A MULTICENTER PROSPECTIVE RANDOMIZED TRIAL OF CORTICOSTEROIDS IN PRIMARY THERAPY FOR KAWASAKI DISEASE: CLINICAL COURSE AND CORONARY ARTERY OUTCOME

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Objective To investigate the role of corticosteroids in the initial treatment of Kawasaki disease (KD).

Study design Between September 2000 and March 2005, we randomly assigned 178 KD patients from 12 hospitals to either an intravenous immunoglobulin (IVIG) group (n = 88; 1 g/kg for 2 consecutive days) or an IVIG plus corticosteroid (IVIG+PSL) group (n = 90). The primary endpoint was coronary artery abnormality (CAA) before a 1-month echocardiographic assessment. Secondary endpoints included duration of fever, time to normalization of serum C-reactive protein (CRP), and initial treatment failure requiring additional therapy. Analyses were based on intention to treat.

Results Baseline characteristics of groups were similar. Fewer IVIG+PSL patients than IVIG patients had a CAA before 1 month (2.2% vs 11.4%; $P = .017$). The duration of fever was shorter ($P < .001$) and CRP decreased more rapidly in the IVIG+PSL group than in the IVIG group ($P = .001$). Moreover, initial treatment failure was less frequent (5.6% vs 18.2%; $P = .010$) in the IVIG+PSL group. All patients assigned to the IVIG+PSL group completed treatment without major side effects.

Conclusions A combination of corticosteroids and IVIG improved clinical course and coronary artery outcome without causing untoward effects in children with acute KD *(J Pediatr 2006;149:336-41)*

Kawasaki disease (KD), an acute multisystem vasculitis of unknown etiology that affects primarily infants and children, is a major cause of acquired heart disease in Japan.[1,2] Standard therapy for this disorder involves high-dose intravenous immunoglobulin (IVIG) with aspirin.[3-5] However, 11% to 23% of patients reportedly still have persistent or recurrent fever after completion of IVIG,[6-9] and coronary artery abnormalities (CAAs) occur in 10% to 15% of patients despite this therapy.[2,9,10] Consequently, new treatments are needed to more effectively prevent CAAs. Research is focused on finding more effective new therapies[11,12] and reassessment of existing drugs such as corticosteroid including earlier use, as well as treatment with drug combinations.[13-15]

Ever since Kato et al[16] reported that corticosteroids might increase risk of coronary artery aneurysm, corticosteroid treatment in KD has been controversial. Concern also has arisen that steroid use in this context may be associated with a number of side effects, including thromboembolic events.[6,17] However, some reported experience[13-15] suggests that corticosteroid therapy in KD may hasten resolution of inflammation and decrease the occurrence of CAAs. Furthermore, IVIG-refractory cases of KD have reportedly been successfully treated by adding corticosteroids after IVIG infusion.[18] However, to date no firm conclusions as to the usefulness of corticosteroids in KD have been reached, because some studies were retrospective and no study included sufficient patients to allow reliable evaluation of the effect of corticosteroids in preventing CAA.

In this study we assessed whether treatment with a combination of prednisolone and IVIG improved the clinical course and coronary artery outcome in patients with acute KD.

CAA	Coronary artery abnormality	IVIG	Intravenous immunoglobulin
CRP	C-reactive protein	KD	Kawasaki disease
IV	Intravenous	PSL	Prednisolone

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METHODS

Study Design

This was a multicenter prospective randomized nonblinded trial conducted at 12 medical institutions in Gunma and Saitama prefectures in Japan. The study was conducted in accordance with good clinical practice and the Declaration of Helsinki and was approved by the Gunma University Ethics Committee in May 2000. Before any subject was enrolled, an outline of the treatment (eg, time schedule and possible drug side effects) was explained in a booklet provided by the registration center, and written informed consent was obtained from a parent.

Randomization

KD was diagnosed when a patient had at least 5 of the following: fever (axillary temperature exceeding 38.0°C); nonexudative conjunctival injection; changes in the oropharynx, including mucosal erythema, dry cracked lips, and "strawberry tongue"; changes in the extremities, including palmar and plantar erythema, edema of the hands and feet, or periungual desquamation in the subacute phase of the disease; rash; and cervical lymphadenopathy. Exclusion criteria included a previous diagnosis of KD, presence of a CAA, or initial consultation after 9 days from the onset of illness, with day 1 defined as the first day of fever. After informed consent was obtained, the enrolling physician contacted a central trial-coordinating center by telephone, and the center randomly assigned the patient to the IVIG or IVIG+PSL group using a centrally maintained table of random numbers.

