Late Intravenous Immunoglobulin Treatment in Patients With Kawasaki Disease

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KEY WORDS
Kawasaki disease, coronary artery aneurysm, immunoglobulin

ABBREVIATIONS
CRP—C-reactive protein
CAL—coronary artery lesion
FC—fractional change
IVIG—intravenous immunoglobulin
KD—Kawasaki disease
WBC—white blood cell

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WHAT'S KNOWN ON THIS SUBJECT: The effectiveness of intravenous immunoglobulin treatment of patients with Kawasaki disease within 9 days of illness has been established. However, the effectiveness of such treatment ≥10 days after illness onset has not yet been clarified.

WHAT THIS STUDY ADDS: Intravenous immunoglobulin treatment ≥10 days after illness onset was observed to be effective for achieving inflammation resolution. Patients who are strongly suspected to have Kawasaki disease and demonstrate ongoing inflammation should therefore be treated as soon as possible.

abstract

OBJECTIVE: To evaluate the effectiveness of intravenous immunoglobulin (IVIG) treatment of Kawasaki disease ≥10 days after illness onset.

METHODS: We selected patients initially treated with IVIG on days 11 to 20 in the database of the 20th nationwide survey in Japan. We then selected pair-matched control subjects of the same gender and age, who were initially treated with IVIG on days 4 to 8 with the same dose at the same institutions. We compared the proportions of additional treatments and coronary artery lesions (CALs) between the groups. We also compared fractional changes in various laboratory data before and after IVIG. Fractional change was defined as follows: (Y − X)/X, in which X represents the data before treatment and Y the data after treatment.

RESULTS: One hundred fifty patients (75 pairs) were studied. The proportion of patients who received additional treatments among those given initial IVIG after days 10 was slightly lower than those treated earlier (12% vs 16%). The fractional changes in the white blood cell count, % neutrophils, and C-reactive protein were similar. Among all patients, the proportions of CALs during the convalescent phase were significantly higher in the late than in the early group (27% vs 1%). Among patients who had not developed CALs before initial treatment, the proportions with CALs during the acute phase were similar (8% vs 8%).

CONCLUSIONS: IVIG treatment ≥10 days after illness onset achieves resolution of inflammation but was found to be insufficient for preventing CALs. *Pediatrics* 2012;129:e291–e297

The effectiveness of intravenous immunoglobulin (IVIG) treatment of preventing coronary artery lesions (CALs) in patients with Kawasaki disease (KD) is well established.[1–6] Because the coronary artery changes usually begin on days 7 to 10,[7] treatment within 10 days, especially within 7 days, of illness onset is optimal.[6,8,9] On the other hand, the effectiveness of treatment on and after 10 days of illness has not yet been clarified.[6,10] There have been no clinical trials comparing the effectiveness of late IVIG with placebo, possibly because of the difficulty of ethically performing such a study. In addition, about half of these patients have already developed CALs at the time of initial IVIG. It is thus difficult to evaluate the effectiveness of IVIG for preventing CALs in these patients. Marasini et al reported the effectiveness of IVIG after day 10 of illness compared with historical controls treated only with aspirin.[10] They found that patients treated with IVIG and aspirin showed more improvement in echocardiographic abnormalities at 1 to 2 years after the onset. However, their study included only a small number of patients, and the effects of other CAL treatments could not be evaluated. Although little evidence is available, the American Heart Association recommends that IVIG be administered to children presenting after the 10th day of illness (ie, children in whom the diagnosis was missed earlier) if they have either persistent fever without another explanation or aneurysms and ongoing systemic inflammation.[6] In the current study, we evaluated the effectiveness of IVIG after 10 days of illness in comparison with that administered after 4 to 8 days of illness.

