	n=120	n=120	..
Proximal right coronary artery	1·97 (0·63)	2·09 (0·72)	0·18
Left main coronary artery	2·36 (0·51)	2·52 (0·46)	0·011
Proximal left anterior descending artery	1·99 (0·47)	2·10 (0·77)	0·17
Z score of coronary artery diameters			
Week 1	n=120	n=120	..
Proximal right coronary artery	1·29 (0·67–1·97)	1·83 (0·76–2·74)	0·0024
Left main coronary artery	1·54 (1·13–2·02)	1·93 (1·46–2·45)	<0·0001
Proximal left anterior descending artery	1·51 (1·04–2·17)	1·90 (1·27–2·43)	0·0087
Week 2	n=120	n=120	..
Proximal right coronary artery	1·33 (0·72–1·89)	1·71 (0·94–3·03)	0·0039
Left main coronary artery	1·56 (1·15–1·95)	1·95 (1·57–2·48)	<0·0001
Proximal left anterior descending artery	1·44 (1·03–2·02)	1·87 (1·24–2·77)	0·0006
Week 4	n=120	n=120	..
Proximal right coronary artery	1·24 (0·64–2·05)	1·62 (0·82–2·54)	0·0083
Left main coronary artery	1·57 (1·24–1·91)	1·90 (1·48–2·48)	<0·0001
Proximal left anterior descending artery	1·48 (1·01–2·03)	1·90 (1·20–2·52)	0·0028
Maximum *Z* score of each coronary artery	n=121	n=121	..
Proximal right coronary artery	1·92 (1·28–2·53)	2·32 (1·58–3·36)	0·0014
Left main coronary artery	1·91 (1·48–2·24)	2·27 (1·83–2·83)	<0·0001
Proximal left anterior descending artery	1·98 (1·45–2·50)	2·26 (1·79–2·91)	0·0007

Data are n/N (%), mean (SD), or median (IQR), unless otherwise indicated. We calculated p values for coronary artery abnormality with Fisher's exact test and those for *Z* scores with the Mann-Whitney U test. IVIG=intravenous immunoglobulin. PSL=prednisolone.

Table 2: **Coronary artery outcomes in the two treatment groups**

Role of funding source

The sponsor of the study had no role in the study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all study data and had final responsibility for the decision to submit for publication.

Results

The study started on Sept 29, 2008. We did the preplanned interim analysis after enrolment of the 200th patient in June, 2010. The analysis showed a significant difference in the incidence of coronary artery abnormalities between the two treatment groups (p<0·0001); therefore, the independent data and safety monitoring committee recommended termination of the study. The study was terminated on Dec 2, 2010. Figure 1 shows the trial profile. Of 2014 patients assessed for trial eligibility, 1436 (71%) did not meet inclusion criteria because they had low risk scores. Of the 467 eligible children, we received parental consent for enrolment for 248 (53%). We randomly assigned 125 patients to the intravenous immunoglobulin plus prednisolone group and 123 to the intravenous immunoglobulin group. We excluded six patients because they were identified as ineligible (figure 1). Thus, we analysed data for 242 patients. Patients in the two study groups had similar baseline characteristics (table 1).

The incidence of coronary artery abnormalities during the study period was significantly lower in the intravenous immunoglobulin plus prednisolone group than in the intravenous immunoglobulin group (table 2; risk difference 0·20, 95% CI 0·12–0·28, number needed to treat was five). Similarly, the incidence of abnormalities at week 4 after enrolment was significantly lower in the intravenous immunoglobulin plus prednisolone group than in the intravenous immunoglobulin group (table 2; risk difference 0·09, 0·02–0·16, number needed to treat was ten). Only one patient in the intravenous immunoglobulin group developed a giant coronary aneurysm (maximum diameter 10·3 mm) in the left descending artery. *Z* scores of the proximal right coronary arteries, left main coronary artery, and proximal left anterior descending arteries were significantly lower in the intravenous immunoglobulin plus prednisolone group than in the intravenous immunoglobulin group at weeks 1, 2, and 4 (table 2). Figure 2 shows a boxplot of maximum *Z* scores for each coronary artery.

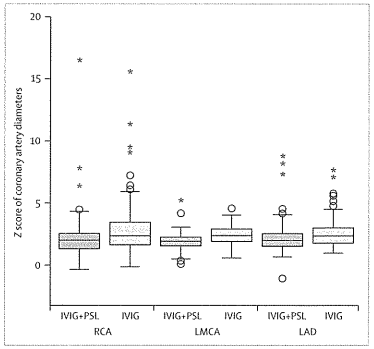

Figure 2: **Maximum *Z* score of each coronary artery**
Boxplot shows median (IQR). Error bars show the largest and smallest values that were not outliers. Circles represent values that are more than 1·5 box lengths from the 25th and 75th percentiles (outliers). Asterisks show values that are more than 3·0 box lengths from the 25th and 75th percentiles (extreme values). Circles and asterisks represent individual patients. IVIG=intravenous immunoglobulin. PSL=prednisolone. RCA=right proximal coronary artery. LMCA=left main coronary artery. LAD=proximal left anterior descending artery.

Patients in the intravenous immunoglobulin plus prednisolone group had more rapid fever resolution than did those in the intravenous immunoglobulin group (table 3). The incidence of additional rescue treatments was lower in the intravenous immunoglobulin plus prednisolone group than in the intravenous immunoglobulin group (table 3; risk difference 0·26, 95% CI 0·16–0·37, number needed to treat was four). Patients in the intravenous immunoglobulin group needed more additional rescue treatment than did those in the intravenous immunoglobulin plus prednisolone group (table 3). About 60% of patients who received additional rescue treatments were retreated with intravenous immunoglobulin (table 3).

Children in the intravenous immunoglobulin plus prednisolone group had higher white-blood cell counts at weeks 1 and 2 and lower counts at week 4; higher percentage of neutrophils at weeks 1 and 2; higher haematocrit at weeks 1, 2, and 4; lower platelet count at week 4; lower aspartate aminotransferase concentrations at weeks 2 and 4; higher serum sodium at week 4; higher total cholesterol at weeks 1, 2, and 4; and lower

	IVIG+PSL (N=121)	IVIG (N=121)	p value
Duration of fever after enrolment (days)	1 (1–1)	2 (1–4)	<0·0001
Patients needing additional therapy*	16 (13%)	48 (40%)	<0·0001
Non-response to primary treatment	6 (5%)	36 (30%)	<0·0001
Relapse	13 (11%)	15 (12%)	0·84
Additional rescue therapies			
Retreatment with IVIG	19/32 (59%)	56/90 (62%)	..
PSL	2/32 (6%)†	14/90 (16%)	..
Pulsed-dose methylprednisolone	4/32 (13%)	11/90 (12%)	..
Increased aspirin dose	0/32 (0%)	3/90 (3%)	..
Ulinastatin	5/32 (16%)	3/90 (3%)	..
Ciclosporin A	2/32 (6%)	0/90 (0%)	..
Infliximab	0/32 (0%)	2/90 (2%)	..
Plasmapheresis	0/32 (0%)	1/90 (1%)	..

Data are median (IQR) or n (%). We calculated p values for duration of fever after enrolment with the log-rank test and those for need for additional therapy, non-response to primary treatment, and relapse with Fisher's exact test. IVIG=intravenous immunoglobulin. PSL=prednisolone. *Three patients in the IVIG+PSL group and three in the IVIG group were unresponsive to primary treatment and subsequently relapsed. These six patients were included in both the non-response to primary treatment group and the relapse group. †Prednisolone dose was increased for these two patients after relapse during tapering of prednisolone.

Table 3: **Clinical outcomes and additional rescue therapy in the two treatment groups**

	IVIG+PSL (N=121)	IVIG (N=121)	p value
White-cell count (×10³/μL)			
Week 1	18·3 (14·7–23·7; 120)	9·5 (7·9–12·6; 120)	<0·0001
Week 2	14·7 (11·3–18·9; 120)	8·0 (6·5–10·3; 120)	<0·0001
Week 4	7·0 (5·5–8·7; 119)	8·4 (6·9–10·1; 117)	<0·0001
Neutrophils (%)			
Week 1	60·0% (15·6; 119)	44·9% (15·8; 115)	<0·0001
Week 2	55·4% (17·3; 119)	42·3% (14·8; 117)	<0·0001
Week 4	38·2% (16·4; 119)	34·7% (10·6; 113)	0·059
Haematocrit (%)			
Week 1	35·9% (2·9; 120)	33·6% (3·4; 120)	<0·0001
Week 2	36·1% (3·0; 120)	33·9% (3·1; 120)	<0·0001
Week 4	36·1% (2·9; 119)	35·1% (2·7; 117)	0·0082
Platelet count (×10⁴/μL)			
Week 1	53·5 (45·5–69·0; 120)	54·0 (44·4–66·9; 120)	0·87
Week 2	49·5 (37·9–59·2; 120)	47·4 (38·7–58·9; 120)	0·92
Week 4	29·4 (23·7–40·6; 119)	35·6 (28·5–44·2; 117)	0·0005
Aspartate aminotransferase (U/L)			
Week 1	37 (30–46; 121)	35 (28–41; 121)	0·20
Week 2	29 (25–36; 120)	37 (32–44; 120)	<0·0001
Week 4	32 (28–39; 119)	35 (29–42; 117)	0·028
Sodium (mmol/L)			
Week 1	136 (135–138; 121)	137 (135–138; 121)	0·12
Week 2	137 (136–138; 121)	137 (136–138; 120)	0·76
Week 4	139 (138–140; 119)	138 (137–139; 117)	0·015
Blood glucose (mmol/L)			
Week 1	5·1 (0·9; 113)	5·2 (1·1; 108)	0·83
Week 2	5·1 (0·9; 118)	5·0 (0·7; 106)	0·55
Week 4	5·1 (0·6; 110)	5·2 (0·6; 104)	0·33
Total cholesterol (mmol/L)			
Week 1	5·6 (1·1; 113)	4·6 (0·9; 109)	<0·0001
Week 2	6·8 (1·7; 117)	5·2 (1·3; 110)	<0·0001
Week 4	5·2 (1·2; 115)	4·7 (1·0; 110)	0·0005
C-reactive protein (mg/L)			
Week 1	2·5 (1·0–5·0; 121)	6·0 (4·0–13·0; 121)	<0·0001
Week 2	0·4 (0·2–1·0; 120)	1·0 (0·5–3·0; 120)	<0·0001
Week 4	0·5 (0·2–2·0; 119)	0·7 (0·2–1·6; 117)	0·72

Data are median (IQR; n) or mean (SD; n). We calculated p values with the Mann-Whitney U test, except those for percentage of neutrophil, haematocrit, blood glucose, and total cholesterol, for which we used the two-sample *t* test. IVIG=intravenous immunoglobulin. PSL=prednisolone.

Table 4: **Laboratory data at 1, 2, and 4 weeks after enrolment**

concentrations of C-reactive protein at weeks 1 and 2 than did those in the intravenous immunoglobulin group (table 4). Other laboratory measures were similar in the two groups (table 4).

Three (2%) of 121 patients in the intravenous immunoglobulin plus prednisolone group and two (2%) of 121 in the intravenous immunoglobulin group had serious adverse events. Events in the intravenous immunoglobulin plus prednisolone group were high total cholesterol in two patients (10·4 mmol/L and 12·0 mmol/L) and neutropenia in one patient (300/μL). Events in the intravenous immunoglobulin group were high total cholesterol (11·8 mmol/L) and a non-occlusive thrombus in the left coronary artery on echocardiography. All adverse events resolved spontaneously.

Discussion

Our findings show that combination treatment with intravenous immunoglobulin plus prednisolone had a significant advantage compared with intravenous immunoglobulin alone for prevention of coronary artery abnormalities, reduced need for additional rescue treatment, and more rapidly resolved fever and inflammatory markers in patients with severe Kawasaki disease (panel). The high incidence of additional rescue treatment in the intravenous immunoglobulin group was because we used the risk score system to select the patients with severe disease and confirms the positive predictive value of the risk score in prediction of no response to initial intravenous immunoglobulin.

Panel: Research in context

Systematic review

We searched PubMed and the Cochrane library for articles in English with a combination of the search terms "Kawasaki disease" and "corticosteroids". We excluded retrospective studies, and those that investigated corticosteroids as an additional rescue treatment for patients who do not respond to intravenous immunoglobulin. We identified two US studies[12,22] and one Japanese study.[13,23] Findings from the US studies showed no decrease in the incidence of coronary artery abnormalities; however, the Japanese study reported a significant decrease in the incidence of such abnormalities. The effect of corticosteroid treatment was assessed in a meta-analysis[24] that included a retrospective study. The investigators noted that the rates of initial treatment failure were significantly lower in patients who received corticosteroid treatment in combination with intravenous immunoglobulin than in those who received intravenous immunoglobulin alone (odds ratio 0·50, 95% CI 0·32–0·79). No significant increase was noted in the incidence of coronary artery lesions or coronary aneurysms in the corticosteroid group (0·67, 0·35–1·28).

