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Randomized Trial of Pulsed Corticosteroid Therapy for Primary Treatment of Kawasaki Disease

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ABSTRACT

BACKGROUND

Treatment of acute Kawasaki disease with intravenous immune globulin and aspirin reduces the risk of coronary-artery abnormalities and systemic inflammation, but despite intravenous immune globulin therapy, coronary-artery abnormalities develop in some children. Studies have suggested that primary corticosteroid therapy might be beneficial and that adverse events are infrequent with short-term use.

METHODS

We conducted a multicenter, randomized, double-blind, placebo-controlled trial to determine whether the addition of intravenous methylprednisolone to conventional primary therapy for Kawasaki disease reduces the risk of coronary-artery abnormalities. Patients with 10 or fewer days of fever were randomly assigned to receive intravenous methylprednisolone, 30 mg per kilogram of body weight (101 patients), or placebo (98 patients). All patients then received conventional therapy with intravenous immune globulin, 2 g per kilogram, as well as aspirin, 80 to 100 mg per kilogram per day until they were afebrile for 48 hours and 3 to 5 mg per kilogram per day thereafter.

RESULTS

At week 1 and week 5 after randomization, patients in the two study groups had similar coronary dimensions, expressed as z scores adjusted for body-surface area, absolute dimensions, and changes in dimensions. As compared with patients receiving placebo, patients receiving intravenous methylprednisolone had a somewhat shorter initial period of hospitalization ($P=0.05$) and, at week 1, a lower erythrocyte sedimentation rate ($P=0.02$) and a tendency toward a lower C-reactive protein level ($P=0.07$). However, the two groups had similar numbers of days spent in the hospital, numbers of days of fever, rates of retreatment with intravenous immune globulin, and numbers of adverse events.

CONCLUSIONS

Our data do not provide support for the addition of a single pulsed dose of intravenous methylprednisolone to conventional intravenous immune globulin therapy for the routine primary treatment of children with Kawasaki disease. (ClinicalTrials.gov number, NCT00132080.)

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The standard of care for children with acute Kawasaki disease is treatment with high-dose intravenous immune globulin and aspirin.[1] Despite receiving high-dose intravenous immune globulin within the first 10 days of illness, approximately 5% of children with Kawasaki disease have subsequent coronary aneurysms and 1% have giant aneurysms, as classified on the basis of criteria of the Japanese Ministry of Health.[2-4] Moreover, when coronary-artery dimensions are adjusted for body-surface area, a far greater proportion of children with Kawasaki disease have coronary-artery dilation than would be detected with the use of unadjusted dimensions.[5]

The role of corticosteroids in the primary treatment of Kawasaki disease has been the subject of retrospective case series and open trials, with insufficient evidence to make recommendations concerning their use. Although one early study showed a detrimental effect of corticosteroid therapy in patients with Kawasaki disease,[6] the results of other studies have suggested that corticosteroids may be beneficial in preventing coronary-artery aneurysms.[7-12] The effect of primary treatment with pulsed corticosteroids on coronary dimensions has not been tested in a double-blind, placebo-controlled trial.

To study the efficacy and safety of pulsed corticosteroid therapy, added to conventional treatment with intravenous immune globulin plus aspirin, in the primary treatment of acute Kawasaki disease, we conducted a multicenter, randomized, double-blind, placebo-controlled trial within the Pediatric Heart Network.[13] Patients were randomly assigned to receive either a pulsed dose of intravenous methylprednisolone or placebo; intravenous immune globulin and aspirin were administered to both groups.

Methods

Patients

Patients were recruited from December 2002 through December 2004 from eight centers in North America. Eligible patients were between days 4 and 10 of illness, with day 1 defined as the first day of fever. At least one of the following was also required for eligibility: the patient met four or more principal clinical criteria[1]; the patient had a coronary-artery z score[1] of 2.5 or more for the proximal right coronary artery or the left anterior descending coronary artery, as measured by two-dimensional echocardiography, and met two principal clinical criteria (for patients younger than 6 months) or three principal clinical criteria (for patients 6 months of age or older); or the patient had a coronary aneurysm as defined according to criteria of the Japanese Ministry of Health[14] and met at least one principal clinical criterion. Exclusion criteria were previous treatment with intravenous immune globulin; treatment with corticosteroids, other than inhaled forms, in the previous 2 weeks; the presence of a disease known to mimic Kawasaki disease[1]; previous diagnosis of Kawasaki disease; contraindication to corticosteroid use; and inability to take aspirin. Written informed consent was obtained from parents or legal guardians; assent from patients was also obtained when appropriate, according to the guidelines of local institutional review boards, which approved the study protocol.