METHODS

Patient Selection

We used the database of the 20th nationwide survey of KD in Japan (Fig 1).[11] The subjects of this survey were patients admitted from January 1, 2007, to December 31, 2008. The total number of reported patients in the survey was 23 337. From this database, 164 patients initially given IVIG on days 11 to 20 were selected. Of these patients, 4 were excluded because they had recurrent disease (n = 3) or because the dose of initial IVIG was not known (n = 1). We then selected pair-matched control subjects of the same gender and age (± 1 year) and who were given initial IVIG on days 4 to 8 with the same dose (± 100 mg/kg/day) at the same hospital. Thirty-seven patients were excluded for lack of appropriate matched control subjects.

Next, we sent a questionnaire to the hospital at which the patients had been treated. The questionnaire included questions about the laboratory parameters before and after initial IVIG and about CALs. In total, 123 questionnaires were mailed, and 87 were returned. Twelve patients were excluded because days of illness at the initial IVIG in the first survey were inaccurate. Consequently, 75 patients (late IVIG group) and 75 control subjects (conventional IVIG group) were studied.

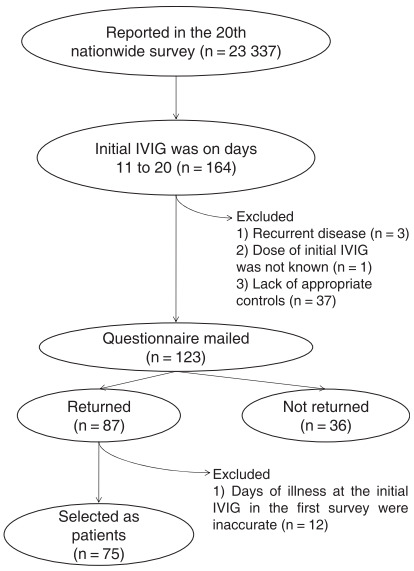

FIGURE 1
Flowchart of the patient and control selections.

Data Collection

The following data were obtained: gender, age, principal symptoms, treatment, laboratory parameters before and after IVIG, and CALs. The diagnosis of KD was made on the basis of the fifth Japanese diagnostic criteria.[12] The diagnosis of complete KD in this survey was based on the patient exhibiting at least 5 of the 6 principal symptoms.

TABLE 1 Characteristics of Studied Patients

	Late IVIG (Days 11–20) (n = 75)	Conventional IVIG (Days 4–8) (n = 75)	P Value
Gender (male:female)	1:1	1:1	Matched
Age (mo)	12 (2–95)	13 (3–87)	.7
Incomplete KD cases	38 (51%)	13 (17%)	<.001
Principal symptoms			
Fever	75 (100%)	75 (100%)	1.0
Conjunctivitis	63 (84%)	71 (95%)	.03
Onset (d)	4 (1–6)	4 (1–7)	.8
Erythema of the lips	54 (72%)	65 (87%)	.02
Onset (d)	4.5 (1–17)	4 (1–7)	.03
Changes in extremities	44 (59%)	64 (85%)	<.001
Onset (d)	10 (3–19)	4 (1–13)	<.001
Rash	48 (64%)	68 (91%)	<.001
Onset (d)	4 (1–12)	3 (1–7)	.06
Cervical lymphadenopathy	34 (45%)	47 (63%)	.03
Onset (d)	5 (1–17)	3 (1–7)	.01
Day of first hospital visit (d)	7 (2–20)	4 (1–7)	<.001
Illness day of initial IVIG (d)	13 (11–20)	5 (4–8)	<.001
Initial IVIG dose (mg/kg/day)	2000 (363–2045)	2000 (370–2045)	.6
Total dose of initial IVIG (mg/kg)	2000 (1000–2045)	2000 (1000–2045)	1.0

Expressed as the median (range), or n (%).

Incomplete KD was defined as ≤4 of these symptoms, with or without CALs.

We collected the CAL data at 3 points during the disease course: (1) before initial IVIG; (2) during the acute phase, defined as the time from just after initial IVIG to within 1 month of onset; and (3) during the convalescent phase, defined as at least 1 month after onset. The criteria for defining a coronary artery aneurysm or arterial abnormality in KD were defined by the Japanese Ministry of Health.[13]

Outcome Measures

For evaluation of the effectiveness of treatment, we compared the proportions of additional treatments, and the development of CALs. We also compared fractional changes (FC) in various laboratory parameters before and after IVIG.[14] FC was defined as follows: FC = (Y − X)/X, in which X represents the data before IVIG and Y the data after IVIG.