Interpretation

Findings from our randomised study show that combination treatment with intravenous immunoglobulin plus prednisolone is better than that with intravenous immunoglobulin alone in prevention of coronary artery abnormalities, reducing the need for additional rescue treatment, and rapid resolution of fever and inflammatory markers in Japanese patients with severe Kawasaki disease. Although the incidence of severe adverse events was similar between the two treatment groups, our study had insufficient statistical power to assess the incidence of rare adverse events. Further study of intensified primary therapy for this disease in a mixed ethnic population is warranted.

In the early stage of coronary arerty lesion development (7–9 days after disease onset), an influx of neutrophils occurs in an affected coronary artery. This influx is followed by rapid transition to large mononuclear cells and lymphocytes (mostly CD8 T cells) and immunoglobulin-A plasma cells.[25,26] At this stage, destruction of the internal elastic lamina occurs, followed by myofibroblast proliferation, which leads to formation of a coronary aneurysm. These findings underscore the importance of immediate treatment of inflammation and vasculitis—ie, before pathological changes become irreversible. Because patients who do not respond to primary treatment with intravenous immunoglobulin are usually identified 24–48 h after completion of treatment, rescue therapies are generally started 2–3 days after diagnosis of Kawasaki disease. Such delays in the start of additional treatments might allow formation of coronary artery abnormalities. Our therapeutic strategy—namely, risk stratification at diagnosis followed by intensive primary treatment in high-risk patients—might effectively suppress inflammation due to Kawasaki disease and subsequent remodelling of the coronary arterial wall.

We previously reported[27] that intravenous immunoglobulin plus prednisolone as primary treatment for patients with this disease rapidly reduced circulating inflammatory cytokines. In the present study, serum concentrations of C-reactive protein rapidly recovered in the intravenous immunoglobulin plus prednisolone group, which is consistent with reduced inflammation and improved coronary outcomes. In a 2007 US study, Newburger and colleagues[12] noted no improvement in efficacy of a regimen of corticosteroid treatment combined with intravenous immunoglobulin. A reason for the difference in the findings of the US study and our study is the time that primary treatment was started: median time until start of treatment was 2 days earlier in our study than in the US report.[12] If the main benefit of corticosteroid treatment for Kawasaki disease is early suppression of vasculitis that precedes vascular remodelling, a delay in start of treatment could play a crucial part in formation of coronary artery abnormalities. A second difference between these studies was the duration of corticosteroid administration. Although the total dose of corticosteroids was similar in the studies, median duration of prednisolone administration was 21 days in our study compared with one course of 30 mg/kg methylprednisolone in the US study. The serum half-life of a pulsed dose of methylprednisolone is about 3 h;[28,29] we administered prednisolone over 3 weeks. The serum half-life of intravenous immunoglobulin is 4 weeks.[30] Although Kawasaki disease is self-limiting, fever caused by the disease persists for about 2–3 weeks if untreated. Thus, duration of corticosteroid administration might be more important than maximum concentration of corticosteroid in suppression of inflammation and vasculitis in this disease.

A third explanation for the different outcomes in the two studies is patient selection. We enrolled patients who, on the basis of high risk scores, were identified as potential non-responders to primary intravenous immunoglobulin. This method of risk stratification increased the statistical power to assess whether intravenous immunoglobulin plus prednisolone had a significant advantage in prevention of abnormalities. Finally, the genetic background of the populations might have affected the results. The patients in our study were ethnically homogeneous, unlike those in the US study. Additionally, findings from a retrospective study[31] showed that initial therapy with methylprednisolone plus intravenous immunoglobulin improved coronary outcomes in patients with severe Kawasaki disease, as defined by another predictive model.

Predicted adverse events in our study included marked leucocytosis, with an increase in neutrophilic leucocytes at weeks 1 and 2, which we noted more often in the intravenous immunoglobulin plus prednisolone group than in the intravenous immunoglobulin group; however, the affected patients recovered by week 4. Concentration of serum cholesterol was substantially increased in the intravenous immunoglobulin plus prednisolone group. Moreover, we could not assess potential adverse effects of corticosteroids—such as severe bacterial infection, thrombosis, bone mineral loss, osteonecrosis of the femoral head, and ophthalmic lesions—because of the short follow-up and insufficient statistical power to exclude the possibility of rare adverse events. Therefore, further study is needed to assess the safety of treatment with intravenous immunoglobulin plus prednisolone.

Additional limitations of this study should be noted in interpretation of our results. First, some concern exists about the generalisability of the risk score. Although the scoring system was validated in a Japanese cohort,[32] it had adequate specificity but poor sensitivity for predicting no response to primary intravenous immunoglobulin in a North American cohort.[33] Additionally, primary treatment with pulsed-dose methylprednisolone plus intravenous immunoglobulin did not improve coronary outcomes in patients who were classified as being at high risk for intravenous immunoglobulin resistance with our scoring system. In other regions, new prospective models that modify our risk-adapted therapeutic strategy might need to be developed. Another concern is the accuracy of prediction of no response to primary intravenous immunoglobulin on the basis of risk score. In this study, the positive predictive value to predict resistance to primary intravenous immunoglobulin with the risk score was 40%, which is fairly low. We anticipate the development of an accurate predictive model, which possibly includes other biomarkers or genetic background.

Contributors

TS, TK, YK, CG, and KI organised the study. TS, HA, TK, TH, MM, KF, CO, AM, and DK edited the manuscript. TN, MO, SF, AM, ES, and FM obtained the data. TO and KT did the statistical analyses. SO, TK, and MS analysed echocardiographic data. MY edited the images and masked the echocardiographic video.

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Conflicts of interest

We declare that we have no conflicts of interest.

Acknowledgments

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ORIGINAL ARTICLE

Serum adipokine profiles in Kawasaki disease

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Abstract Adipokines are cytokines derived from adipose tissue. Recently it has been established that adipokines are closely linked to the pathophysiology of not only metabolic diseases, such as diabetes mellitus, obesity, and atherosclerosis, but also to inflammation and immune diseases. In this study we measured serum levels of adipokines in patients with acute Kawasaki disease to investigate the role of adipokines in the pathophysiology of Kawasaki disease. Serum resistin, high-molecular-weight (HMW) adiponectin, leptin, and visfatin levels were measured by enzyme-linked immunosorbent assay in a total of 117 subjects: 56 patients with acute Kawasaki disease, 30 healthy children, and 31 patients with acute infectious diseases. Serum resistin levels in patients with Kawasaki disease were significantly higher than those of healthy children and patients with acute infectious diseases. In contrast, mean serum HMW adiponectin, leptin, and visfatin levels in patients with Kawasaki disease exhibited no statistically significant differences compared with those in healthy children and patients with infectious diseases. Serum resistin levels decreased significantly after administration of intravenous immune globulin. Serum resistin levels on admission were significantly higher in nonresponders compared with responders to intravenous immune globulin therapy. A multivariate model revealed that C-reactive protein was a factor that was significantly related to elevated serum resistin level in patients with Kawasaki disease. In patients with Kawasaki disease, serum resistin levels were elevated, but decreased to nearly normal after intravenous administration of immune globulin. In contrast, serum HMW adiponectin, leptin, and visfatin levels showed no statistically significant changes. These findings suggest that resistin plays an important role, while other adipokines do not play a major role, in the pathogenesis of Kawasaki disease.

Keywords Adipokines · Resistin · C-reactive protein · Kawasaki disease

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Introduction

Kawasaki disease is a systemic vasculitis of childhood that was first reported by Tomisaku Kawasaki in 1967 [1]. Patients manifest with fever, bulbar conjunctival injection, changes of the oropharyngeal mucosa, changes of the peripheral extremities, cervical lymphadenopathy, and polymorphous rash [2]. In Japan there are approximately 10,000 new patients annually [3]. The most important complication of this disease is development of coronary lesions that result in acute myocardial infarction. Intravenous immune globulin is a standard therapy that is effective in about 70% of patients, but the cause of the disease has been unclear.

Adipokines or adipocytokines including resistin, adiponectin, leptin, and visfatin are bioactive molecules that are produced and secreted by adipose tissue [4]. Adipokines have various actions in the human body that regulate metabolic conditions, and may have a central role in regulation of insulin resistance [5, 6].

Resistin is an amino acid peptide that belongs to a cysteine-rich secretory protein family [7]. Circulating resistin levels are elevated in humans by obesity and diabetes [8]. Resistin levels are also associated with increasing coronary artery calcification and are predictive of coronary atherosclerosis [9]. Adiponectin is a 244-amino-acid polypeptide that has three isoforms: low molecular weight, middle molecular weight, and high molecular weight (HMW). Decreased levels of HMW adiponectin are associated with coronary artery disease and type 2 diabetes [10, 11]. Leptin is a protein of 167 amino acids. Circulating leptin levels reflect adipose tissue mass, and hyperleptinemia is associated with obesity and other metabolic diseases [12, 13]. Visfatin is one of the adipokines identified in 2004, being predominantly produced and secreted in visceral fat; its expression level in plasma increases during development of obesity [14].

These adipokines show obviously links to metabolic diseases, however recent studies have also suggested that some adipokines might play a role in inflammation and immune diseases [15]; for instance, we have previously shown that serum levels of resistin, leptin, and adiponectin were all associated with C-reactive protein (CRP) level in patients with rheumatoid arthritis, suggesting that these adipokines may act as proinflammatory cytokines in this disease [16].

The object of this study is to clarify serum levels of resistin, HMW adiponectin, leptin, and visfatin in patients with Kawasaki disease during treatment with intravenous immune globulin, and to evaluate the relationships between serum adipokines and their clinical measures.

Methods

Patients

Fifty-six patients (36 males and 20 females, mean age 29.8 ± 1.7 months) with acute-phase Kawasaki disease who were admitted to our university hospital participated in this study. All patients met American Heart Association diagnostic criteria for Kawasaki disease [2]. These patients were treated with oral aspirin and 1 or 2 g/kg intravenous immune globulin after admission. As controls, we collected serum samples from 30 healthy children and 31 patients with acute infectious diseases (14 patients with pharyngitis, 9 with bronchitis, 5 with gastroenteritis, and 3 with exanthema subitum). The protocol for the study was approved by the Ethics Committee of Toho University Hospital. Informed consent was obtained from the parents of all patients.

Adipokine measurements

Blood samples were collected from the patients with acute-phase Kawasaki disease upon admission (before intravenous immune globulin) and at 24–48 h after intravenous immune globulin treatment. Serum resistin, HMW adiponectin, leptin, and visfatin were measured using enzyme-linked immunosorbent assay (ELISA) kits. Serum resistin and leptin levels were measured in all 56 patients, but HMW adiponectin and visfatin were measured in 38 patients because the volume of serum samples was too small to perform all four analyses. Resistin and leptin ELISA kits were both purchased from B-Bridge International, Inc. (Sunnyvale, CA, USA). ELISA kits for HMW adiponectin and visfatin were obtained from Fujirebio, Inc. (Tokyo, Japan) and Phoenix Pharmaceuticals, Inc. (Burlingame, CA, USA), respectively.

Biochemical measurements

All of the patients with Kawasaki disease were examined for complete blood cell counts and serum chemistry, including CRP and electrolytes, before immune globulin therapy. Latex nephelometry (Sekisui Medical Co., Tokyo, Japan) was used for CRP measurement.

Statistical analysis

Comparisons between the three groups were made using the Kruskal–Wallis test. Serum adipokine levels before and after intravenous immune globulin were compared by the Wilcoxon matched-pairs signed-rank test. Correlations between serum adipokines and laboratory data were analyzed by simple linear regression analysis. Multiple regression analysis was used for studying multivariable models. Statistical significance was determined at $p < 0.05$. Statistical analyses of the data were conducted using the StatMate III software program (ATMS, Tokyo, Japan).