Procedures

Patients were randomly assigned to receive either intravenous methylprednisolone (30 mg per kilogram of body weight over 2 to 3 hours) or placebo infusion, within strata according to age (<1 year or ≥1 year) and sex, with the use of dynamic balancing at each center. After the study drug was infused, all children received diphenhydramine (Benadryl), 1 mg per kilogram, followed by intravenous immune globulin, 2 g per kilogram over 10 hours. They also received aspirin, 80 to 100 mg per kilogram per day, until they were afebrile for 48 hours; then they received aspirin, 3 to 5 mg per kilogram daily, until study completion. Children who had a temperature of 38.3°C or higher 36 hours or more after completion of the initial treatment with intravenous immune globulin, without another probable source of fever, were retreated with 2 g of intravenous immune globulin per kilogram. A third treatment with intravenous immune globulin, 2 g per kilogram, was administered to patients with recrudescent or persistent fever 36 hours or more after intravenous immune globulin retreatment, without another probable source of fever. Patients with continued fever after the third dose were treated at the discretion of center physicians.

Echocardiograms and laboratory data were obtained at baseline and at means (±SD) of 7.8±1.8 days (median, 8.0) and 36.5±4.3 days (median, 36.0) after randomization. Using two-dimensional echocardiography, we measured the internal lu-

men diameters of the left main coronary artery, the proximal and distal left anterior descending coronary arteries, and the circumflex, posterior descending, and proximal and distal right coronary arteries. In addition, coronary arteries were classified on the basis of the presence or absence of aneurysms according to criteria of the Japanese Ministry of Health.[14] The diagnosis of pericardial effusion required more than 1 mm of fluid. At a core laboratory, all echocardiograms were interpreted in a fashion that was blind to patient identity and illness day.

Temperatures were measured immediately before each aspirin dose was administered, but the site (e.g., rectal) of temperature measurement was not standardized. Children were hospitalized until they had been afebrile for more than 12 hours. Parents recorded the temperatures of the patients daily after discharge.

Adverse events were classified according to severity, expectedness, and attributability (a possible or probable relation to factors in the study). Classification was adjudicated by a Pediatric Health Network subcommittee to ensure consistency across centers.

STATISTICAL ANALYSIS

The primary outcome variable was the larger of the z scores for the right coronary artery and the left anterior descending coronary artery at week 5 after randomization. For the five echocardiograms (2.6%) at week 5 on which only one primary segment was visualized, the maximum z score was based on the dimension of the single segment. We calculated that we needed to enroll 194 patients, including 10% in excess to account for one interim analysis and the possibility of missing data, for the study to have a statistical power of 85% to detect a mean difference of 0.50±1.10 in the maximum z score, with a two-sided significance level of 5%. One interim analysis was reviewed by an independent data and safety monitoring board. All reported P values are two-sided and are not adjusted for multiple testing, unless otherwise specified. P values of less than 0.05 were considered to indicate statistical significance.

We compared the distributions of data between the two study groups as follows: for continuous variables, using a t-test if the data were normally distributed and Wilcoxon's rank-sum test otherwise; for time from admission to initial hospital discharge, using a log-rank test; and for categorical variables, using a Fisher's exact test unless otherwise specified. We compared the numbers of adverse events and episodes of retreatment in each study group using Poisson regression. We transformed coronary-artery dimensions to z scores (standard-deviation units) on the basis of body-surface area.[1] We performed four prespecified subgroup analyses, as well as a post hoc analysis according to the presence or absence of retreatment with intravenous immune globulin, using a test for interaction between the subgroup factor and study group.

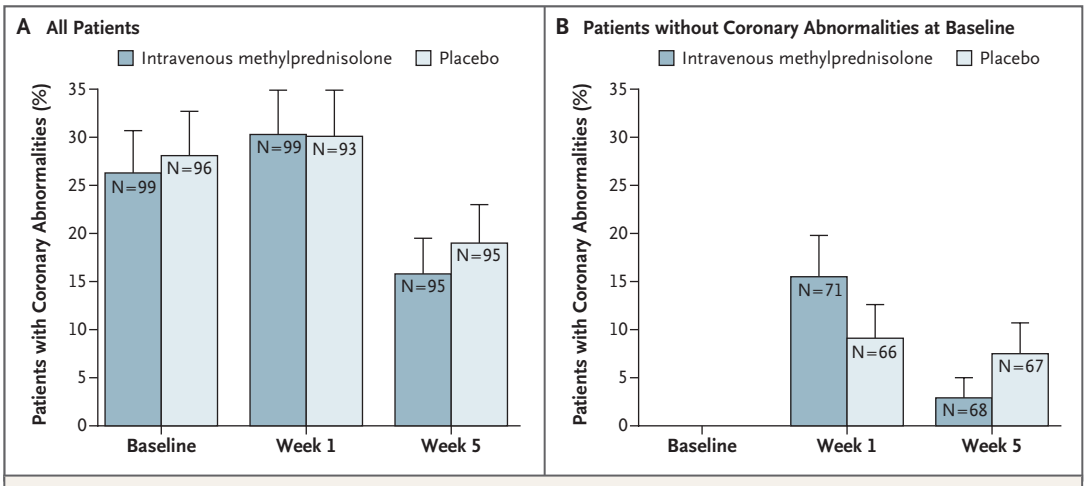

Figure 1. Percentages of Patients with Coronary Abnormalities.

Differences between study groups at each time point were not significant, whether patients with abnormalities at baseline were included (Panel A) or not (Panel B). T bars indicate standard errors.