Statistical Analysis

Nominal data were analyzed using the Fisher exact test. Continuous variables were analyzed using the Student *t*-test (for parametric variables) or the Mann-Whitney *U* test (for nonparametric variables). Multivariate regression analysis after adjusting for gender, age, diagnostic categories, initial IVIG dose per day, and laboratory parameters were used to calculate the odds ratio with 95% confidence interval for CALs. The model was simplified in a stepwise fashion by removing variables that had a P value $> .2$. The goodness of fit of the regression model was tested with the Hosmer and Lemeshow test. $P < .05$ was considered to be statistically significant. Analyses were performed using the SPSS 17.0 software program (SPSS, Chicago, IL).

This study was approved by the review board of the local institution.

TABLE 2 Baseline Laboratory Parameters

	Late IVIG	Conventional IVIG	*P* Value
WBC count (× 10^3/mm^3)	13.8 ± 4.7 (75)	14.3 ± 3.7 (75)	.5
% neutrophils	55.0 ± 13.6 (67)	64.5 ± 15.5 (69)	<.001
Hemoglobin (g/dL)	10.3 ± 1.3 (75)	10.8 ± 1.3 (75)	.03
Hematocrit (%)	31.6 ± 3.4 (75)	32.8 ± 3.4 (75)	.03
Platelet count (× 10^4/mm^3)	63.3 ± 22.3 (75)	36.2 ± 10.6 (75)	<.001
AST (IU/L)	50.7 ± 42.9 (75)	75.8 ± 135.3 (75)	.1
ALT (IU/L)	39.6 ± 43.9 (75)	73.6 ± 92.8 (75)	.005
Total bilirubin (mg/dL)	0.3 ± 0.1 (52)	1.0 ± 1.0 (57)	<.001
Serum albumin (g/dL)	3.5 ± 0.5 (68)	3.7 ± 0.5 (70)	.03
Serum sodium (mmol/L)	137.1 ± 2.4 (71)	135.0 ± 2.7 (72)	<.001
CRP (mg/dL)	5.1 ± 4.1 (75)	7.8 ± 4.1 (75)	<.001

Expressed as means ± SD (*n*). ALT, alanine aminotransferase; AST, aspartate aminotransferase.

TABLE 3 Additional Treatments

	Late IVIG (*n* = 75)	Conventional IVIG (*n* = 75)	*P* Value
Total	9 (12%)	12 (16%)	.5
IVIG	4	10	
Steroid	2	0	
IVIG + steroid	3	1	
IVIG + Infliximab	0	1	

Expressed as *n* (%).

TABLE 4 FCs in Laboratory Parameters

	Late IVIG	Conventional IVIG	*P* value
WBC count	−0.31 ± 0.28 (74)	−0.40 ± 0.30 (75)	0.07
% Neutrophils	−0.37 ± 0.37 (62)	−0.41 ± 0.22 (67)	0.4
Hemoglobin	0.002 ± 0.07 (74)	−0.02 ± 0.07 (75)	0.03
Hematocrit	0.01 ± 0.08 (74)	−0.02 ± 0.07 (75)	0.06
Platelet count	−0.007 ± 0.24 (74)	0.20 ± 0.43 (75)	0.001
AST	0.22 ± 0.56 (71)	0.14 ± 0.89 (75)	0.5
ALT	0.09 ± 0.70 (71)	−0.06 ± 0.81 (75)	0.2
Total bilirubin	−0.08 ± 0.54 (42)	−0.57 ± 0.20 (48)	<0.001
Serum albumin	−0.05 ± 0.11 (61)	−0.12 ± 0.09 (64)	<0.001
Serum sodium	0.0009 ± 0.02 (67)	0.02 ± 0.02 (68)	<0.001
CRP	−0.50 ± 0.48 (74)	−0.53 ± 0.28 (74)	0.7

Fractional change = ([Data after IVIG] − [Data before IVIG]) / (Data before IVIG). Expressed as means ± SD (*n*). ALT, alanine aminotransferase; AST, aspartate aminotransferase.