Results

Characteristics of the study population

The characteristics of the 3 groups are shown in Table 1. There were no statistically significant differences in age, gender or body weight among the 3 groups of children. In patients with Kawasaki disease, mean ± SD age was

Table 1 Background characteristics of the three patient groups

	Age (months)	Gender (M/F)	Body weight (kg)
Patients with Kawasaki disease ($n = 56$)	29.8 ± 21.7	36/20	12.1 ± 3.6
Patients with acute infectious diseases ($n = 31$)	29.2 ± 17.5	20/11	12.1 ± 3.5
Healthy children ($n = 30$)	26.9 ± 13.0	19/11	11.7 ± 2.4

Values are mean ± SD

Table 2 Clinical characteristics of the patients with Kawasaki disease

	Age (months)	Days on IVIG	Serum CRP conc. (mg/dl)	WBC counts ($\times 10^3/\mu l$)	Sodium conc. (mEq/l)	IVIG responder*	CAL
Male 36	26 ± 18	4.5 ± 1.8	7.2 ± 5.2	14.2 ± 5.2	131.5 ± 2.8	21 (58.3%)	3 (8.3%)
Female 20	37 ± 25	4.9 ± 1.9	4.7 ± 4.6	7.5 ± 3.1	135.5 ± 2.3	17 (85.0%)	1 (5.0%)

Values are mean ± SD or cases (percentages)

IVIG intravenous immune globulin therapy, *CRP* C-reactive protein, *conc.* concentrations, *WBC* white blood cell, *CAL* coronary arterial lesion

* Patients who had cessation of fever (<37.5°C) after IVIG and needed no additional therapy

29.8 ± 21.7 months. The clinical profiles of patients with Kawasaki disease are presented in Table 2. Thirty-eight patients (67.9%, 21 males, 17 females) responded to intravenous immune globulin infusion. Four patients had coronary lesions detected by echocardiography at discharge, even after immune globulin therapy.

Serum adipokine levels in patients with Kawasaki disease

Serum adipokine levels are shown in Fig. 1. Serum resistin levels were significantly higher in patients with Kawasaki disease (mean 31.5 ± 20.0, median 27.5 ng/ml) compared with healthy controls (mean 5.0 ± 6.8, median 3.3 ng/ml, $p < 0.001$) and patients with acute infectious diseases (mean 10.6 ± 9.2, median 6.9 ng/ml, $p < 0.001$). However, serum HMW adiponectin, leptin, and visfatin levels in patients with Kawasaki disease (HMW adiponectin: mean 10.8 ± 5.1, median 10.1 μg/ml; leptin: mean 2.4 ± 4.0, median 1.6 ng/ml; visfatin: mean 11.1 ±5.5, median 9.5 ng/ml) showed no statistically significant differences compared with those in healthy controls (HMW adiponectin: mean 23.5 ±9.9, median 22.7 μg/ml; leptin: mean 2.0 ±0.7, median 1.9 ng/ml; visfatin: mean 14.9 ±15.7,

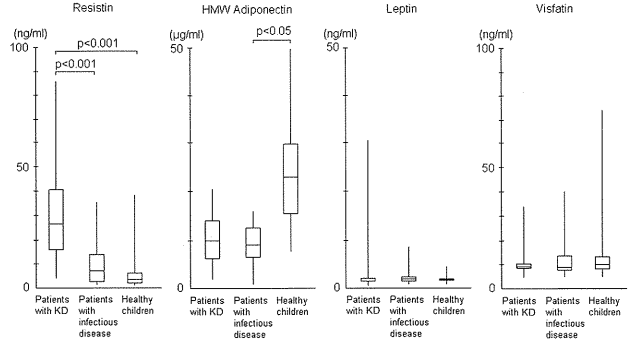

Fig. 1 Serum adipokine levels in the three groups. In the *box plots*, *horizontal lines* indicate median values, and the *lower* and *upper ends* of *boxes* represent the 25th and 75th percentiles. In patients with Kawasaki disease, serum resistin levels were significantly higher than in patients with infectious diseases and in healthy children ($p < 0.001$). Serum high-molecular-weight adiponectin, leptin, and visfatin levels in patients with Kawasaki disease exhibited no statistically significant differences compared with those in healthy controls and patients with acute infectious diseases. *KD* Kawasaki disease, *HMW* high molecular weight

median 11.0 ng/ml) and patients with infectious diseases (HMW adiponectin: mean 9.8 ±4.0, median 8.8 μg/ml; leptin: mean 2.2 ±1.3, median 1.9 ng/ml; visfatin: mean 11.7 ±8.0, median 9.1 ng/ml).

Adipokine levels before and after intravenous immune globulin therapy

Figure 2 shows the changes in serum adipokine levels after intravenous immune globulin treatment. Serum resistin levels decreased significantly after treatment (mean 28.7 ± 18.4 to 9.2 ± 8.3, median 24.5 to 6.7 ng/ml, $p < 0.001$). However, there were no significant changes in serum HMW adiponectin (mean 11.7 ± 5.5 to 11.3 ± 4.8, median 11.9 to 11.1 μg/ml), leptin (mean 3.0 ± 5.9 to 2.2 ± 2.4, median 1.7 to 1.7 ng/ml) or visfatin (mean 11.0 ± 5.3 to 10.9 ± 3.0, median 9.0 to 10.7 ng/ml) levels after intravenous immune globulin.

Comparison of serum adipokine levels in responders and nonresponders to intravenous immune globulin therapy

We compared serum adipokine levels in patients who responded to intravenous immune globulin infusion and in those who did not respond to the treatment, and found that serum resistin levels on admission were significantly ($p < 0.05$) higher in nonresponders (mean 37.2 ± 17.0, median 33.4 ng/ml) compared with responders (mean 28.9 ± 21.0, median 22.9 ng/ml). Serum HMW adiponectin, leptin, and visfatin levels were not significantly different between responders (HMW adiponectin: mean 11.1 ± 9.9, median 10.0 μg/ml; leptin: mean 1.7 ± 0.7, median 1.6 ng/ml; visfatin: mean 11.5 ±6.3, median 9.4 ng/ml) and nonresponders (HMW adiponectin: mean 10.0 ±5.8, median 10.1 μg/ml; leptin: mean 3.7 ± 1.7, median 1.7 ng/ml; visfatin: mean 10.2 ± 2.0, median 10.0 ng/ml).

Correlations between serum resistin levels and clinical data in patients with Kawasaki disease

Since significant elevation of only serum resistin levels was observed in Kawasaki disease, we further analyzed the relationship between serum resistin levels and clinical conditions. Table 3 presents the correlations between serum resistin levels and clinical data considered to be related to disease severity of Kawasaki disease before intravenous immune globulin therapy. Significant univariate predictors of severity included age, CRP, peripheral white blood cell count, and serum sodium level. Simultaneous inclusion of univariate predictors into a multivariate model revealed that high CRP level was a predictor of elevated serum resistin level.

Discussion

In this study, we found that serum resistin levels were elevated in patients with Kawasaki disease compared with in healthy children and in patients with acute infectious diseases. However, there were no significant differences in serum levels of HMW adiponectin, leptin, and visfatin between the various patient groups. Nozue et al. [17] recently reported that serum resistin levels in patients with Kawasaki disease were significantly higher than in healthy controls; however, they did not measure the levels of other adipokines.

Human resistin is produced and released mainly in mononuclear cells (monocytes/macrophages) rather than adipocytes [18, 19]. Mononuclear cells are also important in the pathogenesis of Kawasaki disease, and histopathological

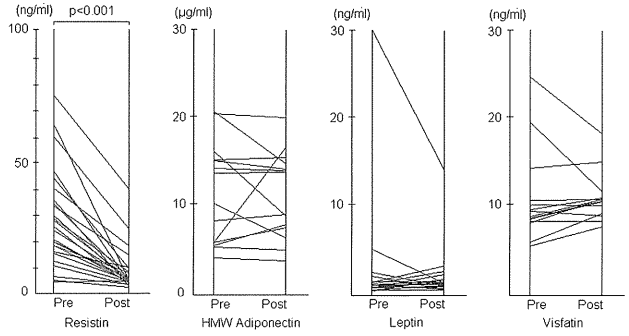

Fig. 2 Adipokine changes after treatment with intravenous immune globulin. Serum resistin levels decreased significantly after administration of intravenous immune globulin ($p < 0.001$). However, serum high-molecular-weight adiponectin, leptin, and visfatin levels did not exhibit any statistically significant changes after intravenous immune globulin treatment. *HMW* high molecular weight

Table 3 Correlations between serum resistin levels and clinical data in patients with Kawasaki disease

Characteristic	Univariate			Multivariate	
	β	*p*	R^2	*β*	*p*
Female	4.887	0.387	0.014	4.013	0.471
Age	0.266	*0.034*	0.081	0.146	0.677
Weight	1.334	0.077	0.057	−0.327	0.871
CRP	1.609	*0.001*	0.205	1.151	*0.022*
WBC	0.001	*0.041*	0.075	0.000	0.373
Sodium	−2.062	*0.019*	0.098	−1.163	0.199
				R^2 0.276	

β regression coefficient, *CRP* C-reactive protein, *WBC* white blood cell

Italics mean significant *p* values

findings in Kawasaki disease include panvasculitis with infiltration of mononuclear cells [20]. It has been reported that CD14+ monocytes/macrophages play an important role in cytokine production during acute Kawasaki disease [21]. The elevated serum resistin levels in Kawasaki disease shown in our study might have been caused by overproduction by monocytes/macrophages. It was recently shown that resistin competes with lipopolysaccharide for binding to toll-like receptor 4 (TLR4) on peripheral blood mononuclear cells. Torkowski [22] suggested that resistin may partly act as a proinflammatory cytokine via TLR4. It has also been reported that expression of TLR4 is upregulated during the acute phase of Kawasaki disease [23]. These reports and our clinical data of the present study suggest that resistin may be a key cytokine involved in the pathophysiology of Kawasaki disease, possibly as a ligand for TLR4.

After administration of intravenous immune globulin, which is a standard therapy for acute Kawasaki disease, serum resistin levels decreased significantly to nearly normal levels. This suggests that high resistin levels indicate high disease activity. We then examined the correlations between serum resistin level and laboratory parameters considered to be related to disease activity of Kawasaki disease [24, 25].

On simple regression analysis, inflammatory markers (CRP and peripheral white blood cell count) had significant positive correlations with serum resistin levels, while serum sodium levels had a negative correlation with serum resistin levels. Hyponatremia is a common finding in patients with severe Kawasaki disease [26]. Simultaneous inclusion of univariate predictors into a multivariate model resulted in a final parsimonious model with CRP in our study. In contrast, Nozue et al. [17] showed that the only variable significantly associated with resistin concentrations before intravenous immune globulin therapy was body mass index. There were no obvious differences in the background characteristics of patients, including age, gender, weight, and CRP levels on admission, between their study and our present study. We were not able to identify any reasons for the differences in the studies other than the different cohorts of patients.

In our present study, we also compared serum resistin levels in responders and nonresponders to intravenous immune globulin treatment. Serum resistin levels were significantly higher in patients who did not respond to intravenous immune globulin therapy. This result suggests that high serum resistin level may be a predictor of nonresponsiveness to intravenous immune globulin therapy. There were only four patients with coronary arterial lesions, and they had no trend for increased serum resistin levels compared with patients without coronary lesions [serum resistin levels in the four patients with coronary artery lesions: 19.8, 25.8, 29.2, 54.2 ng/ml, patients without coronary lesions ($n = 52$): mean 31.5 ± 20.3, median 28.8 ng/ml].

There has been one previous report dealing with adipokines other than resistin in Kawasaki disease. Takeshita et al. [27] reported that plasma total adiponectin levels in patients with acute Kawasaki disease were significantly lower than in those with convalescent Kawasaki disease or acute febrile disease or in healthy children. In our study, HMW adiponectin in patients with Kawasaki disease had a trend toward being lower than the serum levels in healthy children, but the difference was not statistically significant. Since the HMW fraction of adiponectin is associated more strongly with coronary artery disease than other fractions [10, 11], the trend toward a lower levels might not be highly attributable to the complications of coronary lesions in Kawasaki disease. This may be because of the differences in the pathogenesis of coronary lesions. Coronary lesions in Kawasaki disease are generally panarteritis with acute inflammatory cell infiltrations, in contrast to the progressive atherosclerotic changes associated with adult coronary lesions [28].

We have previously suggested that serum adiponectin level is elevated in adult patients with rheumatoid arthritis [16]. It was also shown that adiponectin stimulates the production of interleukin-8 [29] and prostaglandin E_2 [30] by rheumatoid synovial fibroblasts, suggesting that adiponectin might act as a proinflammatory cytokine in rheumatoid inflammation. Adiponectin is secreted by not only adipocytes, but also in synovial fibroblasts in patients with rheumatoid arthritis [31]. Therefore, the differences in serum adiponectin levels between patients with Kawasaki disease and rheumatoid arthritis may be related to differences in the major affected organs or cells. The different adiponectin levels between Kawasaki disease and rheumatoid arthritis may also be related to their acute and chronic inflammatory condition, respectively.