Table 1. Demographic, Laboratory, and Echocardiographic Characteristics at Randomization.*

Characteristic	Intravenous Methylprednisolone	Placebo
Age at enrollment (199 patients)		
Median (yr)	2.9	2.9
IQR (yr)	1.3–5.0	1.6–4.4
Age <1 yr (%)	16	17
Male sex (%) (199 patients)	62	62
Race or ethnic group (199 patients)†		
White (%)	63	52
Black (%)	17	20
Asian (%)	14	14
American Indian or Alaskan Native (%)	1	2
Native Hawaiian or other Pacific Islander (%)	1	0
More than one (%)	4	10
Other or unknown (%)	0	1
Hispanic (%)	17	17
Days of illness at enrollment (199 patients)		
Median	6.0	6.0
IQR	6.0–8.0	5.0–7.0
Hemoglobin (g/dl) (198 patients)	11.0±1.1	10.9±1.2
White-cell count (198 patients)		
Median ($\times 10^{-3}$/mm^3)	13.5	12.9
IQR ($\times 10^{-3}$/mm^3)	10.4–16.6	10.0–17.1
Platelet count ($\times 10^{-3}$/mm^3) (198 patients)	394±138	393±147
Erythrocyte sedimentation rate (187 patients)		
Median (mm/hr)	65.5	67.0
IQR (mm/hr)	45.0–90.0	40.0–93.0
C-reactive protein (138 patients)		
Median (mg/dl)	7.2	6.8
IQR (mg/dl)	3.3–14.0	3.7–18.4
Albumin (g/dl) (182 patients)	3.3±0.6	3.3±0.6

We performed secondary analyses of all outcome variables, excluding data for six patients who were discovered after enrollment to have met an exclusion criterion, for two patients who did not receive corticosteroid therapy despite randomization to the intravenous methylprednisolone group, and for eight patients who were enrolled because they had coronary abnormalities but who would not have met the classic criteria for Kawasaki disease.[1] The inferences reached were similar to those derived from analysis of the entire data set.

RESULTS

During the 2-year study period, 589 children were treated for Kawasaki disease (Fig. 1). Of these, 276 were ineligible for the trial; 185 met at least one exclusion criterion, most often being ill for more than 10 days (102 patients), and the remaining 91 did not meet the inclusion criteria. Of the 313 eligible children, 199 (64%) had parental consent for enrollment in the study. Of these, 101 were randomly assigned to receive intravenous methylprednisolone, 30 mg per kilogram, and 98

Table 1. (Continued.)

Characteristic	Intravenous Methylprednisolone	Placebo
IgA (158 patients)		
Median (mg/dl)	79	95
IQR (mg/dl)	50–112	55–147
IgG (158 patients)		
Median (mg/dl)	668	731
IQR (mg/dl)	519–833	512–915
IgM (157 patients)		
Median (mg/dl)	109	110
IQR (mg/dl)	78–146	65–140
Body-surface area–adjusted coronary-artery dimensions		
Maximum z score (195 patients)‡	1.70±1.45	1.60±1.52
Proximal LAD z score (193 patients)	1.05±1.58	1.14±1.49
Proximal RCA z score (190 patients)	1.19±1.23	1.17±1.52
LMCA z score (194 patients)	0.84±1.04	0.93±1.19
Aortic root z score (162 patients)	0.77±0.85	0.84±0.85
No. of patients with coronary-artery abnormalities/no. with echocardiogram (%) (195 patients)§	26/99 (26)	27/96 (28)

* Plus–minus values indicate means ±SD. No between-group comparisons were significant (all P values >0.10). IQR denotes interquartile range, LAD left anterior descending coronary artery, RCA right coronary artery, and LMCA left main coronary artery.
† Race or ethnic group was assigned by the parent or physician. Percentages exceed 100 because patients could be assigned both to a racial group and to the Hispanic ethnic group.
‡ Maximum z score was defined as the larger of the proximal LAD and the proximal RCA z scores.
§ Patients with coronary-artery abnormalities had a proximal LAD or proximal RCA z score of 2.5 or more or at least one coronary artery that met the criteria of the Japanese Ministry of Health for aneurysms.[14]

were randomly assigned to receive placebo. Patients in the two study groups had similar baseline characteristics (Table 1).

The study groups did not differ significantly in coronary-artery outcomes at week 1 or week 5 after randomization (Table 2), with the exception of a smaller mean diameter of the posterior descending artery in the intravenous methylprednisolone group than in the placebo group (0.12±0.03 cm vs. 0.13±0.03 cm, P=0.01), based on only half the patients in the study because of poor visualization of this artery. The primary end point was the z score of the left anterior descending coronary artery or that of the right coronary artery at week 5, whichever was larger; the intravenous methylprednisolone group and placebo group had similar mean values (1.31±1.55 and 1.39±2.03, respectively; P=0.76). The percentage of children with coronary-artery abnormalities — defined as those meeting the criteria of the Japanese Ministry of Health for aneurysms or those associated with z scores for the proximal left anterior descending coronary artery or right coronary artery of 2.5 or more — was not significantly different between the two groups (Table 2 and Fig. 1). The groups also had similar z scores for the proximal right coronary artery and the left anterior descending coronary artery, similar absolute dimensions of the seven measured coronary segments, and similar changes in dimensions from baseline to week 1 and week 5, with the exception of the data for the posterior descending artery at week 5 and its change from baseline. Excluding patients in whom only the left main coronary artery was dilated, potentially owing to preexisting anatomic variation, four patients (two in each group) had coronary-artery abnormalities that were more than mild (coronary-artery diameter >4 mm); only one (in the placebo group) had an aneurysm with a maximum diameter exceeding 6 mm.