RESULTS

Characteristics of the Studied Patients

Compared with the final cohorts, patients for whom the second questionnaires were not returned consisted of a higher percentages of boys (2.6 vs 1.0, $P = .004$), incomplete KD cases (67% vs 51%, $P = .2$), and those who received additional treatments (22% vs 12%, $P = .2$). The proportions of CALs during the acute (36% vs 48%, $P = .3$) and convalescent phases (22% vs 27%, $P = .8$) tended to be lower in these patients.

Table 1 shows a comparison of characteristics between the conventional and late treatment groups. The proportion of incomplete KD cases in the late group was significantly higher than that in the conventional group. The proportions of principal symptoms other than fever were lower in the late group than in the conventional group. Eighty-one percent of patients were treated with 2 g/kg. There were no patients who received adjunctive treatments with the initial IVIG other than aspirin. Table 2 shows a comparison of the baseline laboratory

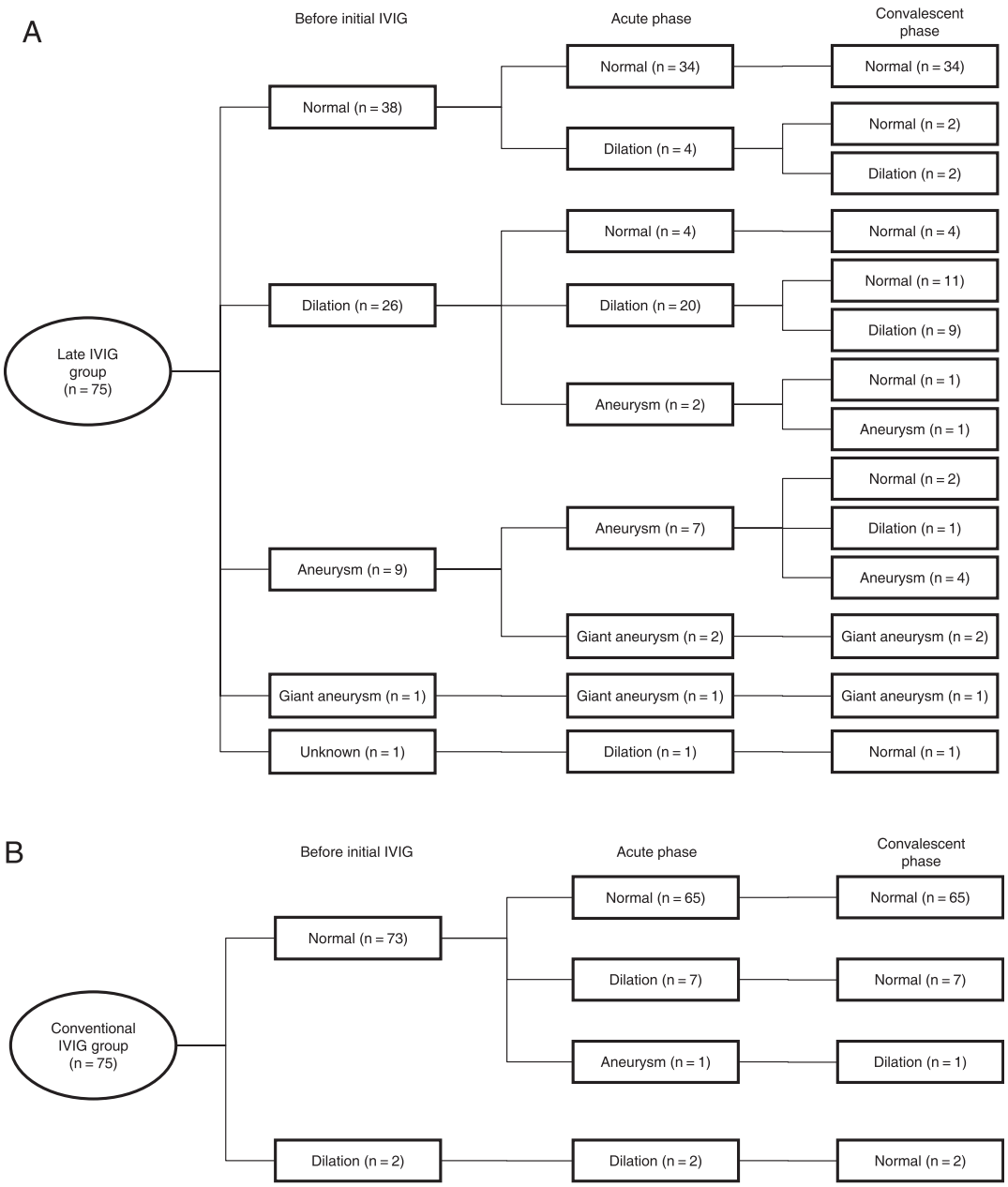

FIGURE 2

A, Flowchart of coronary artery outcomes in the late IVIG group. B, Flowchart of coronary artery outcomes in the conventional IVIG group. The acute phase was defined as the time from immediately after initial IVIG to within 1 month of onset. The convalescent phase was defined as at least 1 month after KD onset.

parameters. The mean illness days in the late and conventional groups were 4.9 and 13.4, respectively. Markers of inflammation, such as the white blood cell (WBC) count, % neutrophils, and C-reactive protein (CRP), were higher in the conventional than in the late group, and some differences were statistically significant. In addition, aspartate aminotransferase, alanine aminotransferase, and total bilirubin were also higher in the conventional group. On the other hand, the platelet count, generally known to be high during the convalescent phase, was higher in the late group.