Study Therapy

The patients assigned to the IVIG group received IVIG 1 g/kg/day for 2 consecutive days, given over 12 hours. The patients in the IVIG+PSL group received IVIG as just specified plus prednisolone sodium succinate 2 mg/kg/day, 3 times daily, given by intravenous (IV) injection until the fever resolved and then orally until the C-reactive protein (CRP) level normalized (< 0.5 mg/dL). In the IVIG+PSL group, IVIG administration was preceded by the first IV injection of prednisolone. Once CRP normalized, prednisolone doses were tapered over 15 days in 5-day steps (2 mg/kg/day for 5 days, 1 mg/kg/day for 5 days, and 0.5 mg/kg/day for 5 days). If difficulty with oral administration was anticipated or encountered, then prednisolone was given IV until completion of tapering. The IVIG used was S-sulfonated human immunoglobulin (Kenketsu Venilone I; Teijin Pharma, Tokyo, Japan). Patients in both groups received aspirin (30 mg/kg) and dipyridamole (2 mg/kg/day). The aspirin dose was decreased to 5 mg/kg/day after CRP normalized. Additional therapy was given for a patient with persistent fever lasting more than 24 hours (initial treatment failure) or recrudescent fever associated with KD symptoms after an afebrile period (recurrence). The patient was considered afebrile when the axillary temperature remained below 37.5°C for more than 24 hours.

Analysis

The severity score was defined as the number of the following 7 criteria satisfied within 24 hours before the start of treatment: white blood cell count > 12,000 /mm^3; platelet count < 350,000 /mm^3; serum CRP > 5.0 mg/dL; hematocrit < 35%; serum albumin concentration < 3.5 g/dL; male sex; and age either 12 months or younger or 5 years or older. These criteria were based on the scoring systems of Harada[19] and Yanagawa et al.[20] Safety and tolerability of therapy were assessed in all patients who received at least 1 dose of active study drug.

Efficacy Assessments

The primary endpoint was detection of a CAA at follow-up evaluations during the first month of illness. CAAs were assessed by 2-dimensional echocardiography performed before randomization and then between 6 and 8 days, 12 and 16 days, 18 and 22 days, and 25 and 30 days after the onset of illness. A coronary artery was defined as abnormal when the luminal diameter exceeded 3.0 mm in a child under age 5 years or exceeded 4.0 mm in a child age 5 years or older, when the internal diameter of a segment was at least 1.5 times that of an adjacent segment, or when the luminal contour was clearly irregular.[21] Echocardiography was performed by highly skilled investigators at each institution, and findings were reviewed in an nonblinded manner. Secondary endpoints included duration of fever after the initial treatment, time to normalization of CRP level, and incidence of initial treatment failure and recurrence. Laboratory studies were performed at the time of enrollment and repeated at least twice weekly until CRP normalized.

Safety Assessments

Patients were monitored clinically for adverse events daily during administration of the study therapy and then for the subsequent 4 weeks to assess whether any adverse event was related to the study therapy. Safety assessments involved recording all adverse events; conducting physical examinations, including vital sign monitoring; and carrying out laboratory assessments, including hematology, urinalysis, and serum chemistry screening.

Statistical Analysis

The required sample size was calculated based on the assumption that IVIG plus corticosteroids would reduce the fraction of patients with CAAs from 15%[2] to 4%. With a 2-sided test, an α level of 0.05, and a power of 80%, the analysis would require 338 patients. Assuming that 10% of the patients would not complete the study, a total sample of 372 patients would be required. Analyses were performed according to the intent-to-treat principle and included all patients who underwent randomization. Data are presented as mean ± standard deviation or as counts or proportions. Differences between groups were assessed using the Mann-Whitney *U* test for continuous variables. Time to normaliza-

tion of CRP was further estimated by Kaplan-Meier analysis and compared using the log-rank test. Proportions of patients between groups were compared using Fisher's exact test. All analyses were carried out using the SPSS statistical package version 13.0 (SPSS Japan, Tokyo). Two-tailed P values $< .05$ were considered to indicate statistical significance.

RESULTS

Patient Population

On March 31, 2005, the data monitoring committee terminated the trial at the time of the deadline, even though the enrollment rate was lower than expected. During the study period, 588 patients were referred to 12 medical institutions. Among these patients, a total of 410 subsequently proved to be ineligible: 389 because the parents decided against participation, 17 because a previous history of KD was present, and 4 because a CAA was present before randomization.

To exclude the possibility that the forgoing eligibility-based selection of the enrolled group of patients might have introduced bias, we compared baseline characteristics of enrolled patients with those of unenrolled patients. Sex and age distributions, laboratory data (white blood cell count, platelet count, hematocrit, serum CRP, and serum albumin), and risk score showed no difference between these groups (data not shown).