Aortic-root z scores, although larger in our patients than in the general population, were simi-

Table 2. Coronary-Artery Outcomes at Week 1 and Week 5 after Randomization.*

Variable	Intravenous Methylprednisolone	Placebo	Difference	P Value†
	mean ±SD (no. of patients)		*mean ±SE (95% CI)*	
z Score				
Maximum‡				
Week 1	1.77±1.66 (98)	1.69±2.00 (92)	0.08±0.27 (–0.44 to 0.61)	0.76
Week 5	1.31±1.55 (95)	1.39±2.03 (95)	–0.08±0.26 (–0.59 to 0.44)	0.76
Proximal LAD				
Week 1	1.12±1.63 (97)	1.12±1.75 (92)	–0.01±0.24 (–0.49 to 0.48)	0.98
Week 5	0.63±1.63 (93)	0.75±1.92 (94)	–0.12±0.26 (–0.63 to 0.40)	0.65
Proximal RCA				
Week 1	1.17±1.48 (98)	1.21±1.98 (90)	–0.05±0.25 (–0.54 to 0.46)	0.86
Week 5	0.93±1.61 (93)	0.94±1.88 (95)	–0.02±0.26 (–0.52 to 0.49)	0.95
	no./total no. (%)			
Coronary-artery abnormalities§				
All patients				
Week 1	30/99 (30.3)	28/93 (30.1)	0.2±6.6 (–12.8 to 13.2)	1.00
Week 5	15/95 (15.8)	18/95 (18.9)	–3.2±5.5 (–13.9 to 7.6)	0.70
Patients without abnormalities at baseline¶				
Week 1	11/71 (15.5)	6/66 (9.1)	6.4±5.6 (–0.05 to 17.3)	0.31
Week 5	2/68 (2.9)	5/67 (7.5)	–4.5±3.8 (–12.0 to 3.0)	0.27

* CI denotes confidence interval, proximal LAD left anterior descending artery, and proximal RCA right coronary artery.
† Difference was defined as the value for the intravenous methylprednisolone group minus the value for the placebo group. P values for z scores were calculated with the use of the two-sample t-test, and the P values for coronary-artery abnormalities with the use of a Fisher's exact test. The P value for maximum z score at week 5 was adjusted for one interim analysis.
‡ Maximum z score was defined as the larger of the proximal LAD and the proximal RCA z scores.
§ Patients with coronary-artery abnormalities had a proximal LAD or proximal RCA z score of 2.5 or more or at least one coronary artery that met the criteria of the Japanese Ministry of Health for aneurysms.[14]
¶ Patients without a determination of coronary-artery abnormality status at baseline or with abnormalities at baseline were excluded.

lar in the intravenous methylprednisolone group and the placebo group at week 1 (0.93±0.83 and 0.95±0.82, respectively; P=0.88) and week 5 (0.86±0.88 and 0.83±0.86, respectively; P=0.84). The precentages of patients with mitral regurgitation were similar in the two study groups; in the combined groups, mild or moderate mitral regurgitation was present in 27% of patients at baseline, 15% at week 1, and 9% at week 5. No patients had severe mitral regurgitation. Aortic regurgitation occurred in one patient in each group at baseline, in two patients in the intravenous methylprednisolone group at week 1, and in one patient in the intravenous methylprednisolone group at week 5. At baseline, the mean left ventricular shortening fraction was marginally higher in the intravenous methylprednisolone group than in the placebo group (37±6% and 35±6%, respectively; P=0.08) but was similar in the two groups at week 1 and week 5. The prevalence of pericardial effusion was similar in the two groups: 2% at baseline, 3% at week 1, and 0% at week 5.

The time to first hospital discharge was marginally shorter in the intravenous methylprednisolone group than in the placebo group, but the two groups had similar total numbers of days in the hospital (including readmissions) and days of fever both after randomization and after the onset of illness (Table 3). Similarly, the groups did not differ significantly in the percentage of patients who were retreated at least once with intravenous immune globulin or in the total number of episodes of retreatment with intravenous immune globulin (Table 3).