Outcome Measures

Table 3 shows the proportions of patients who required additional treatments. The proportion of patients who received additional treatments in the late group was slightly lower than that in the conventional group. Interestingly, the proportion of patients who received steroids as an additional treatment was higher in the late group than in the conventional group.

Table 4 shows the FCs in laboratory parameters. The mean intervals from

TABLE 5 Outcomes of Late IVIG Treatment

Authors	Late IVIG (n)	Conventional IVIG (n)	Initial IVIG failure	CALs (Timing of assessment)
This study	Day 11-20 (75)	Day 4-8 (75)	12% vs 16%	49% vs 3% (before initial IVIG) [a] 49% vs 13% (after initial IVIG to within 1 month of onset) [a]27% vs 1% (> 1 month after onset) [a]
Anderson et al [15]	≥ Day 11 (25)	< Day 11 (81)	–	28% vs 19% (not reported)
Juan et al [18]	≥ Day 11 (14)	< Day 11 (64)	–	43% vs 14% (not reported) [a]
Du et al [19]	≥ Day 10 (181)	< Day 10 (871)	7% vs. 14% [a]	34% vs 18% (1 to 2 w after onset) [a] 13% vs 3% (3 to 6 w after onset) [a]
Sittiwangkul et al [20]	≥ Day 11 (20)	< Day 11 (150)	–	75% vs 19% (not reported) [a]

[a] $P < .05$.

obtaining data until the initial IVIG treatment in the late and conventional groups were 2.7 and 3.0 days, respectively. The FCs in markers of inflammation, such as the WBC count, % neutrophils, and CRP, were similar in the 2 groups.

Figure 2 shows the flowchart of coronary artery outcomes in both groups. Among all patients, the proportions with CALs before initial IVIG (49% vs 3%, $P < .001$), during the acute phase (49% vs 13%, $P < .001$), and during the convalescent phase (27% vs 1%, $P < .001$) were significantly higher in the late group.