There have been no previous reports about leptin and visfatin in Kawasaki disease. We found that serum levels of these adipokines in patients with Kawasaki disease exhibited no statistically significant differences compared with in healthy children and patients with acute infectious diseases. In our previous study, significant elevation in serum leptin level was observed in patients with rheumatoid arthritis, and a significant correlation between serum leptin and CRP levels was shown by multivariate analysis in these patients [16]. It was reported that serum levels of visfatin are higher in patients with rheumatoid arthritis, but not in patients with systemic lupus erythematosus and systemic sclerosis [32]. The differences in serum levels of these adipokines in different inflammatory diseases remain to be studied.

In conclusion, we demonstrate herein that serum resistin levels were elevated in patients during the acute phase of Kawasaki disease and decreased to nearly normal after intravenous immune globulin treatment. In contrast, serum HMW adiponectin, leptin, and visfatin levels showed no significant changes. Although further investigations are needed to better understand the detailed roles of adipokines in Kawasaki disease, our data suggest that, among these four adipokines, only resistin participates in the pathogenesis of this disease.

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Conflict of interest None.

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PEDIATRIC RHEUMATOLOGY

RESEARCH Open Access

Clinical characteristics of aseptic meningitis induced by intravenous immunoglobulin in patients with Kawasaki disease

Yasushi Kemmotsu*, Tomotaka Nakayama, Hiroyuki Matsuura and Tsutomu Saji

Abstract

Background: Aseptic meningitis is a serious adverse reaction to intravenous immunoglobulin (IVIG) therapy. We studied the clinical characteristics of patients with acute Kawasaki disease (KD) who developed IVIG-induced aseptic meningitis.

Methods: A retrospective analysis of the medical records of patients with KD who developed aseptic meningitis after IVIG treatment was performed.

Results: During the 10-year period from 2000 through 2009, among a total of 384 patients with Kawasaki disease, 4 (3 females and 1 male; age range, 19-120 months) developed aseptic meningitis after IVIG. All 4 developed aseptic meningitis within 48 hours (range, 25-40 hours) of initiation of IVIG. The analyses of cerebrospinal fluid (CSF) revealed elevated white blood cell counts (22-1,248/μL) in all 4 patients; a predominance of polynuclear cells (65%-89%) was noted in 3. The CSF protein level was elevated in only 1 patient (59 mg/dL), and the glucose levels were normal in all 4 patients. Two patients were treated with intravenous methylprednisolone; the other 2 children were observed carefully without any special therapy. All patients recovered without neurological complications.

Conclusions: In our patients with Kawasaki disease, aseptic meningitis induced by IVIG occurred within 48 hours after initiation of IVIG, resolved within a few days, and resulted in no neurological complications, even in patients who did not receive medical treatment.

Keywords: Kawasaki disease, intravenous immunoglobulin, aseptic meningitis

Background

Intravenous immunoglobulin (IVIG) is a blood product that is widely used in the treatment of a number of medical conditions, including immunodeficiency disorders, inflammatory diseases, and autoimmune diseases.

Kawasaki disease (KD) is a self-limited systemic vasculitis syndrome of childhood that was first reported by Tomisaku Kawasaki in 1967 [1]. Patients typically develop a fever, bulbar conjunctival injection, changes in the oropharyngeal mucosa and peripheral extremities, cervical lymphadenopathy, and a polymorphous rash. Coronary aneurysm and myocardial infarction are the most serious complications of this disease. In Japan, there are approximately 10,000 incident cases per year [2]. The etiology of the disease is not well understood, but high-dose IVIG is known to prevent the coronary complications [3,4].

There have been a number of reports regarding IVIG-induced adverse reactions, including mild reactions such as tachycardia, headache, facial flushing, nausea, diarrhea, and rash, as well as serious adverse reactions such as anaphylaxis, acute renal failure, and thromboembolic events [5]. Aseptic meningitis is a neurologic adverse event that can be caused by IVIG. Although there have been case reports describing IVIG-induced aseptic meningitis, few studies have described the characteristics of a group of such patients. In this study, we describe the clinical and laboratory characteristics of IVIG-induced aseptic meningitis in 4 patients with KD.

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Patients and methods

Patients

To investigate the clinical characteristics of IVIG-induced meningitis in KD patients, we retrospectively reviewed the medical records of patients who were admitted to our university hospital during the 10-year period from 2000 through 2009. All patients met the Japanese criteria for typical KD on admission. They were treated with oral aspirin and 1 or 2 g/kg of IVIG, the latter of which was administered over 12 or 24 hours, respectively. The IVIG products were freeze-dried sulfonated (Kenketsu Venilon®-I, Chemo-Sero-Therapeutic Research Institute, Kumamoto, Japan) and freeze-dried, polyethylene glycol (PEG) -treated (Kenketsu Glovenin®-I, Nihon Pharmaceutical Co, Ltd, Tokyo, Japan) human normal immunoglobulin. Testing of the CSF was done soon after the diagnosis of suspected IVIG-induced meningitis, and a diagnosis of meningitis was made on the basis of clinical symptoms such as fever and headache, meningeal irritation signs, and CSF pleocytosis. A final diagnosis of aseptic meningitis was made by negative bacterial culture results.

Results

Characteristics of the study population and IVIG products

A total of 384 patients with KD were admitted to our hospital; 4 developed aseptic meningitis after IVIG. Table 1 shows the background characteristics of these 4 patients. Three were females older than 5 years. The other patient was a 1-year-old male. Their serum C-reactive protein (CRP) levels and white blood cell counts before IVIG treatment were 3.3-5.5 mg/dL and 6,500-27,100/μL, respectively. Sulfonated immunoglobulin was given to 2 patients, and a polyethylene glycol-treated product was given to the other 2 patients. Two patients were treated with 1 g/kg IVIG, and the other 2 received 2 g/kg IVIG. There were no adverse reactions during the IVIG administration in any of the patients.

Clinical course and laboratory findings

All 4 patients responded well to initial IVIG: their fevers ceased and the clinical symptoms of KD improved. Table 2 shows the clinical course of the patients. Aseptic meningitis developed within 48 hours (range, 25-40 hours) after initiation of IVIG. All 4 patients developed a sudden, severe fever. Their recorded highest body temperatures were 38.0, 38.7, 38.8, and 39.1°C. The 3 females complained of headache, and the 1-year-old male was irritable and vomited frequently. On physical examination, there were typical signs of meningeal irritation, including neck rigidity, Kernig's sign, and Brudzinski's sign. Table 3 shows the CSF findings of the 4 patients. The initial pressure was recorded in 1 patient and was mildly elevated (24 cm H_2O). The analyses of the CSF revealed elevated white blood cell counts (22-1,248/μL) in all 4 patients, 3 of whom were neutrophil-predominant (65%-89%). The CSF protein level was elevated in only 1 patient (59 mg/dL), and the glucose levels were normal in all 4 patients (51-77 mg/dL). The CSF chloride and lactate dehydrogenase (LDH) levels were measured in 3 patients and were normal (123-128 mEq/L and 33-40 U/L, respectively). In addition, the results of CSF bacterial culture were negative in all patients. There was no worsening of inflammatory markers, ie, serum CRP and peripheral white blood cell counts, at the onset of meningitis (mean ± SD CRP: 4.3 ± 4.1 mg/dL, WBC: 9,300 ± 7,700/μL), as compared with the levels at admission (mean ± SD CRP: 5.9 ± 2.0 mg/dL, WBC: 14,800 ± 9,000/μL). Two patients were treated with a single dose of 15 mg/kg of intravenous methylprednisolone; the other 2 patients recovered without medical treatment. Fever and signs of meningeal irritation disappeared in 1 or 2 days, and no patient developed any neurological complications such as seizures or disturbances in consciousness. There was no recurrence of KD in any of the patients, and all four patients were discharged without coronary artery aneurysms.

Discussion

Aseptic meningitis after IVIG was first reported in 1988 [6]. Since then, there have been similar case reports of IVIG-induced meningitis in patients with medical conditions such as idiopathic thrombocytopenic purpura

Table 1 Background characteristics of the patients

Age	Sex	KD criteria	CRP(mg/dL)/WBC(/μL) on admission	IVIG product and dose	Day on IVIG
1 y	male	5/6	5.5/6,500	PEG-treated 2 g/kg	8
6 y	female	5/6	7.1/15,600	Sulfonated 1 g/kg	5
7 y	female	6/6	7.8/27,100	Sulfonated 2 g/kg	5
10 y	female	6/6	3.3/9,900	PEG-treated 1 g/kg	4

KD = Kawasaki disease; CRP = C-reactive protein; WBC = white blood cell; IVIG = intravenous immunoglobulin; PEG = polyethylene glycol.

Table 2 The clinical course of the patients

Patient	Time from start of IVIG to onset, hrs	Treatment	Time to recovery
1 y male	33	15 mg/kg mPSL	1 day
6 y female	40	15 mg/kg mPSL	2 days
7 y female	25	None	2 days
10 y female	31	None	1 day

IVIG = intravenous immunoglobulin; mPSL = methylprednisolone.

(ITP), myasthenia gravis, and inflammatory demyelinating neuropathy [7-9]. There has previously been only 1 case report describing this complication in a patient with KD [10].

The rate of aseptic meningitis after IVIG was 1% (4 of 384) in this study, but the frequency varies widely, from 0% to 11%, in reports of patients with different underlying diseases [11,12]. It was also reported that the development of aseptic meningitis was not correlated with the patient age or the type of underlying neuromuscular disease [12].

Hamrock reported that most patients who developed aseptic meningitis received 2 g/kg of IVIG, and that meningitis did not occur in any of their patients receiving a standard replacement dose of IVIG for a congenital immunodeficiency [5]. All of our patients received high-dose IVIG at a dose of 1 or 2 g/kg. Our patients almost equally received sulfonated IVIG or PEG-treated IVIG, and 2 patients in each group (total 4) developed meningitis, thus indicating that there are no apparent differences in the effects of sulfaonated or PEG-treated IVIG with regard to the development of meningitis. In this study, patients were exposed to either sulfonated IVIG or PEG-treated IVIG, but not to products manufactured by other processes such as cold ethanol Cohn fractionation/ultrafiltration, ion exchange, or low-PH treatment. The inability to further explore the possible etiological factors related to specific IVIG brand or manufacturing lots may be a limitation of this study. There were no obvious differences of clinical and laboratory data, including the severity of KD on admission, day of initiating IVIG, or changes of inflammatory markers after IVIG between patients who developed meningitis and those who did not.

In the present study, aseptic meningitis developed within 25 to 40 hours after initiation of IVIG. In previous case reports, most patients also developed meningitis within 48 hours of beginning IVIG. Although all of our patients developed a fever and typical meningeal irritation signs, it may be possible that milder cases of aseptic meningitis could be misdiagnosed as IVIG-refractory KD, since the onset of fever after completion of IVIG therapy is often interpreted as recrudescence of KD. It is important to consider the possibility of IVIG-induced meningitis with careful physical examinations to avoid unnecessary therapies, such as additional IVIG, steroids, and infliximab.

CSF examinations revealed neutrophilic pleocytosis in 3 of our 4 patients, slight elevation of the protein level in 1 patient, and normal glucose levels in all 4 patients. These findings were similar to those of previous reports. The analysis of the CSF in patients with aseptic meningitis usually shows pleocytosis with neutrophil predominance, normal or slightly elevated protein, and normal glucose levels. It may therefore be difficult to differentiate IVIG-induced meningitis from viral meningitis by the CSF findings, as it has been reported that the CSF protein levels are normal to mildly elevated, glucose levels are normal to slightly depressed, and neutrophil predominance is also seen in pediatric patients with viral meningitis [13,14].

All of our patients recovered without developing any neurological complications. Two were treated with intravenous methylprednisolone, and the other 2 were monitored without medical treatment. Jayabose et al. reported that children with ITP who were given prednisone had a lower risk of neurological complications after IVIG [15]. However, it has also been reported that such symptoms are self-limiting, and that there is no specific therapy that shortens the duration of symptoms. Thus, it may be advisable to carefully observe such patients and avoid systemic therapy [5]. In our study, there were no obvious differences in the clinical courses between patients treated with intravenous methylprednisolone and those who received no medical treatment,

Table 3 Cerebrospinal fluid findings

Patient	Cells (/μL)	Glucose (mg/dL)	Protein (mg/dL)	LDH (U/L)
1 y male	1,248 (P 89%)	51	59	39
6 y female	120 (P 13%)	54	23	33
7 y female	648 (P 83%)	77	30	40
10 y female	21 (P 65%)	52	37	NT

LDH = lactate dehydrogenase; P = polynuclear cells; NT = Not tested.

which suggests that systemic steroid administration is not beneficial for IVIG-induced meningitis.