We enrolled 178 patients, who were allocated randomly to either the IVIG group (n = 88) or the IVIG+PSL group (n = 90). The groups were well balanced with respect to demographic and clinical characteristics (Table I). All patients were followed up for at least 2 months (range, 2 to 50 months). One patient in each group discontinued protocol treatment because of adverse events.

In the IVIG+PSL group, excluding the patient whose steroid treatment was discontinued at the discretion of the treating physician, the duration of steroid administration ranged from 18 to 100 days (median, 23 days). The total dose of prednisolone ranged from 23.5 to 90 mg/kg (median, 34 mg/kg).

Table I. Baseline characteristics of study patients

	IVIG group (n = 88)	VIG+PSL group (n = 90)
No. of males	51	51
Age at onset, months		
Median, range	23, 2 to 85	23, 2 to 110
Mean ± SD	27.7 ± 20.3	28.6 ± 23.3
Duration of illness before treatment, days		
Median, range	5, 2 to 8	4, 2 to 8
Mean ± SD	4.6 ± 1.2	4.5 ± 1.2
White blood cell count, $\times 10^4/mm^3$		
Median, range	13.9, 6.6 to 28.3	13.5, 5.5 to 24.1
Mean ± SD	14.7 ± 4.5	13.9 ± 3.9
Hematocrit, %		
Median, range	34.2, 27.1 to 41.0	34.2, 24.3 to 42.4
Mean ± SD	34.1 ± 2.7	34.1 ± 3.1
Platelet count, $\times 10^4/mm^3$		
Median, range	34.6, 17.1 to 62.6	34.4, 14.7 to 62.2
Mean ± SD	35.8 ± 9.9	35.1 ± 9.2
CRP, mg/dL		
Median, range	7.8, 1.7 to 23.8	8.3, 2.0 to 24.1
Mean ± SD	9.1 ± 5.1	8.9 ± 4.9
Albumin, g/dL		
Median, range	4.0, 2.9 to 4.7	4.0, 3.2 to 5.0
Mean ± SD	4.0 ± 0.4	4.0 ± 0.4
Severity score		
Median, range	4, 1 to 6	4, 0 to 6
Mean ± SD	3.7 ± 1.0	3.7 ± 1.1

Table II. Primary endpoint

	IVIG group (n = 88)	IVIG+PSL group (n = 90)	P value
Coronary artery dilation until 1 month, no. (%)	10 (11.4)	2 (2.2)	.017
Coronary artery dilation at 1 month, no. (%)	3 (3.4)	0 (0.0)	.119
Giant coronary aneurysm, no. (%)	0 (0.0)	0 (0.0)	-

Primary Endpoint

With respect to the primary endpoint, results in the intent-to-treat population showed a significant difference between the 2 treatment groups (Table II). We noted an association with CAA within 1 month in 10 of the 88 subjects in the IVIG group and in 2 of the 90 subjects in the IVIG+PSL group (11.4% vs 2.2%; $P = .017$). A persistent CAA at 1 month was infrequent, seen in only 3 patients (3.4%) in the IVIG group and in no patients in the IVIG+PSL group ($P = .119$; Table II). Two patients exhibited mild dilation in the right coronary artery; the third patient, a 9-month-old boy, had a medium-sized aneurysm (4.6 mm) in the right coronary artery and mild dilation of the proximal segment in the left coronary artery. None of the patients had giant coronary aneurysm with internal diameter > 8 mm.

Secondary Endpoints

Patients in the IVIG+PSL group showed more rapid resolution than those in the IVIG group. Mean duration of fever after initiation of treatment was 0.6 ± 0.5 days in the IVIG+PSL group and 1.5 ± 1.0 days in the IVIG group ($P < .001$). Similarly, time to normalization of CRP was significantly shorter in the IVIG+PSL group than in the IVIG group (Table III; Figure).

The incidence of initial treatment failure was significantly higher in the IVIG group than in the IVIG+PSL

Table III. Secondary endpoints

	IVIG group (n = 88)	IVIG+PSL group (n = 90)	*P* value
Duration of fever after treatment, days			<.001
Median, range	1, 0 to 15	0, 0 to 8	
Mean ± SD	1.5 ± 1.0	0.6 ± 0.5	
Duration to normalization of CRP level, days			.001
Median, range	9.0, 4 to 42	8.0, 3 to 20	
Mean ± SD	11.2 ± 6.6	8.4 ± 3.7	
Need for additional therapy			
Initial treatment failure, no. (%)	16 (18.2)	5 (5.6)	.010
Recurrence, no. (%)	2 (2.2)	4 (4.4)	.682