Among patients who had not developed CALs before initial IVIG treatment, the proportions with CALs during the acute phase were similar (8% vs 8%, $P = 1.0$). However, more patients tended to have CALs during the convalescent phase in the late group (5% vs 1%, $P = .3$). During the convalescent phase, CALs in both groups were all dilations of the coronary artery. Multivariate logistic regression analysis showed that there was no significant difference in the proportion of CALs during either the acute phase (odds ratio: 0.75, [95% confidence interval: 0.080–7.1], $P = .8$) or the convalescent phase (odds ratio: 1.37 [95% confidence interval: 0.006–327], $P = .9$) between the 2 groups.

Among patients who had already developed CALs before initial IVIG in the late group, about half showed normalization during the convalescent phase.

DISCUSSION

Patients diagnosed with KD and given IVIG ≥10 days after illness onset are not rare and reportedly comprise 10% to 25% of KD patients.[15–20] It is more common in younger (<6 months of age) and incomplete KD cases.[16,20] In addition, these have been reported as risk factors for CALs.[15,21–24] Table 5 summarizes outcomes of late IVIG treatment. The proportion with CALs among these patients was reported to be higher than among patients treated earlier. However, because approximately half of patients in the late group have already developed CALs before initial IVIG, it is difficult to determine the effectiveness of IVIG after 10 days based only on coronary outcomes. Therefore, we evaluated IVIG effectiveness based on 3 outcomes in the current study.

The first outcome measure was the proportion of additional treatments. We previously reported that patients who required additional treatment had a higher risk for coronary artery aneurysms.[25] The proportion in the late group was slightly lower than that in the conventional group. This result is consistent with the report by Du et al.[19] Because KD is a self-limited disease, the fever generally resolves a mean of 11 days after onset.[6] Therefore, the fevers in some patients in the late group might have resolved spontaneously rather than in response to IVIG.

The second outcome was the FCs of laboratory parameters. Various markers, such as % neutrophils, alanine aminotransferase, total bilirubin, serum sodium, and CRP, reportedly associated with initial IVIG failure,[26–28] were lower in the late group at baseline in the current study. Similar results were reported by Juan et al.[18] However, there was no difference in laboratory parameter improvements between the 2 groups. In particular, the FCs of the WBC count and CRP, which were reported to be associated with CALs,[14] were similar in the 2 groups.

The third outcome was the proportion with CALs. Among patients who had not developed CALs before initial IVIG, the proportions with CALs during the acute phase were similar. However, the proportion with CALs during the convalescent phase was slightly higher in the late group than in the conventional group. This is likely because more patients in the late group had already begun to develop coronary artery changes not detectable by echocardiography at the start of treatment, such that more patients would continue to develop CALs after IVIG even if IVIG effectively resolves inflammation. Because approximately half of patients in the late group had already developed CALs before initial IVIG, the proportion with CALs in this group was significantly higher than among all patients. Therefore, late IVIG is less effective for preventing CALs.

Patients whose symptoms do not meet the classic KD criteria are problematic, and the diagnosis is often delayed. In 2004, the American Heart Association proposed a new algorithm for diagnosing these patients.[6] However, its usefulness is controversial.[29–31] A specific diagnostic test is desirable. The same guidelines recommend that IVIG be administered to children presenting

after the 10th day of illness (ie, children in whom the diagnosis was missed earlier) if they have either persistent fever without another explanation or aneurysms and ongoing systemic inflammation.[6] The results of the current study support this recommendation.

This study has several limitations. First, there were lower proportions of CALs in both groups, especially the late group, than in previous studies. One possible reason for these discrepancies is that some patients might not have had KD. However, the conclusion of this study would not change, because other results (the proportions of additional treatments, and laboratory parameter improvements) are consistent with these findings. Second, the study was limited by its retrospective design, such that we could not accurately determine the risk for CAL development. Finally, we used the criteria of the Japanese Ministry of Health for defining CALs, which might have resulted in underdiagnosis of the true prevalence of CALs.[32]

CONCLUSIONS

Although IVIG treatment ≥10 days after the onset of illness is considered to be effective for suppressing ongoing systemic inflammation, it is insufficient for preventing CALs. Physicians should therefore treat such patients with IVIG as soon as possible when a diagnosis of KD is strongly suspected.

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