The mechanisms underlying IVIG-induced meningitis are not clear. One possible cause is an allergic hypersensitivity reaction caused by direct entry of the IVIG preparation into the CSF compartment. This is supported by the fact that CSF eosinophilia has been observed in some patients [11]. In our study, one patient exhibited peripheral eosinophilia (11% of the total 5,800/μL white blood cells) but CSF eosinophilia was not observed in any of our patients. None of our patients developed exanthema after IVIG. Although our patients received no pre-treatment, it may be useful to give antihistamines prior to IVIG if allergic reaction is one of the mechanisms responsible for IVIG-induced meningitis. Recently, it was reported that there were increased levels of CSF monocyte chemoattractant protein-1 (MCP-1) in ITP patients with IVIG-induced meningitis, which suggests a role for monocytes in the inflammation of the meninges [16]. On the other hand, Jarius et al. reported that aseptic meningitis was frequently associated with neutrophillic pleocytosis in the CSF and *in vivo* activation of TNF-α-primed neutrophils by atypical antineutrophil cytoplasmic antibodies in IVIG might contribute to aseptic meningitis [17]. In our present study, the CSF cytokines or chemokines were not measured.

Meningitis is also a known complication of KD. Dengler et al reported that one-third of patients with KD who underwent a lumbar puncture had CSF pleocytosis with mononuclear cell predominance [18], which is in contrast to the polynuclear cell predominance observed in IVIG-induced meningitis. Meningitis as a complication of KD usually occurs early in the course of the disease and improves after KD treatment, which is mainly IVIG therapy [19]. Table 4 shows a comparison between IVIG- and KD-induced meningitis. It is not difficult to differentiate IVIG-induced meningitis from aseptic meningitis complicating KD, as both the time of onset and CSF findings differ.

Conclusions

In conclusion, IVIG-induced meningitis developed within 48 hours of initiating IVIG and resolved in a few days, without neurological complications, and systemic steroid administration was not beneficial in our patients. Further investigations of the pathophysiology of IVIG-induced meningitis, including a detailed analysis of the underlying mechanisms, are needed.

Table 4 A comparison between IVIG- and KD-induced meningitis

	Meningitis due to IVIG	Meningitis due to KD
Appearance	Within 48 hrs after IVIG	Early in the stage, before IVIG
Clinical findings	Typical meningeal signs	Can lack meningeal signs
CSF findings	Polynuclear cell predominance	Mononuclear cell predominance
Effective therapy	No special therapy	Therapy for KD

IVIG = intravenous immunoglobulin; KD = Kawasaki disease; CSF = Cerebrospinal fluid.

Authors' contributions
YK contributed by taking care of the patients. All authors contributed to the analysis and interpretation of the data. All authors read and approved the final manuscript.

Competing interests
The authors declare that they have no competing interests.

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PEDIATRIC RHEUMATOLOGY

SHORT REPORT Open Access

Mizoribine provides effective treatment of sequential histological change of arteritis and reduction of inflammatory cytokines and chemokines in an animal model of Kawasaki disease

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Abstract

Background: Intravenous immunoglobulin (IVIg) treatment results in an effective response from patients with acute-phase Kawasaki disease (KD), but 16.5% of them remain nonresponsive to IVIg. To address this therapeutic challenge, we tried a new therapeutic drug, mizoribine (MZR), in a mouse model of KD, which we have established using injections of *Candida albicans* water-soluble fractions (CAWS).

Methods: CAWS (4 mg/mouse) were injected intraperitoneally into C57BL/6N mice for 5 consecutive days. MZR or IgG was administered for 5 days. After 4 weeks, the mice were sacrificed and autopsied, the hearts were fixed in 10% neutral formalin, and plasma was taken to measure cytokines and chemokines using the Bio-Plex system. The incidence of panvasculitis in the coronary arteries and aortic root was 100% in the control group. The incidence of panvasculitis in the MZR group decreased to 50%. Moreover, the scope and severity of the inflammation of those sites were significantly reduced in the MZR group as well as the IgG group. On the other hand, increased cytokines and chemokines, such as IL-1α, TNF-α, KC, MIP-1α, GM-CSF, and IL-13, in the nontreatment group were significantly suppressed by treatment with MZR, but the MCP-1 level increased. In addition, IL-1α, TNF-α, IL-10, IL-13, and MIP-1α were suppressed by treatment in the IgG group.

Results: The incidence of panvasculitis in the coronary arteries and aortic root was 100% in the control group. The incidence of panvasculitis in the MZR group decreased to 50%. Moreover, the scope and severity of the inflammation of those sites were significantly reduced in the MZR group as well as the IgG group. On the other hand, increased cytokines and chemokines, such as IL-1α TNF-α, KC, MIP-1α, GM-CSF, and IL-13, in the nontreatment group were significantly suppressed by treatment with MZR, but the MCP-1 level increased. In addition, IL-1α, TNF-α, IL-10, IL-13, and MIP-1α were suppressed by treatment in the IgG group.

Conclusion: MZR treatment suppressed not only the incidence, range, and degree of vasculitis, but also inflammatory cytokines and chemokines in the plasma of the KD vasculitis model mice, suggesting that MZR may be useful for treatment of KD.

Keywords: Kawasaki disease, an animal model, IVIg, coronary arteritis, inflammatory cytokines and chemokines, mizoribine

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Background

Kawasaki disease (KD) is an acute febrile illness that manifests mainly in infancy and early childhood [1]. The most important complication of KD is coronary arteritis, which leads to formation of aneurysms. KD has attracted special interest because it may cause ischemic heart disease in children due to thrombosed coronary aneurysms [2]. Since the etiology and development of KD are thought to be due to the dysfunction of the immune system, intravenous immunoglobulin (IVIg) during the early acute phase has been used with an excellent response in most patients [3]. However, 16.5% of patients did not respond to the first IVIg treatment [4], and some nonresponders to the first IVIg treatment manifested severe coronary arteritis with large aneurysm [5]. Therefore, additional treatments have been tried on the nonresponders to the first treatment with IVIg. To date, a second IVIg treatment [6], plasmapheresis [7-10], pulse steroids [11], cyclophosphamide plus steroids [12], ulinastatin as an elastase inhibitor [13-16], cyclosporin A plus steroids and methotrexate plus steroids [17,18], and anti-tumor necrosis factor-α (infliximab) therapy [19-23] have been tried. Thus, for treatment of patients with KD who do not respond to IVIg, other medicines for immune response and suppression of lymphocyte proliferation have been applied due to immune dysfunction in the patients. One immune modulating medicine, mizoribine (MZR), a drug that inhibits synthesis of purine compounds (GMP), blocks proliferation of lymphocytes and will be useful for application to nonresponders to IVIg treatment. MZR has long been used as therapy for kidney transplantation, lupus nephritis, nephrotic syndrome, and rheumatoid disease with few side-effects [24]. Moreover, it has been reported to have been used for lupus nephritis, nephrotic syndrome, and IgA nephritis in children [25-28], and as a maintenance therapy in anti-neutrophil cytoplasmic autoantibody (ANCA)-associated renal failure, frequently relapsing nephrotic syndrome, and purpura nephritis [29,30]. Therefore, MZR will be a valuable therapeutic strategy for patients with KD who are nonresponsive to IVIg.

Prior to a clinical trial in children with KD, it was necessary to test MZR in a mouse model of KD, which has been established. The model we chose was the mouse model in which coronary arteritis can be induced by administration of *Candida albicans* water-soluble fractions (CAWS) [31]. This model mouse has previously been useful for evaluation of other drug treatments.

Therefore, in the present study, we tested MZR as a immunomodular for treatment of this CAWS-induced coronary arteritis. The evaluation of MZR was performed by histopathological findings and profiles of chemokines and cytokines. Also, this treatment effect was compared with that of IgG.

Methods

Animals

Four-week-old male C57BL/6N mice were purchased from Charles River Japan (Yokohama, Japan). All mice were kept under specific pathogen-free (SPF) conditions, according to the guidelines for animal care of the National Institute of Infectious Diseases in Tokyo (NIID).

Preparation of CAWS

CAWS was prepared from *C. albicans* strain IFO1385 in accordance with the reported method [31]. Briefly, 5 liters of medium (C-limiting medium) was added to a glass incubator, and the culture was maintained for 2 days at 27°C while air was supplied at a rate of 5 liters/min and the mixture was swirled at 400 rpm. Following culture, an equal volume of ethanol was added. After allowing this to stand overnight, the precipitate was collected. After dissolving the precipitate in 250 ml of distilled water, ethanol was added and the mixture was allowed to stand overnight. The precipitate was collected and dried with acetone to obtain CAWS.

Administration of MZR and IgG to the mice

CAWS (4 mg/mouse/day) in a volume of 0.2 ml was intraperitoneally injected into a C57BL/6N mouse (4-week old male) on each of 5 consecutive days. Subsequently, MZR (a kind gift of Asahikasei Pharma Corporation (Tokyo, Japan)) was administered at a dose of 30 mg/kg/day intraperitoneally for 5 days from the third day of CAWS injection (MZB group), according to the schecule for treatments such as IgG for patients with KD, and the dosage as described elsewhere [32]. Mice for the control group were intraperitoneally treated with 0.2 ml of Dulbecco's phosphate-buffered saline (PBS). After 35 days, the mice were sacrificed by carbon dioxide asphyxiation; autopsy was performed to obtain plasma, and hearts were fixed with 10% neutralized formalin. For a positive control, treatment with intraperitoneal human IgG (Kenketsu Glovenin I, a kind gift of Nihon Pharmaceutical Co. Ltd., Tokyo, Japan) was performed at a dose of 400 mg/mouse/day, or for a negative control saline containing 0.1% glucose (SG) was injected for 5 days according to the same procedures as described elsewhere (IgG group) [33]. The start date of the drug administration was based on the results that the administration from the third experimental day had been the most effective to suppress the development of vasculitis.

Histological evaluation

The fixed hearts were embedded in paraffin and sectioned. To observe the histological changes in the coronary arteries and the aorta in detail, 20 to 30 horizontal step sections per mouse were made every 20 μm. Hematoxylin and eosin (H&E)-stained sections were prepared by using routine techniques for examination by light microscopy [31]. First, we investigated the incidence of mice with panvasculitis in each group. Panvasculitis was defined as inflammation of all layers of the walls of the coronary arteries and/or the aorta. Then, for quantitative evaluation of vascular inflammation, we divided the area of the aortic root and coronary arteries into five segments and graded the intensity of inflammation in each segment as follows: score 3, panvasculitis; score 2, inflammation involving the tunica intima and adventitia; score 1, inflammation localized to the tunica intima; and score 0, no inflammatory cell infiltration in the vascular wall. A section with the severe inflammation was observed in each segment. The scope of inflammation was defined as the number of segments evaluated as score 1 or more in each mouse, and the severity of the arteritis was defined as the average score of the five segments in each mouse.

Measurement of cytokines and chemokines with Bio-Plex

Cytokines and chemokines in the plasma of mice autopsied were measured by a Bio-Plex system. An aliquot of serum (12 μl) collected from peripheral blood and diluted 4-fold with the dilution solution was measured for concentration of cytokines by the 23-Plex kit using Bio-Plex 200 according to the manufacturer's protocol and analyzed by the Bio-Plex Luminex 100 XYP instrument (Bio-Rad, Hercules, California, USA). We assayed the following 23 cytokines and chemokines: IL-1α, IL-1β, IL-2, IL-3, IL-4, IL-5, IL-6, IL-9, IL-10, IL-12p40, IL-12p70, IL-13, IL-17, eotaxin, G-CSF, GM-CSF, INF-γ, KC, MCP-1, MIP-1α, MIP-1β, RANTES, and TNF-α as estimated with a single assay to a single standard curve described in the kit instructions. Concentrations of cytokines and chemokines were calculated using Bio-Plex Manager 3.0 software (Bio-Rad, Tokyo) with a five-parameter curve-fitting algorithm applied for standard curve calculations [34].

Statistical analysis

Fisher's exact probability test was used to analyze the differences in the incidence of arteritis among the groups. The data on the scope and severity of the arteritis and cytokine/chemokine levels were analyzed using the two-sample *t*-test. A value of $P < 0.05$ was considered statistically significant.

Results

Histological evaluation of panvasculitis in treatment with MZR

Panvasculitis developed in the coronary arteries and the aortic root, and histology was similar to that previously described [33]. Specifically, vascular changes were classified as proliferative inflammation that consisted mainly of large mononuclear cells such as histiocytes and fibroblasts and of a small number of neutrophils. The normal structure of the arteries was completely destroyed, and the internal elastic lamina, external elastic lamina, and smooth muscle layer of the tunica media were severely damaged. However, fibrinoid necrosis was not observed in any of the mice. In addition, the histology of panvasculitis was similar in the three groups (Figure 1).