Children treated with intravenous methylprednisolone, as compared with those treated with

Table 3. Duration of Hospital Stay, Duration of Fever, and Retreatment with Intravenous Immune Globulin (IVIG).*

Variable	Intravenous Methylprednisolone (N=101)	Placebo (N=97)	P Value
No. of days from randomization until first hospital discharge			0.05†
Median	3	3	
IQR	2–3	3–4	
Total no. of days spent in the hospital after randomization			0.40‡
Median	3	3	
IQR	3–3	3–4	
No. of days of fever after randomization			0.14‡
Median	0	1	
IQR	0–1	0–1	
No. of episodes of IVIG retreatment	13	20	0.19§
Patients retreated with IVIG — no. (%)	12 (11.9)	15 (15.5)	0.54¶

* One patient in the placebo group withdrew from the trial shortly after randomization, before receiving the study drug, and these data were not collected. IQR denotes interquartile range.
† The P value was calculated with the use of the log-rank test.
‡ The P value was calculated with the use of the Wilcoxon rank-sum test.
§ The P value was calculated with the use of Poisson regression.
¶ The P value was calculated with the use of a Fisher's exact test.

placebo, had a lower erythrocyte sedimentation rate at week 1 (P=0.02), lower serum IgG levels at week 1 and week 5 (P=0.06 and P=0.03, respectively), lower serum IgA level at week 1 (P=0.05), and tendencies toward a lower C-reactive protein level at week 1 (P=0.07) and a higher hemoglobin level at week 5 (P=0.09). Other laboratory measures were similar in the two groups at weeks 1 and 5 (Table 4).

One or more adverse events occurred in 26 children (26%) in the intravenous methylprednisolone group and in 22 children (23%) in the placebo group (P=0.62) (Table 5). The total number of adverse events did not differ significantly between the intravenous methylprednisolone group and the placebo group (37 and 24 events, respectively; P=0.18). Two children in each group had serious adverse events, none of which were considered to be related to intravenous methylprednisolone or placebo. The serious events in the methylprednisolone group included shock and respiratory failure, with negative blood cultures 3 days after initial hospital discharge, and profound sensorineural hearing loss; those in the placebo group included possible nonocclusive thrombus in the right coronary artery on echocardiography (treated with abciximab) and anaphylaxis to intravenous immune globulin. Adverse events were attributed to intravenous methylprednisolone or placebo in five patients, all in the intravenous methylprednisolone group (P=0.06). These included four episodes of hypotension during infusion of the study drug and one episode of hypokalemia. The incidence of adverse events believed to be related to Kawasaki disease or to treatment with intravenous immune globulin did not differ significantly between the two groups.

The effect of intravenous methylprednisolone on coronary-artery outcomes at week 5 was consistent across predetermined subgroups: male or female, less than 1 year of age or 1 year or older, presence or absence of coronary-artery abnormalities at baseline, and less than 7 days or 7 or more days of illness at randomization. Similarly, we did not observe any significant interaction between subgroups and treatment assignment with regard to the time to initial discharge from the hospital, the total numbers of days in the hospital or days of fever, or the presence or absence of retreatment.

To explore whether the effect of intravenous methylprednisolone on coronary outcomes dif-

Table 4. Laboratory Data at Week 1 and Week 5 after Randomization.*

Variable	Intravenous Methylprednisolone	Placebo	P Value
Hemoglobin (g/dl)			
Week 1			
No.	96	92	
Mean ±SD	11.1±1.2	10.9±1.3	0.25
Week 5			
No.	91	94	
Mean ±SD	12.0±0.9	11.7±1.0	0.09
White-cell count ($\times 10^{-3}$/mm^3)			
Week 1			
No.	96	92	
Median	9.5	9.6	0.68‡
IQR	7.9–12.1	7.6–12.3	
Week 5			
No.	91	94	
Median	7.7	8.0	0.54‡
IQR	6.2–9.2	6.4–9.3	
Platelet count ($\times 10^{-3}$/mm^3)			
Week 1			
No.	96	92	
Mean ±SD	645±174	661±189	0.55
Week 5			
No.	91	94	0.27
Mean ±SD	391±95	406±97	
Erythrocyte sedimentation rate (mm/hr)			
Week 1			
No.	93	88	
Median	57.0	69.0	0.02
IQR	35.0–88.0	46.5–100.0	
Week 5			
No.	88	91	
Median	11.0	12.0	0.33
IQR	5.5–18.5	8.0–20.0	
C-reactive protein (mg/dl)			
Week 1			
No.	91	88	
Median	0.25	0.43	0.07
IQR	0.08–0.57	0.10–0.90	
Week 5			
No.	84	89	
Median	0.02	0.03	0.13
IQR	0.02–0.07	0.02–0.11	

Table 4. (Continued.)

Variable	Intravenous Methylprednisolone	Placebo	P Value
Albumin (g/dl)			
Week 1			
No.	94	91	
Mean ±SD	3.65±0.44	3.57±0.45	0.23
Week 5			
No.	91	93	
Mean ±SD	4.18±0.32	4.17±0.33	0.83
IgG (mg/dl)			
Week 1			
No.	94	92	
Median	1920	2050	0.06
IQR	1690–2210	1690–2490	
Week 5			
No.	88	93	
Median	1050	1140	0.03
IQR	894–1180	959–1340	
IgA (mg/dl)			
Week 1			
No.	93	92	
Median	94	126	0.05
IQR	60–172	73–185	
Week 5			
No.	88	93	
Median	59	70	0.21
IQR	32–113	39–111	
IgM (mg/dl)			
Week 1			
No.	93	92	
Median	145	163	0.14
IQR	111–194	120–215	
Week 5			
No.	88	93	
Median	104	109	0.74
IQR	70–123	73–137	

