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ORIGINAL ARTICLE

Masaaki Mori · Takako Miyamae · Tomoyuki Imagawa
Shigeki Katakura · Kazuhiro Kimura · Shumpei Yokota

Meta-analysis of the results of intravenous gamma globulin treatment of coronary artery lesions in Kawasaki disease

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Abstract The objective of this study was to evaluate the efficacy of intravenous gamma globulin (IVGG) therapy on the prevention of coronary artery lesions (CALs) in patients with Kawasaki disease (KD), with reference to the literature on meta-analyses in randomized controlled studies. Studies from 1984 to the end of 2000 obtained from the National Library of Medicine or from the bibliographies of these articles were used in the analysis. The total number of patients with KD covered in 17 articles was 4020. All the articles were examined for the number of doses per day, the duration of administration, and the total number of IVGG doses. The number of patients in each group was counted, and the incidence of CALs was evaluated at 30 or 60 days after onset. The results of these searches were further analyzed by meta-analytical methods. The administration of IVGG significantly decreased the incidence of CALs in a dose-dependent manner: At 30 days after onset the incidence of CALs was 29.4% without IVGG but 21.6% with a total dosage of IVGG $<$ 1000 mg/kg, 10.8% with a total dosage of 1000–2000 mg/kg, and 10.2% with a total dosage of $\geq$2000 mg/kg. Compared with the incidence of CALs without IVGG, the odds ratio (OR) was 0.662 [95% confidence interval (CI) 0.519–0.815)] at $<$1000 mg/kg, 0.292 (95% CI 0.222–0.371) with 1000–2000 mg/kg, and 0.274 (95% CI 0.207–0.349) with $\geq$2000 mg/kg. At 60 days, the values had decreased to 17.3%, 13.8% [OR 0.767 (95% CI 0.585–1.005)], 5.8% [OR 0.296 (95% CI 0.200–0.436)], and 4.9% [OR 0.244 (95% CI 0.170–0.349)], respectively. The meta-analyses also indicated that high doses of IVGG ($\geq$2000 mg/kg per day) given in a single dose prevented CALs more effectively than the same dosages divided into five daily doses in the patients with KD: The incidence of CALs at 30 days after disease onset was 2.4% with a single dose versus 12.9% with divided doses. Compared with divided doses, the OR with a single dose was 0.164 (95% CI 0.064–0.393) and 2.8% versus 6.1% at 60 days [OR 0.450 (95% CI 0.206–0.956)]. We clearly confirmed that higher doses of IVGG ($\geq$2000 mg/kg per day) administered in a single infusion were more effective for preventing CALs, as evaluated during both the subacute and convalescent phases of KD.

Key words Coronary artery lesions (CALs) · Gamma globulin · Kawasaki disease (KD) · Meta-analysis · Mucocutaneous lymph node syndrome

Introduction

Kawasaki disease (KD) is an acute illness of early childhood characterized by prolonged fever, diffuse mucosal inflammation, indurative edema of the hands and feet, polymorphous skin rash, and nonsuppurative lymphadenopathy.[1] Coronary artery lesions (CALs) may develop as a characteristic finding in up to 25% of untreated patients.[2,3] Furusho et al. first reported the beneficial effects of intravenous gamma globulin (IVGG) on reducing the incidence of CALs in children with KD in 1984.[4] Recent observations have indicated that the marked activation of the immune system during the acute phase results in hypercytokinemia[5,6] and may induce endothelial cell activation and intimal injury of the coronary arteries in KD.[7,8] It is known that the administration of IVGG improves the clinical status and reduces the frequency of CALs from 25% to 5%.[9–11] The dose of IVGG has gradually been increased to a single infusion of 1000 or 2000 mg/kg, as recommended in Japan[9] and most Western countries.[10]

In this study, we reviewed and meta-analyzed the published articles with randomized controlled studies on dose dependence and administration method to evaluate the effectiveness of IVGG therapy in preventing CALs.

M. Mori (✉) · T. Miyamae · T. Imagawa · S. Katakura · S. Yokota
Department of Pediatrics, Yokohama City University School of Medicine, 3-9 Fuku-ura, Kanazawa-ku, Yokohama 236-0004, Japan
Tel. +81-45-787-2670; Fax +81-45-787-0461
e-mail: mmori@med.yokohama-cu.ac.jp

K. Kimura
Department of Public Health, Yokohama City University School of Medicine, Yokohama, Japan

Methods

Criteria for inclusion

The results of studies cited in other meta-analyses and reviews were examined. All the published studies in any language that were identified through the National Library of Medicine from 1984 to the end of 2000 were considered for analysis. One by Furusho et al.[4] first stated that IVGG was effective in preventing the coronary artery lesions of KD. The medical subject headings "Kawasaki disease/mucocutaneous lymph node syndrome" and "coronary artery aneurysm/coronary artery abnormalities" were used to obtain a list of articles for analysis. Additional articles identified from the bibliographies of these articles were also included in the analysis. All the potentially relevant manuscripts were independently abstracted by two investigators, and disagreements or uncertainties were resolved by discussion.

For complete analysis, articles satisfying the following four criteria were retained for the study: (1) articles in which the children who were studied satisfied at least four of the following criteria for KD: persistent high fever, bilateral conjunctival injection, indurative edema of the hands and feet, acute nonpurulent cervical adenopathy, polymorphous exanthema, and erythema of the lips and oral mucosa: (2) prospective and retrospective studies that reported the incidence of CALs, which included follow-up data on the incidence at 14–30 days (acute stage, hereafter referred to as 30 days) or at 60 days after disease onset (subacute late phase, hereafter referred to as 60 days), or both; (3) articles defining CALs by echocardiographic or angiographic studies as: (a) a coronary artery lumen diameter of at least 3 mm in children younger than 5 years of age and at least 4 mm in children 5 years of age or over or (b) a coronary artery segment in which the lumen is clearly irregular even when the greatest internal diameter is less than 3 mm[12]; (4) studies in which the daily IVGG dose, the duration of administration, and the total dose administered were clearly specified. In this study, reports that included patients with preexisting CALs, patients with atypical KD, or patients treated with corticosteroids were excluded from further analysis.