Decrease of coronary arteritis by treatment with MZR

Panvasculitis of the coronary arteries and the aortic root was observed in 5 of 5 mice (100%) in the nontreated control group. On the other hand, the incidence of panvasculitis in the MZR group was 3 of 6 mice (50%), and the IgG group as an effective control showed 3 of 7 (43%) (Figure 2A). In addition, the number of segments evaluated as score 1 or more in each MZR group was decreased compared with the nontreated control group ($P = 0.06$), and the scope of inflammation in IgG groups was significantly lower than in the control group ($P < 0.05$) (Figure 2B). Furthermore, the severity of the arteritis, i.e., the scores of each of five segments in the mice in the MZR and IgG groups, was significantly lower than in the nontreated control group ($P < 0.01$) (Figure 2C).

Reduction of inflammatory cytokines and chemokines by treatment with MZR and IgG

Inflammatory cytokines IL-1α, TNF-α, chemokines KC, MIP-1α, GM-CSF, and Th2, and cytokine IL-13 in plasma of mice, which were inoculated with CAWS in the control group, were elevated (Figure 3). However, in the MZR group, plasma levels of inflammatory cytokines IL-1α ($P < 0.01$) and TNF-α ($P < 0.05$), and chemokines KC ($P < 0.01$), MIP-1α ($P < 0.01$), and GM-CSF ($P < 0.05$) were significantly suppressed (Figure 3A). Inversely, the MCP-1 level increased with MZR treatment (Figure 3A). On the other hand, IL-1α ($P < 0.05$), TNF-α ($P < 0.05$), IL-10 ($P < 0.05$), and IL-13 ($P < 0.01$) were suppressed by administration of IgG (Figure 3B).

Furthermore, we analyzed levels of cytokines/chemokines in plasma, which were related with suppression of the development of coronary arteritis by treatment with MZR. As shown in Figure 4A, the suppression levels were almost the same in all plasmas of MZR-treated mice. These results are not the same as those in the IgG

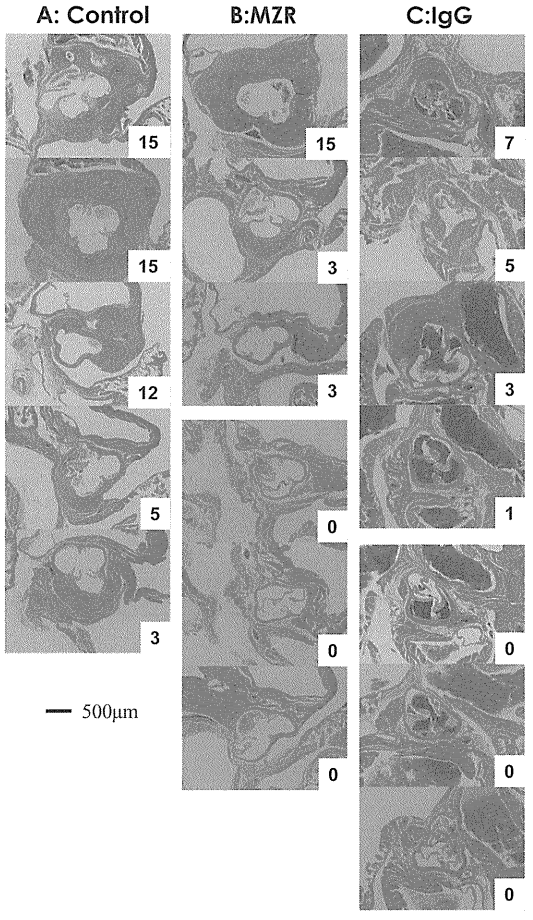

Figure 1 Histological observations of coronary arteritis induced by treatment with MZR and IgG. A, Control (PBS); B, MZR group; C, IgG group. Each micrograph represents an individual mouse. H&E stain, Bar: 500 μm. Numbers (white) are coronary arteritis score.

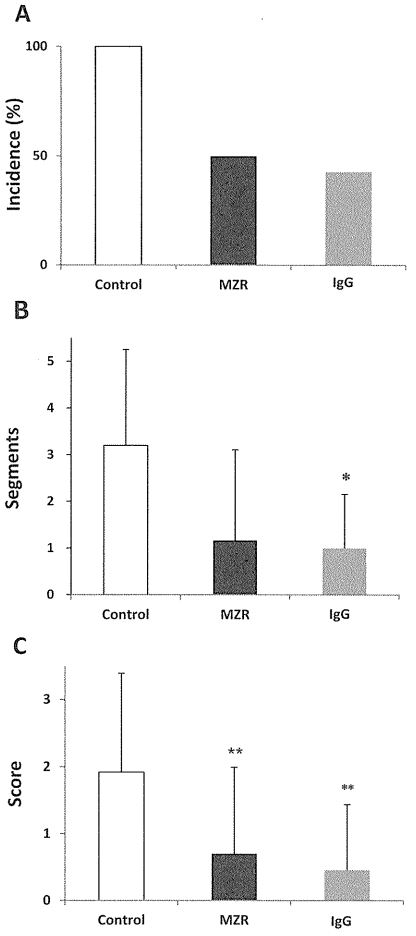

Figure 2 Decrease of incidence of panvasculitis, segment score, and severity score of coronary arteritis by treatment with MZR and IgG. A, incidence of development of panvasculitis; B, scope as number of segments with inflammation evaluated as score 1 or more at aortic root and coronary arteries; C, severity score of each segment. Data are expressed as mean ± SD of results from three individuals. *$P < 0.05$ and **$P < 0.01$ (Student's *t*-test).

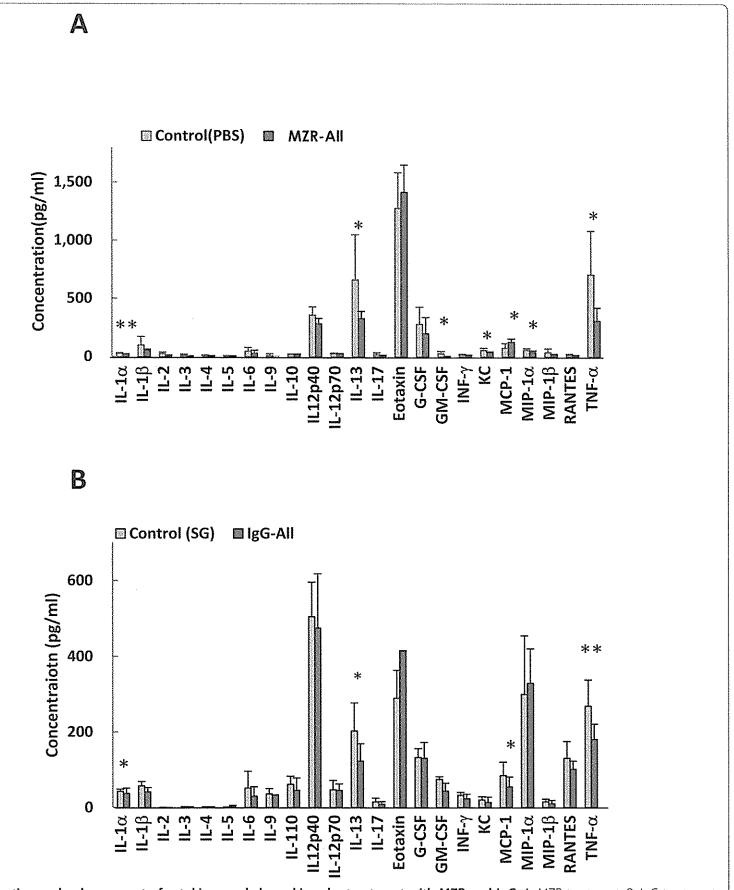

Figure 3 Reduction and enhancement of cytokines and chemokines by treatment with MZR and IgG. A, MZR treatment; B, IgG treatment. SG: saline including 0.1% glucose. Data are expressed as mean ± SD of results from three individuals. *$P < 0.05$ and **$P < 0.01$.

group, showing good response for suppression of the development of coronary arteritis (Figure 4B).

Discussion

Decrease of coronary arteritis by treatment with MZR

We here have shown the efficacy of MZR on vascular inflammation by using a KD vasculitis mouse model to develop alternative treatments for KD patients who are nonresponsive to IVIg treatment. The results here show that the incidence, scope, and degree of inflammation of the coronary arteries and the aortic root were suppressed by MZR administration. Coronary arteritis in this CAWS-induced vasculitis mouse model is also suppressed after administration of IVIg [33]. Furthermore,

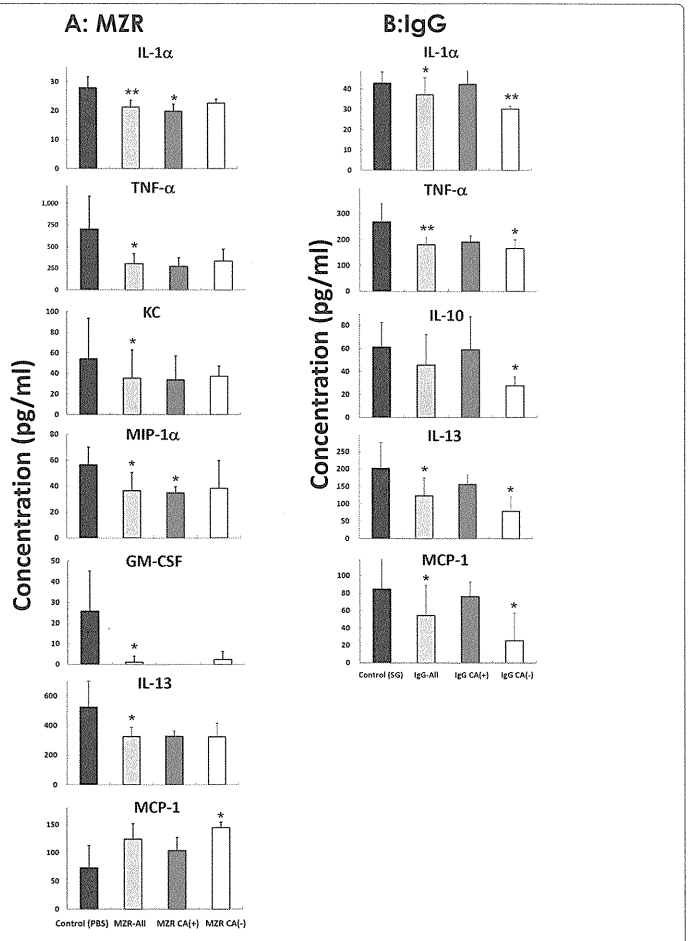

Figure 4 Reduction and enhancement of cytokines and chemokines in coronary arteritis treated with MZR and IgG. A, MZR treatment; B, IgG treatment. CA(+): coronary arteritis score > 0, CA(-): coronary arteritis score = 0, SG: saline including 0.1% glucose. Data are expressed as mean ± SD of results from three individuals. *$P < 0.05$ and **$P < 0.01$.

we have also demonstrated that the anti-TNF-α therapy that has been shown to be effective in treating some children unresponsive to IVIg therapy also dramatically suppresses the development of vasculitis in this mouse model of KD (manuscript in preparation). Thus this mouse model appears to be valuable for evaluation of alternative therapies for KD arteritis.

Reduction of inflammatory cytokines and chemokines by treatment with MZR

Some cytokines and chemokines such as IL-1β, IL-2, sIL-2R, IL-4, IL-6, IL-8, IL-10, IL-12, IL-15, RANTES, MCP-1, M-CSF, G-CSF, and MIPs are elevated in the blood of patients with acute-phase KD. Some elevated cytokines and chemokines are decreased by IVIg treatment in the acute phase, when it is effective [35]. On the other hand, IL-6, TNF-α, IL-4, and IL-12 were increased in the plasma of the KD mouse model induced with *C. albicans*-derived substances (CADS) [36]. Moreover, IL-6 and IFN-γ in splenocytes administered CAWS in C57BL/6 mice were elevated [37]. With IVIg treatment of KD model mice induced with CAWS, elevated proinflammatory cytokines IL-1α, TNF-α, IL-10, IL-13, and MCP-1 were decreased in our data. Furthermore, chemokines IL-1α, TNF-α, KC, GM-CSF, IL-13, and MIP-1α in plasma of autopsied mice were decreased in the MZR treatment group in the present study. The results with MZR treatement show similar effects as well as IgG treatment for KD model mice. However, supression levels of IL-1α, TNF-α, IL-10, IL-13, and MIP-1α in the recovery group from the coronary arteritis (CA(-)) in the MZR group differed from those in the IgG group. Levels in the recovery group (CA(-)) after MZR treatment were not suppressed, whereas those in the CA (-) group after IgG treatment were suppressed in the present study, which suggests that MZR may have a stronger effect than a high dose of IgG (400 mg/kg/day for 5 days). Because these cytokines/chemokines decrease slightly after MZR treatment, they may have a role in the development of coronary arteritis in the KD model.