* P values were calculated with the use of the Wilcoxon rank-sum test except those for hemoglobin, platelet count, and albumin, which were calculated with the use of the two-sample t-test. IQR denotes interquartile range.

fered according to the severity of illness, we performed a post hoc comparison of the efficacy of the drug in the 27 patients with persistent fever who required retreatment with intravenous immune globulin (12 in the intravenous methylprednisolone group and 15 in the placebo group) with the efficacy in the 172 children who did not require retreatment (those who had a response to intravenous immune globulin). The efficacy of intravenous methylprednisolone at week 1 and

Table 5. Adverse Events.*

Variable	Intravenous Methylprednisolone (N=101)	Placebo (N=97)	P Value
Total no. of events	37	24	0.18†
Events per patient — no. of patients (%)			0.18‡
0	75 (74)	75 (77)	
1	18 (18)	20 (21)	
2	6 (6)	2 (2)	
3	1 (1)	0	
4	1 (1)	0	
≥1 Adverse event — no. of patients (%)§	26 (26)	22 (23)	0.62
Related to IVMP or placebo	5 (5)	0	0.06
Related to IVIG	9(9)	11 (11)	0.64
Related to study protocol	2 (2)	0	0.50
Occurred in the hospital	18 (18)	12 (12)	0.33
≥1 Serious adverse event — no. of patients (%)	2 (2)	2 (2)	1.00
Events typically associated with IVIG — no. of patients (%)			
Congestive heart failure	0	0	1.00
Headache	5 (5)	3 (3)	0.72
Hemolytic anemia	1 (1)	0	1.00
Hypotension¶	5 (5)	1 (1)	0.21
Anaphylaxis	0	1 (1)	0.49
Shock	1 (1)	0	1.00

* One patient in the placebo group withdrew from the trial shortly after randomization, before receiving the study drug, and adverse events were not monitored. P values were calculated with the use of a Fisher's exact test, unless otherwise specified. IVMP denotes intravenous methylprednisolone, and IVIG intravenous immune globulin.
† The P value was calculated with the use of Poisson regression.
‡ The P value was calculated with the use of the Mantel–Haenszel test for linear trend.
§ All relations of adverse events with a study drug or protocol were possible or probable.
¶ Hypotension was defined as systolic blood pressure below the 5th percentile.

week 5 differed between these two subgroups with regard to mean maximum z scores (P=0.03 and P=0.006, respectively) and the percentages of patients with coronary-artery abnormalities (P=0.02 and P<0.001, respectively). Among the patients who were retreated with intravenous immune globulin, the mean maximum z score tended to be lower in the intravenous methylprednisolone group than in the placebo group at week 1 (1.35±1.21 and 2.73±2.40, respectively; P=0.07) and was significantly lower at week 5 (0.77±0.86 vs. 2.66±2.37, P=0.01). Correspondingly, the percentages of patients with coronary-artery abnormalities in the intravenous methylprednisolone group and the placebo group were 25% (3 of 12 patients) and 67% (10 of 15 patients), respectively, at week 1 (P=0.05) and 0% (0 of 11 patients) and 60% (9 of 15 patients), respectively, at week 5 (P=0.002). Images for one patient at week 5 were insufficient for the classification of the presence or absence of coronary abnormalities.

The patients retreated with intravenous immune globulin in the intravenous methylprednisolone group had a shorter time to first hospital discharge than did those in the placebo group (median, 3 days and 4 days, respectively; P=0.05 by the log-rank test), but the two subgroups had similar numbers of days of fever and days in the hospital, as well as similar laboratory results. Five of the children retreated with intravenous immune

globulin (two in the intravenous methylprednisolone group and three in the placebo group) received rescue intravenous methylprednisolone because of persistent or recrudescent fever after two episodes of retreatment with intravenous immune globulin.

DISCUSSION

We found that primary therapy with pulsed intravenous methylprednisolone, administered as a single dose of 30 mg per kilogram before conventional therapy with intravenous immune globulin (2 g per kilogram), did not improve coronary-artery outcomes at week 1 or week 5 after study enrollment. Pulsed intravenous methylprednisolone somewhat shortened the duration of the initial period of hospitalization and accelerated the recovery of some laboratory markers of the acute-phase response, but the total number of days of fever and of hospitalization did not differ significantly between study groups. The addition of intravenous methylprednisolone to conventional therapy was not associated with fewer adverse side effects. In post hoc subgroup analyses of children with persistent fever who received retreatment with intravenous immune globulin, coronary outcomes were better in the intravenous methylprednisolone group than in the placebo group. Thus, children at highest risk for resistance to intravenous immune globulin and for coronary abnormalities may benefit from corticosteroid therapy. However, a single pulsed dose of intravenous methylprednisolone in addition to conventional therapy is not indicated for routine primary treatment of all children with Kawasaki disease.