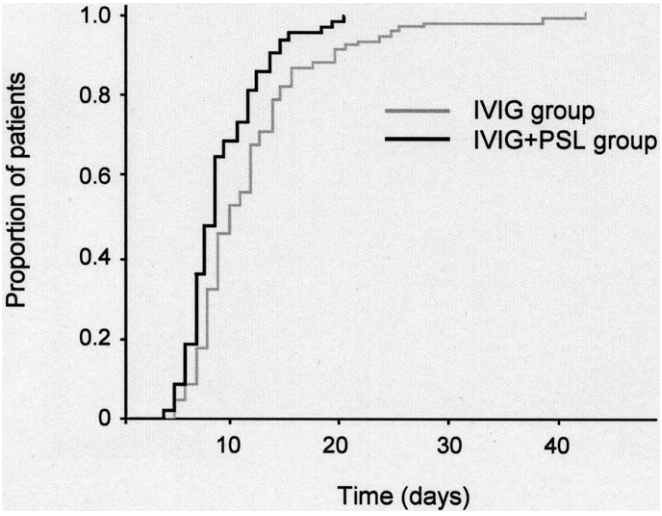

Figure. Kaplan-Meier curve of time to normalization of CRP levels after initiation of treatment ($P < .001$, log-rank test).

group (18.2% vs 5.6%; $P = .010$) (Table III). In the IVIG group, 15 of the 86 patients who did not respond to initial therapy were retreated with 1 to 3 courses of IVIG (4 patients), prednisolone (1 patient), or both in combination (10 patients). In the IVIG+PSL group, 4 patients with initial treatment failure were retreated with 1 or 2 more courses of IVIG (1 g/kg) because of persistent fever. As for recurrence of KD, 2 patients in the IVIG group and 4 patients in the IVIG+PSL group had recrudescent fever; each was retreated with another course of IVIG or an increased prednisolone dose.

Adverse Events

Three patients in the IVIG+PSL group had adverse events. A 12-month-old boy who could not maintain a standing posture 10 days after administration of IVIG later recovered spontaneously. Electroencephalography and brain magnetic resonance imaging revealed no abnormalities. A 12-month-old girl developed a urinary tract infection at 34 days of illness that was successfully treated with antibiotics. A 15-month-old girl developed rotavirus gastroenteritis at 8 days of illness; the attending physician ordered early discontinuation of prednisolone, and the patient was discharged home with no apparent sequelae. No patient assigned to the IVIG+PSL group experienced any major side effects from corticosteroid treatment. One patient in the IVIG group developed shock shortly after IVIG administration.

DISCUSSION

Our study was a prospective multicenter randomized trial comparing IVIG with IVIG plus corticosteroid as initial treatment of children with KD. Because characteristics of the study patients and the incidence of CAAs in the control regimen were comparable to those described in a report of a nationwide survey of KD,[2] the results of this trial would appear to be generalizable to the overall KD patient population. Our results demonstrate that a combination of IVIG plus corticosteroid has a significant advantage over IVIG alone with respect to prevention of CAAs and rapid resolution of inflammation.

Treatment failure was more frequent than that reported in the United States and other countries. However, the definition of treatment failure differs among reports, in part because of differences in the timing of IVIG doses and in the definition of fever. We defined initial treatment failure as fever persisting for at least 24 hours after completion of 2 IVIG infusions (1 g/kg/day on 2 consecutive days), whereas fever lasting at least 36 hours after a single infusion of 2 g/kg was the definition commonly used in other reports.[6-9] In addition, the definition of fever after initiation of treatment in our trial might have contributed to a higher reported incidence. We considered a patient afebrile when the axillary temperature remained below 37.5°C for more than 24 hours, whereas in the United States fever generally is defined as a rectal or oral temperature of 38.3°C or higher. Therefore, whether our results regarding treatment failure can be replicated using other definitions in the United States and elsewhere remains uncertain.[6-9]

Corticosteroids have been considered a less-than-effective treatment since Kato et al[16] reported in 1979 that 65% of 17 patients who received prednisolone later developed coronary aneurysm. Accordingly, a textbook published in 1996[22] stated that "corticosteroids are contraindicated in KD." However, methodological flaws are evident in Kato et al's report; for example, the study groups were not randomized, and prednisolone was administered to patients who did not respond to initial treatment. In addition, no aneurysm was identified in any patient who received prednisolone plus aspirin.