Effective treatment with MZR of model mice for KD induced by CAWS

In the present study, MZR treatment of the KD model mice significantly suppressed the development of coronary arteritis associated with significant suppression of levels of proinflamatory cytokines and chemokines in plasma. These results suggest association of the suppression of lymphocyte proliferation with MZR [38]. The mode of action of MZR is that it mainly blocks immunosuppression related to lymphocyte proliferation through inhibition of purine synthesis [32,39,40]. In the present study, the incidence of panarteritis decreased to half, and both the scope and severity of inflammation were limited after administration of MZR. In addition to the lymphocyte action, these observations suggest that MZR may act on functions of monocytes/macrophages and neutrophils, which are mainly involved in the development of inflammation, resulting in the possible suppression of coronary arteritis through suppression of proinflammatory cytokines and chemokines released from these cells. Indeed, recently, MZR acted to inhibit functions of lymphocytes as well as those of macrophages, such as migration and production of Nitrous Oxide Systems (NOS), IL-1β, and TNF-α in a dose-dependent manner [41,42]. Furthermore, in the mixed lymphocyte reaction method (MLR) of human peripheral blood mononuclear cells, the IC_{50} is 1 μg/ml [43]. In addition, MLR of T-cells in human peripheral blood, which are stimulated with anti-CD3 monoclonal antibody, shows an IC_{50} of less than 1 μg/ml for MZR and also phorbol myristate stimulation less than 5 μg/ml [44]. In addition, MZR also inhibits activation of M1 macrophages [42], which are classified as inflammatory, showing tissue injury and activation with IFN-γ. In the present study, suppression profiles of proinflammatory cytokines and chemokines by MZR treatment of KD model mice seem to be associated in the literature with those in the M1 macrophage. Therefore, the effect of MZR on KD model mice may be to inhibit the proliferation of lymphocytes and activation of macrophages and neutrophils associated with elevation of proinflamatory cytokines and chemokines.

Based on these observations, suppression of development of coronary arteritis associated with suppression of proinflammatory cytokines and chemokines by MZR treatment for the KD model mice suggests that MZR may be useful for patients with KD in the acute phase. MZR has been used as therapy for kidney transplantation, lupus nephritis, nephrotic syndrome, and rheumatoid disease with few side effects [24]. Furthermore, MZR has been used as maintenance treatment for ANCA-associated vasculitis, frequently relapsing nephrotic syndrome, and purpura nephritis [29,30]. Clinical use will be recommended for immune dysfunctions when the safety of long-time use becomes known. Therefore, MZR is a possible therapy for patients with KD who are nonresponsive to IVIg.

Conclusions

MZR treatment suppressed not only the incidence, range, and degree of vasculitis, but also inflammatory cytokines and chemokines in the plasma of the KD vasculitis model mice. It appears likely that MZR may prove to be a useful for alternative treatment for KD.

Abbreviations used

ANCA: anti-neutrophil cytoplasmic autoantibody; CAWS: *Candida albicans* water-soluble fractions; H&E: hematoxylin and eosin; IVIg: intravenous immunoglobulin; KD: Kawasaki disease; MLR: mixed lymphocytes reaction method; MZR: mizoribine; NOS: Nitrous Oxide Systems: PBS; Dulbecco's phosphate- buffered saline; SG: saline containing 0.1% glucose.

Contribution of authors

KT: Histological evaluations of coronary arteritis. TO: Histological evaluations of coronary arteritis. TN: Measurement and analysis of cytokines and chemokines. YY: Measurement and analysis of cytokines and chemokines. HY: Histological evaluations of coronary arteritis. NNM: Preparation of CAWS. NO: Preparation of CAWS. TS: Planning treatments with MZR and IgG, and clinical evaluation. TO: Planning treatments with MZR and IgG, and clinical evaluation. KS: Measurement and analysis of cytokines and chemokines, correspondence to all evaluation of this study. All authors read and approved the final manuscript.

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Competing interests

The authors declare that they have no competing interests.

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⑩ 川崎病

群馬大学大学院 小児科学分野
助教 **小林　徹**

1997年群馬大学卒業後，主に群馬県立小児医療センターで小児循環器疾患の診療に携わり，2008年より現職。先天性心疾患診療と共に川崎病に関連した臨床研究を行い，現在，重症川崎病患者に対する大規模臨床試験（RAISE Study）の研究事務局代表として新たな治療法の開発に携わっている。

東邦大学医療センター大森病院
小児科 教授 **佐地　勉**

川崎病は乳児・幼児に発症する原因不明の血管炎症候群である。川崎病全国調査結果によると，現在年間１万人以上の新規川崎病患者が発生しており（図），累積患者数は20万人を超える。罹患率は性差があり（男女比1.4：１），人種差も認める（日本人＞アジア系＞黒人＞白人）。後遺症として冠動脈病変（心臓を栄養する血管のこぶ）を合併することが知られており，先進国における後天性心疾患最大の原因である。

本稿では，川崎病の病態，臨床症状，治療，後遺症等を概説し，看護のポイントについて解説する。次に挙げるホームページより川崎病関連の情報を得ることができるため，一度サイトを訪れていただくことをお勧めする。

●日本川崎病学会ホームページ
http://www.jskd.jp/

●日本川崎病研究センターホームページ
http://www.kawasaki-disease.org/index2.html

●自治医科大学公衆衛生学ホームページ（川崎病全国調査結果）
http://www.jichi.ac.jp/dph/kawasaki.html

●RAISE Studyホームページ　http://raise.umin.jp/

●急性期川崎病治療のガイドライン
http://www.jskd.jp/info/pdf/guide.pdf

●川崎病心臓血管後遺症の診断と治療に関するガイドライン（2008年改訂版）
http://www.j-circ.or.jp/guideline/pdf/JCS2008_ogawasy_h.pdf

●川崎病の管理基準（日本川崎病研究会運営委員会編〈2002年改訂〉）
http://www.jskd.jp/info/pdf/kawakijun.pdf

川崎病の基礎知識

■病態

川崎病は，小児期に好発する原因不明の血管炎症候群であり，組織学的には全身の小～中型動脈における血管炎である。その疫学像からは，何らかの感染症がきっかけになって体内で免疫システムの異常活性化が生じ，さまざまな臨床症状・合併症が出現すると考えられている。流行はするが伝染はしないため，病棟内で集団発生することはない。

急性期はさまざまな免疫反応を誘導する炎症性サイトカインの上昇が報告されており，高サイトカイン血症が川崎病の主病態であることが分かってきた。歴史的にも多くの病原体の関与が研究されてきたが，いずれも確証とはなっていない。この宿主側の因子としては，リンパ球の異常な活性を示す一部の子どもたちがかかりやすく，後遺症を残しやすいことが判明している。

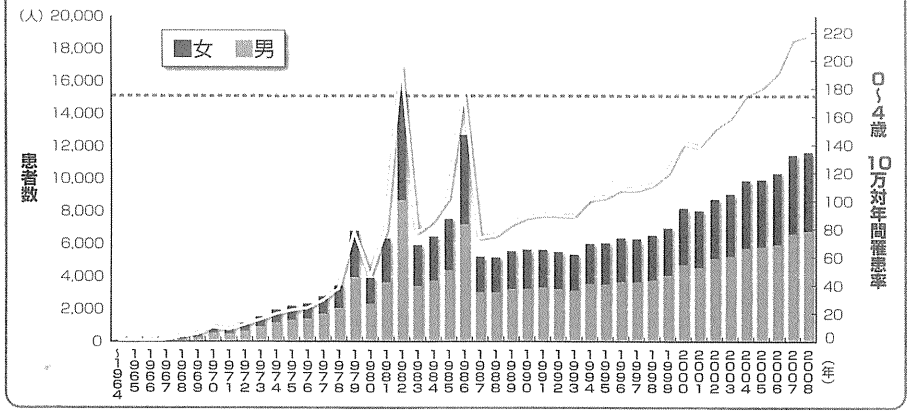
■臨床症状と臨床経過

川崎病は，疾患概念の提唱後40年が経過したが，いまだ原因は特定されていない。そのため，川崎病に特徴的な症状に基づき，いわゆる症候群として確定診断されている。川崎病は，川崎病診断の手引き改訂５版（付表）に基づき，診断する。主要症状の特徴を次に示す[1)]。

発熱

通常初発症状が発熱で，39℃以上の高熱であ

図■新規川崎病患者数と罹患率（第20回川崎病全国調査成績）



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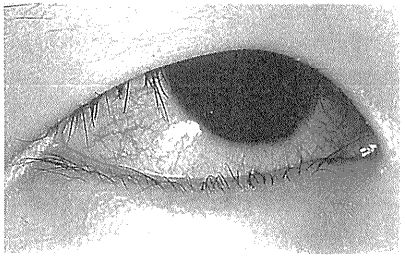

写真１■眼球結膜充血

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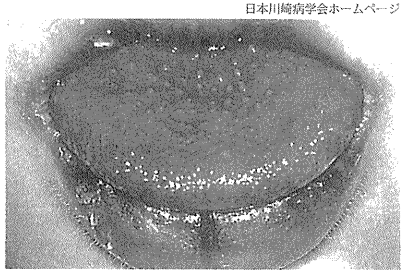

写真２■口唇の紅潮といちご舌

ることが多い。乳児ではぐったりとして非常に機嫌が悪く，年長児では全身倦怠感を訴えることが多いため，多くの症例で一般感冒とは異なる重症感を感じる。

眼球結膜充血

片側ではなく両側の眼球結膜（いわゆる白眼）の血管が拡張し，結膜全体がピンク～赤色に充血する（写真１）。眼脂はないかごくわずかであるところがアデノウイルス感染症（プール熱）と異なる。

口唇・口腔所見

口唇は口紅を塗ったように赤くなり，所見の強い症例では口唇全体が腫脹して亀裂や出血を伴うことがある。舌は全体的に発赤腫脹し，舌乳頭の肥大が起こるため，溶連菌感染症類似の「いちご舌」の所見を認める（写真２）。口腔粘膜は全体に発赤するが，扁桃に白苔が付着することがほとんどないところがEBウイルス感染症や溶連菌感染症と異なる点である。

不定形発疹

どのような発疹でも川崎病の主要症状の一つとなり得るとされているが，典型的な発疹の形態は多形滲出性紅斑のような大小不同で部分的に癒合する平坦，ないしはやや膨隆する斑状疹である（写真３－①）。左上腕のBCG接種部位が発赤・腫脹することは年少児における特徴的な所見である（写真３－②）。BCG発赤は，接種後１年以内に生じるものが大部分のため，年長児における診断価値は乏しい。川崎病診断基準としては参考条項として位置づけられている。

日本川崎病学会ホームページ

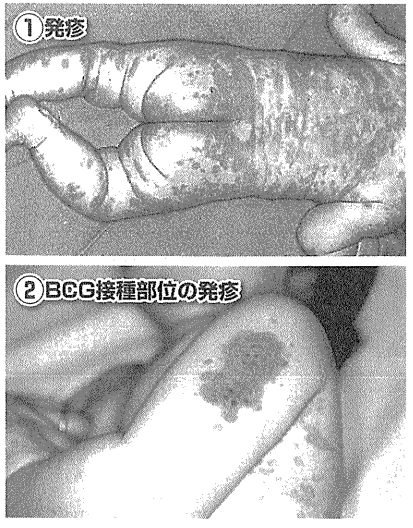

写真３■不定形発疹

日本川崎病学会ホームページ

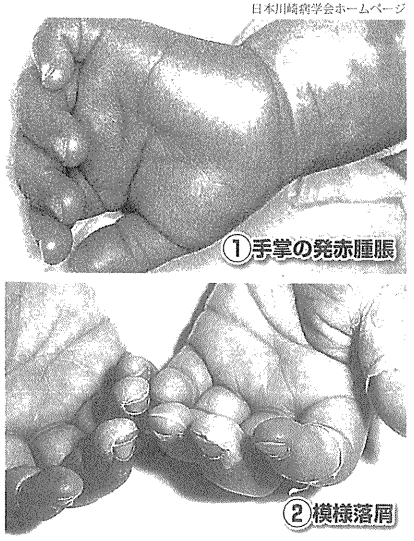

写真４■四肢末端の変化

四肢末端の変化

手掌と足底や指関節部分が発赤腫脹し，指で圧迫しても圧痕が残らない硬性浮腫を呈する。典型的な症例では，指全体がソーセージのように腫脹して光沢を持つ（写真４－①）。病状が回復期に入ると（発症後１～２週間程度）指先部と爪床の境界（指の最先端）からべろっと皮が一塊になって剝け落ちる膜様落屑を認める（写真４－②）。四肢末端の発赤腫脹の程度が強かった症例ほど膜様落屑の範囲・程度共に増強し，手袋を取ったように手掌全体が膜様落屑する症例もある。