Previous prospective studies of the use of corticosteroids in primary treatment of children with Kawasaki disease have been inconclusive with regard to the effect on coronary-artery abnormalities. The authors of a meta-analysis concluded that, if combined with aspirin-containing regimens as initial therapy, corticosteroids significantly reduced the incidence of coronary-artery aneurysms.[11] Of the eight studies included,[6,10,15-20] only one had blind interpretation of echocardiography[15]; two were prospective,[15,16] and one included intravenous immune globulin administration according to current guidelines.[15] The conclusions from the meta-analysis are therefore limited by the quality and design of the studies.[21,22] Recently, Inoue et al.[12] performed a multicenter, prospective randomized trial in which intravenous immune globulin and aspirin were administered with or without the addition of intravenous prednisolone until defervescence, followed by the daily administration of oral prednisolone until C-reactive protein levels normalized. Patients in the corticosteroid group had a lower prevalence of coronary dilation (as defined according to criteria of the Japanese Ministry of Health) during the first month of illness than did the conventional group. Beyond 1 month, this difference was no longer significant. Assignment to corticosteroids or placebo and interpretation of echocardiograms, performed at local centers, were not blind. Our study, a larger-scale clinical trial, involved the optimal, currently recommended regimen of intravenous immune globulin in all patients, was double-blind and placebo-controlled, and included blind interpretation of echocardiograms.

Although intravenous methylprednisolone did not affect coronary-artery outcomes among patients whose fevers responded to intravenous immune globulin, it appeared to be beneficial in patients who required retreatment with intravenous immune globulin. The post hoc nature of these analyses and practical limitations in prospectively identifying patients who do not have a response to intravenous immune globulin are important caveats to this conclusion. However, in several recent publications, investigators have constructed risk scores for the Japanese population in order to predict resistance to intravenous immune globulin from baseline data.[23-26] More aggressive primary treatment with corticosteroids might benefit children who are determined at baseline to be at high risk for such resistance.

Additional study limitations should be noted. We studied a single dose of intravenous methylprednisolone only, since we believed that this regimen was the safest addition to standard treatment with intravenous immune globulin in a relatively low-risk population.[27-30] The results of our trial do not preclude the efficacy of other corticosteroid regimens for primary treatment or that of corticosteroid rescue therapy for children with persistent fever or aneurysms after conventional primary treatment.[9,30-33] The anatomical site of temperature measurement was not standardized, which decreased the accuracy of fever assessment. Data were not collected beyond week 5 after random-

ization. However, new coronary aneurysms rarely develop after the first month of illness, and approximately half of coronary aneurysms regress, through myointimal proliferation, to a normal internal lumen diameter.[1] Thus, any differences between the two groups at week 5 would only have diminished over time. Finally, the study was underpowered for subgroup analyses and for detection of between-group differences in the numbers of adverse events.

In summary, our data do not provide support for the addition of a single dose of pulsed intravenous methylprednisolone to conventional therapy in the routine primary treatment of Kawasaki disease. Although pulsed corticosteroid therapy was associated with more rapid resolution of serum inflammatory markers and a somewhat shorter initial length of stay in the hospital than placebo, it did not improve coronary-artery outcomes or reduce the numbers of adverse events, days in the hospital, or days of fever. Since post hoc subgroup analysis suggested that primary therapy with intravenous methylprednisolone might benefit children with persistent fever after treatment with intravenous immune globulin, future prospective studies should explore the usefulness of corticosteroid or other immunomodulatory therapies in children at highest risk for resistance to intravenous immune globulin.

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APPENDIX

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REFERENCES

1. Newburger JW, Takahashi M, Gerber MA, et al. Diagnosis, treatment, and long-term management of Kawasaki disease: a statement for health professionals from the Committee on Rheumatic Fever, Endocarditis, and Kawasaki Disease, Council on Cardiovascular Disease in the Young, American Heart Association. Circulation 2004;110:2747-71.
2. Dajani AS, Taubert KA, Takahashi M, et al. Guidelines for long-term management of patients with Kawasaki disease: report from the Committee on Rheumatic Fever, Endocarditis, and Kawasaki Disease, Council on Cardiovascular Disease in the Young, American Heart Association. Circulation 1994;89:916-22.
3. Terai M, Shulman ST. Prevalence of coronary artery abnormalities in Kawasaki disease is highly dependent on gamma globulin dose but independent of salicylate dose. J Pediatr 1997;131:888-93.
4. Durongpisitkul K, Gururaj VJ, Park JM, Martin CF. The prevention of coronary artery aneurysm in Kawasaki disease: a meta-analysis on the efficacy of aspirin and immune globulin treatment. Pediatrics 1995; 96:1057-61.
5. de Zorzi A, Colan SD, Gauvreau K, Baker AL, Sundel RP, Newburger JW. Coronary artery dimensions may be misclassified as normal in Kawasaki disease. J Pediatr 1998;133:254-8.
6. Kato H, Koike S, Yokoyama T. Kawasaki disease: effect of treatment on coronary artery involvement. Pediatrics 1979; 63:175-9.
7. Newburger JW. Treatment of Kawasaki disease: corticosteroids revisited. J Pediatr 1999;135:411-3.
8. Kijima Y, Kamiya T, Suzuki A, Hirose O, Manabe H. A trial procedure to prevent aneurysm formation of the coronary arteries by steroid pulse therapy in Kawasaki disease. Jpn Circ J 1982;46:1239-42.
9. Wright DA, Newburger JW, Baker A, Sundel RP. Treatment of immune globulin-resistant Kawasaki disease with pulsed doses of corticosteroids. J Pediatr 1996; 128:146-9.
10. Shinohara M, Sone K, Tomomasa T, Morikawa A. Corticosteroids in the treatment of the acute phase of Kawasaki disease. J Pediatr 1999;135:465-9.
11. Wooditch AC, Aronoff SC. Effect of initial corticosteroid therapy on coronary artery aneurysm formation in Kawasaki disease: a meta-analysis of 862 children. Pediatrics 2005;116:989-95.
12. Inoue Y, Okada Y, Shinohara M, et al. A multicenter prospective randomized trial of corticosteroids in primary therapy for Kawasaki disease: clinical course and coronary artery outcome. J Pediatr 2006;149: 336-41.
13. Mahony L, Sleeper LA, Anderson PA, et al. The Pediatric Heart Network: a primer for the conduct of multicenter studies in children with congenital and acquired heart disease. Pediatr Cardiol 2006;27: 191-8.
14. Research Committee on Kawasaki Disease. Report of subcommittee on standardization of diagnostic criteria and reporting of coronary artery lesions in Kawasaki disease. Tokyo: Ministry of Health and Welfare, 1984.
15. Sundel RP, Baker AL, Fulton DR, New-