On the other hand, the results of some studies and retrospective analyses have suggested a beneficial effect of corticosteroids on the clinical course in acute KD. In 1999, we retrospectively analyzed 299 patients, concluding that pred-

nisolone might reduce the incidence of coronary artery aneurysm.[13] Subsequently, Jibiki et al[14] investigated the effect of IVIG 2 g/kg/day over 4 to 5 days combined with dexamethasone 0.15 mg/kg twice a day for 3 consecutive days on clinical outcome. After the completion of the initial IVIG regimen, the mean serum CRP concentration was 2.6 mg/dL (median, 0.9 mg/dL; range, 0 to 24.7 mg/dL) in the dexamathasone group and 2.7 mg/dL (median, 1.2 mg/dL; range, 0.2 to 19.5 mg/dL) in the control group ($P = .033$; Mann-Whitney U test). This result is consistent with the Kaplan-Meier curve findings in the present study. Furthermore, a recent small randomized prospective trial by Sundel et al[15] also demonstrated that initial treatment of KD with IVIG (2 g/kg/day) plus pulse-dose IV methylprednisolone (30 mg/kg with a maximum of 1.5 g for 1 day) resulted in more rapid resolution of fever and decreases in markers of inflammation, including CRP, as well as shorter hospitalization compared with IVIG alone.

Mechanisms accounting for the beneficial effect of corticosteroids in KD remain to be identified. Because the development of CAAs in KD appears to depend in part on the duration of inflammation, a shortened period of inflammation could account for the low incidence of CAAs in our IVIG+PSL group. In addition, KD patients with CAAs were found to have more abundant circulating proinflammatory cytokines than patients with normal coronary arteries.[23-26] We recently found that adding corticosteroids to IVIG rapidly ameliorated symptoms while reducing circulating cytokines, including interleukin-2, -6, -8, and -10, in children with KD.[27] Therefore, rapid down-regulation of cytokine secretion by exogenous corticosteroid might attenuate the development of CAAs in KD.

Because of limited follow-up and lack of statistical power to exclude the possibility of rare adverse events, routine use of corticosteroids in patients with KD may necessitate particularly close clinical monitoring.[17] First, immunosuppressive effects and potential side effects (eg, superimposed infections, thrombosis, hyperglycemia, electrolyte imbalance, bone mineral loss) must be considered. For example, Wallace et al[6] reported thromboses in 2 of 15 patients given pulse-dose IV methylprednisolone after failure to respond to initial IVIG therapy. Second, timely detection of many serious steroid side effects, such as bone mineral loss and adrenal suppression, is difficult without specific testing. We do not know whether or not a short course of corticosteroids can lead to lasting suppression of osteoblastic activity and/or stimulation of osteoclastic activity causing bone mineral loss. Moreover, previous studies[28,29] have confirmed that a single course of high-dose corticosteroids may be associated with transient suppression of the hypothalamic-pituitary-adrenal axis during treatment. Third, a high corticosteroid dose given for a limited time could have adverse consequences if proinflammatory cytokine levels rose after corticosteroid withdrawal in the presence of cytokine receptors that remained up-regulated.[30] Clinically, rebound exacerbation of KD as a result of corticosteroid discontinuation remains an unassessed possibility.

For our trial, we designed a regimen based on a short IV course of prednisolone and subsequent daily oral prednisone administration. This scheme of the protocol was based on our experience and was found to be safe.[13] To minimize the risk of adverse effects from tapering, we lowered the dose of prednisolone gradually while monitoring inflammatory variables, including CRP, to detect any possible corticosteroid dependence early during tapering. Because of differences in trial protocols, comparing the relationship between outcome and the cumulative dose of corticosteroids given in our trial with that in the other studies was difficult. Compared with other regimens, the duration of steroid administration was relatively long and the dose was high.[14,15]

Caution must be exercised when interpreting our results. First, the IVIG dosage used in this study (1 g/kg/day for 2 days), a standard regimen in Japan, differs from the single infusion of 2 g/kg recommended in the United States and elsewhere. Whether our results can be replicated using other IVIG regimens, such as a single infusion of 2 g/kg, is uncertain. Second, the routine use of dipyridamole in this setting is not widely accepted outside of Japan. Third, our initial dose of aspirin, also common in Japan, is lower than that used in the United States. However, high-dose aspirin therapy in the acute phase of KD has been reported to show no appreciable advantage over the doses used in our study in preventing failure of IVIG therapy or CAA formation, or in shortening the duration of fever.[31] Therefore, the dose of aspirin is unlikely to have affected our results. Fourth, CAAs were diagnosed according to Japanese Ministry of Health criteria, which are simple and easy to use in clinical settings. Note, however, that using the Japanese Ministry of Health criteria might result in underestimation of the true incidence of CAAs in patients with KD.

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