非化膿性頸部リンパ節腫脹

観察できる頸部リンパ節腫脹の多くは胸鎖乳突筋下リンパ節腫脹である。典型例では，大人の拇指頭大以上（直径1.5cm以上）の大きさとなり，１個以上のリンパ節が集塊として触知される。リンパ節は，しばしば片側性で，比較的硬く，波動を生じず，穿刺しても膿は吸引されない。鶏卵大以上の大きな頸部リンパ腫大を呈する症例では，周辺皮膚は発赤し，強い圧痛がある（写真５）。痛みのため患側に首を曲げ続ける症例も時に認める。

他の主要症状と比較してその出現頻度は70%前後と低く，特に１歳以下の乳児ではさらに低頻度である。しかし４歳以上の年長例においては，発熱と共に病初期から出現することが多く，川崎病早期診断の大きな補助所見となる。抗菌剤に反応不良な化膿性頸部リンパ節炎や流行性耳下腺炎として治療をされる場合もあるため，注意が必要である。

各症状の出現する順序は症例によって異なり，同時にいくつかの主要症状が出現することもあれば，１つずつ出現して気づかれる場合もある。また，いくつかの症状が同時に出現していることも

日本川崎病学会ホームページ

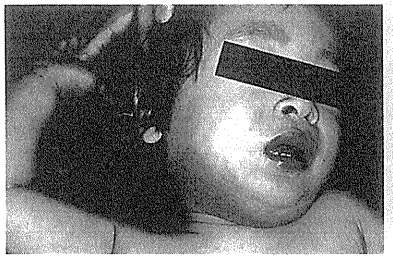

写真５■非化膿性頸部リンパ節腫脹

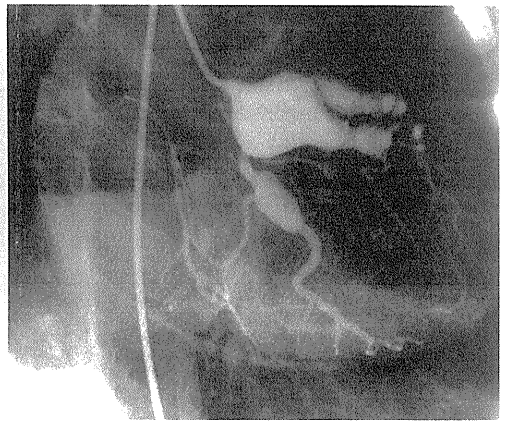

写真６■巨大冠動脈瘤

あれば，出現している日が別のこともあるため，注意深く経過を観察し，記録しておくことが，正しく川崎病を診断する上で重要な点である。

川崎病は，無治療でも数週間の経過で解熱し，すべての急性期症状は消失する。しかし，発熱が長期間続いた症例ほど，後遺障害である冠動脈障害の出現頻度が増すため，早期診断と早期治療による冠動脈障害出現の予防が重要となる。

■合併症・後遺症

川崎病に起因する急性期合併症は非常に多彩である（『川崎病診断の手引き改訂５版』参考条項参照）。中でも，肝逸脱酵素上昇，無菌性膿尿，胆嚢腫大，麻痺性イレウスは比較的頻度が高く，川崎病の早期診断において有用な所見である。

川崎病の後遺障害で最も重要なものは，心臓障害，特に冠動脈病変である。冠動脈病変は狭心症や心筋梗塞，突然死といった心事故を起こす原因となるため，川崎病急性期治療最大の目標は，いかに冠動脈病変を抑制するかの１点に尽きる。冠動脈病変は，無治療ではその25％に形成するが，近年の治療法の進歩によって，冠動脈瘤の頻度は急性期では10％，１カ月時では３％程度にまで減少した。しかし，高率に心事故を起こす冠動脈内径８mm以上の巨大冠動脈瘤患者（**写真６**）は年間30例程度新たに発生しており，しかも巨大冠動脈瘤患者は近年減少傾向が認められないことが大きな問題である。

治療

■急性期治療

基本的には，2003年に日本小児循環器学会より提唱された『川崎病急性期治療のガイドライン』に沿って治療する。急性期治療の核となる治療法は，２g/kg１回投与の免疫グロブリン超大量（IVIG）療法と，アスピリン30mg/kg/dayの併用である。診断後できるだけ早期にIVIGを行うことが，冠動脈病変抑制のためには極めて重要である。遅くとも，発症後10病日以内にIVIGを実施することを目標とする。

一方で，IVIG後も臨床症状や血液検査所見が改善しないIVIG不応例も約15～20％存在する。このような重症川崎病患者に対する治療法は，残念ながらいまだ確立されていない。現在は，IVIGの再投与，ステロイドやシクロスポリンなどの免疫抑制薬，生物学的製剤であるインフリキシマブ，エラスターゼ阻害薬であるウリナスタチン，血漿交換などの追加治療が各施設の方針に従って実施されている。

また，一般的な管理方法として，過剰な輸液を避けることは極めて重要である。川崎病急性期は，血管炎によって血漿成分が血管外に漏出しており，抗利尿ホルモンの過剰分泌によって体内は水分過多となっている。過剰輸液は冠動脈に対する圧力を増加する方向に働くため，冠動脈障害を助長する。そのため筆者は，IVIG投与中はIVIG以外の輸液を行わず，体重が増加していく児やIVIG不応例といった重症患者に対しては利尿剤やβ遮断薬を積極的に使用し，できる限り血管に対する圧力を下げるよう心がけている。

■慢性期治療

解熱し，急性期症状が消失した児に対しては，冠動脈病変の程度によって治療法を選択する。

冠動脈病変を生じなかった患者には，２カ月間抗血小板薬を継続する。アスピリンは３～５mg/kg/day分１に減量して投与し，２カ月後の検査で異常所見がないことを確認したら内服終了とする。軽度～中程度の冠動脈病変を残存した患者には，アスピリンの投与を継続し，冠動脈病変が正常化するようならアスピリンの投与を中止する。８mmを超える重度の冠動脈病変を合併した患者は，心事故の高リスク群であるため，抗血小板薬に抗凝固療法（ワーファリン0.05～0.1mg/kg分１）を併用する。ワーファリンの効果は個人差が大きいため，PTINRを2.0前後に保つよう用量を調節する。

看護のポイント

■患児へのケアポイント

診断前

川崎病患者の中には，急性期症状がそろう前に入院となり，入院中に川崎病と診断される症例も散見される。特に６カ月未満の乳児は不明熱として入院となり，４歳以上の幼児は化膿性頸部リンパ節炎の初期診断で入院することもある。そのような患者の場合は，発疹や眼球結膜の充血，手足の発赤やむくみ，口唇の所見が出現しないか，注意深く観察することが重要である。

急性期

川崎病と診断された症例の大部分はIVIGが投与されるが，IVIG投与時にショック症状（血圧低下，頻脈，顔色不良，多呼吸）を呈する患者が２％程度存在するため，注意が必要である。IVIG製剤の投与速度が速いほどショック症状を起こしやすいため，投与開始直後は投与速度を遅くし，心電図やSpO_2モニターを装着して頻繁に血圧や心拍数，呼吸数等をモニタリングすることが重要である。ショック症状がないことを確認できたら，投与速度を上げる。

また，冷蔵保存されている液状製剤を室温に戻さずに投与するとショック症状を起こしやすいため，液状製剤は必ず室温に戻してから投与する。自施設では，投与前，５分，10分，15分，30分とバイタルチェックを行い，ショック症状がないことを確認した後に投与速度を上げ，バイアル交換時にバイタルサインのチェックを行っている。

川崎病患者のIVIG投与時のクリニカルパスを作成することが望ましい。

IVIG投与によって主要症状がどのように変化するかを詳細に観察することも重要である。一般的

には，より早期に主要症状が改善した患者では冠動脈病変の合併頻度が低い。一方で，IVIG投与後24時間たっても37.5℃未満に解熱しないIVIG不応例は，冠動脈病変合併頻度の高リスク群である。適切な追加治療を行うと共に，主要症状の変化，心不全症状の有無の観察，尿測，水分バランスの測定，定期的な体重測定による適切な水分管理が求められる。

亜急性期

解熱し，全身状態が改善した亜急性期の川崎病患者は，冠動脈病変の有無によってその対応が異なる。

中等度～重度の冠動脈病変を合併した患者は，冠動脈内血栓を形成し，心筋梗塞を起こす可能性があるため，心電図モニターを装着して心電図変化を観察すること，虚血症状の有無について観察することが求められる。抗凝固療法を行っている患児は転落予防や出血症状の有無を観察する。特に，抗凝固療法開始直後はPTINRの値が安定していないため，血栓形成や出血に十分注意する。

冠動脈病変を合併しなかった患者は，心筋梗塞を起こすリスクはほとんどない。膜様落屑部位をいじって出血したり，口唇の亀裂から出血したりして痛みを訴える患児には，白色ワセリンなどを塗布し，患部の保護をする。BCG接種部位が強く発赤した患児は，発赤した部位が大きく痂皮化するが，痂皮を人為的に剝がすと出血するため，自然に剝け落ちるのを待つ。

■再燃した場合の対処

主要症状がいったん改善した後，再発熱と共に再び症状が出現する再燃は，川崎病患者全体で４％ほど存在する。感冒様症状の有無や主要症状の変化を観察し，再燃が強く疑われるようならば，適切な追加治療を行う。

■家族へのアプローチのポイントと精神的支援・不安軽減

川崎病という病名は比較的知られているものの，公害病や気管支喘息と間違って認識されている場合も多い。まずは，正確な情報を家族に提供することが肝心である。

先に紹介したRAISE Studyホームページでは，川崎病の歴史や病態，合併症，治療法などを動画で解説している[2]ので，一覧いただきたい（http://raise.umin.jp/dvd.html）。また，日本川崎病学会が作成した「川崎病と免疫グロブリン療法について」[3]は，IVIGの安全性と有効性が詳細に説明されているので，家族への情報提供にご活用いただきたい。これは，同学会のホームページからフリーでダウンロードできる（http://www.jskd.jp/info/pdf/globulin2.pdf）。

いまだ原因不明の川崎病ではあるが，治療法の進歩によって予後は改善していることを丁寧に説明すれば，家族の不安軽減の一助となる。

■退院の指導と後遺症・外来フォロー

IVIGを投与し速やかに解熱した患児は，１週間前後の入院期間で退院となることが多い。しかし，川崎病の炎症は数カ月単位で残存するため，「退院＝完治」ではないことを十分理解してもらい，次のことを指導することが重要である。

①激しい運動を避ける
②アスピリンの内服をきちんと継続する
③アスピリン内服中は出血が止まりにくいため，転落や外傷には十分に注意する
④ライ症候群発症のリスクをできるだけ下げるため，インフルエンザや水痘患者との接触を極力避ける
⑤再発熱時に川崎病症状が複数出現していないか観察する
⑥定期的に受診し，検査をする
⑦経口ポリオを除く生ワクチンはIVIG投与後６カ月間は接種しない

後遺症を残した患児にも基本的にこれらの指導を行うが，ワーファリンを内服している患児には，特に出血のリスクを詳細に説明すると共に，出血が止まりにくい場合は薬が効きすぎていることもあり得るので，受診して血液検査するよう指導する。

また，川崎病に罹患した患者は数十年後に冠動脈疾患に罹患するリスクが高いことが予想されている。そのため，川崎病罹患時の情報を患者から内科医に提供できるように準備することはとても重要である。急性期にどのような症状が出現し，どのような治療が行われたか，心臓障害はどの程度かを記載する「川崎病急性期カード」が現在広く用いられている。主治医に記載を依頼し，家族には母子手帳に入れて保管していただくよう指導する。

看護師さんへ アドバイス

川崎病看護のポイントは，発見者である川崎富作氏がおっしゃるように，「丁寧に患者を観察すること」だと思う。診断，免疫グロブリンの安全性，有効性いずれも臨床症状やバイタルサインの変化で判断する。

患者の最も近くにいる看護師の視点やバイタルチェックの結果は，医師が治療方針を決断する際にとても重要な所見となる。ご自分が川崎病診療の最前線で戦っていることを意識していただくと共に，家族の不安が少しでも和らぐよう，さまざまな資料を活用して患者と家族を支援していただくことを期待している。

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