burger JW. Corticosteroids in the initial treatment of Kawasaki disease: report of a randomized trial. J Pediatr 2003;142:611-6.
16. Okada Y, Shinohara M, Kobayashi T, et al. Effect of corticosteroids in addition to intravenous gamma globulin therapy on serum cytokine levels in the acute phase of Kawasaki disease in children. J Pediatr 2003;143:363-7.
17. Kan Z, Hashino K. Effectiveness of steroid-aspirin combined therapy for Kawasaki disease. J Pediatr Pract 1990;53:328-31.
18. Kusakawa S. Long-term administrative care of Kawasaki disease. Acta Paediatr Jap 1983;25:205-9.
19. Neudorf U. New therapeutic aspects in Kawasaki syndrome and personal experiences. Infusionsther Transfusionsmed 1993;20:Suppl 1:137-9. (In German.)
20. Sone K, Suzuiku A. Multidrug therapy for MCLS. J Pediatr Pract 1987;50:1175-80.
21. Ioannidis JP, Cappelleri JC, Lau J. Issues in comparisons between meta-analyses and large trials. JAMA 1998;279:1089-93.
22. Borzak S, Ridker PM. Discordance between meta-analyses and large-scale randomized, controlled trials: examples from the management of acute myocardial infarction. Ann Intern Med 1995;123:873-7.
23. Sano T, Kurotobi S, Matsuzaki K, et al. Prediction of non-responsiveness to standard high-dose gamma-globulin therapy in patients with acute Kawasaki disease before starting initial treatment. Eur J Pediatr 2007;166:131-7.
24. Egami K, Muta H, Ishii M, et al. Prediction of resistance to intravenous immune globulin treatment in patients with Kawasaki disease. J Pediatr 2006;149:237-40.
25. Muta H, Ishii M, Furui J, Nakamura Y, Matsuishi T. Risk factors associated with the need for additional intravenous gammaglobulin therapy for Kawasaki disease. Acta Paediatr 2006;95:189-93.
26. Kobayashi T, Inoue Y, Takeuchi K, et al. Prediction of intravenous immune globulin unresponsiveness in patients with Kawasaki disease. Circulation 2006;113:2606-12.
27. Ito S, Kusunoki Y, Oka T, Ito Y, Okuno A, Yoshioka H. Pharmacokinetics of high-dose methylprednisolone in children. Dev Pharmacol Ther 1992;19:99-105.
28. Suzuki N, Seguchi M, Kouno C, Inukai K, Kito H, Kobayashi H. Rupture of coronary aneurysm in Kawasaki disease. Pediatr Int 1999;41:318-20.
29. Imai Y, Momma K, eds. Pathological study of ruptured coronary artery aneurysms of Kawasaki disease. New York: Futura, 1997.
30. Hashino K, Ishii M, Iemura M, Akagi T, Kato H. Re-treatment for immune globulin-resistant Kawasaki disease: a comparative study of additional immune globulin and steroid pulse therapy. Pediatr Int 2001;43:211-7.
31. Shulman ST. Is there a role for corticosteroids in Kawasaki disease? J Pediatr 2003;142:601-3.
32. Dale RC, Saleem MA, Daw S, Dillon MJ. Treatment of severe complicated Kawasaki disease with oral prednisolone and aspirin. J Pediatr 2000;137:723-6.
33. Wallace CA, French JW, Kahn SJ, Sherry DD. Initial intravenous gammaglobulin treatment failure in Kawasaki disease. Pediatrics 2000;105:E78.

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