Statistical analysis

The total dose of aspirin was examined for statistical significance using Student's *t*-test. The chi-square test with Yates' correction for 2×2 tables was used to compare the incidence of CALs among some treatment groups. Especially, the Cochran-Armitage test was used to examine whether the incidence of CALs decreased in a dose-dependent manner. All odds ratios are presented with the 95% confidence interval (CI), and a two-tailed *P* value of less than 0.05 was considered to indicate statistical significance.[13]

Results

Subjects

The authors and locations, numbers of patients, total IVGG doses administered, and incidences of CALs at 30 and 60 days after disease onset are shown in Table 1.[4,10,14–29] Briefly, 17 randomized controlled studies with a total of 4020 patients were subjected to our meta-analysis. Thirty-day follow-up data were available for 3720 patients, including 643 with CALs (17.3%); and 60-day follow-up data were available for 3314 patients, including 350 with CALs (10.6%). Although all the patients in this study received aspirin in various doses, there was no difference in the incidence of CALs between the low-dose group (<80 mg/kg) and the high-dose group (≥80 mg/kg) ($P = 0.245$).

Total IVGG dose and outcome

To investigate whether the prevention of CALs was dependent on the total dose of IVGG, the statistical parameters concerning the incidence of CALs at 30 and 60 days after onset were analyzed using the odds ratio (OR), the 95% CI, and the *P* value in the four groups with different total IVGG doses (Table 2). The incidence of CALs at 30 days was 29.4% without IVGG, 21.6% with the total IVGG dose <1000 mg/kg, 10.8% with a total IVGG of 1000–2000 mg/kg, and 10.2% when the total IVGG was ≥2000 mg/kg; the corresponding values at 60 days were 17.3%, 13.8%, 5.8%, and 4.9%, respectively. The incidence of CALs decreased significantly in a dose-dependent manner, as indicated by the odds ratio and 95% CI (Table 2). In the group with an IVGG of ≥2000 mg/kg in particular, CALs were clearly inhibited compared to those in the group without IVGG at both 30 and 60 days.

Method of administration of IVGG and outcome

To assess the difference in the incidence of CALs between patients given a single infusion and those placed on a divided-infusion regimen, we analyzed the statistical parameters concerning the incidence of CALs at 30 and 60 days in the patients administered IVGG at ≥1000 mg/kg. As Table 3 shows, the patients treated with a single infusion of ≥2000 mg/kg (1016 patients at 30 days and 947 at 60 days) significantly developed fewer CALs at 30 and 60 days. The incidence of CALs at 30 days was 12.9% with a divided-infusion regimen and 2.4% with a single infusion; the corresponding values at 60 days were 6.1% and 2.8%, respectively. Furthermore, the odds ratio and the 95% CI intervals were 0.164 (95% CI 0.064–0.393) at 30 days and 0.450 (95% CI 0.206–0.956), respectively. Thus, we suggest that in patients with KD a high IVGG dose (≥2000 mg/kg) given in a single infusion reduced the incidence of CALs compared to that seen with a divided-infusion regimen.

Table 1. Meta-analysis of published randomized controlled studies of IVGG therapy for Kawasaki disease

No.	Location	Author	No. of patients	IVGG dose/day (mg/kg)	Duration (days)	Total IVGG dose (mg/kg)	Administration method	Evaluation at 30 days	No. of CAL(+) patients at 30 days after onset	Evaluation 60 days	No. of CAL(+) patients at 60 days after onset
1	USA	Barron[14]	22	1000	1	1000	Single	Done	2	Done	2
			22	400	4	1600	Divided	Done	1	Done	1
2	Japan	Furusho[4,15]	45	0	0	0	None	Done	19	Done	14
			40	400	5	2000	Divided	Done	6	Done	3
			92	200	5	1000	Divided	Done	18	Done	3
			53	400	5	2000	Divided	Done	11	Done	6
			49	0	0	0	None	Done	19	Done	9
			49	200	5	1000	Divided	Done	9	Done	5
			53	100	5	500	Divided	Done	10	Done	4
3	Japan	Harada[16]	74	0	0	0	None	Done	15	Done	11
			139	100	5	500	Divided	Done	31	Done	24
			95	0	0	0	None	Done	21	Done	20
			171	100	5	500	Divided	Done	17	Done	15
			117	100	5	500	Divided	Done	14	Done	12
			114	400	5	2000	Divided	Done	7	Done	4
4	Taiwan	Hwang[17]	43	0	0	0	None	Done	19	Done	7
			7	200	5	1000	Divided	Done	3	Done	2
			49	400	5	2000	Divided	Done	24	Done	9
5	Canada	Klassen[18]	100	0	0	0	None	Not done	0	Done	18
			100	400	4	1600	Divided	Not done	0	Done	6
			100	2000	1	2000	Single	Not done	0	Done	4
6	Japan	Matsushima[19]	17	0	0	0	None	Done	3	Not done	0
			17	400	5	2000	Divided	Done	1	Not done	0
7	Japan	Morikawa[20]	170	200	5	1000	Divided	Done	7	Not done	0
			152	400	5	2000	Divided	Done	27	Not done	0
			152	200	5	1000	Divided	Done	0	Not done	0
8	Japan	Nagashima[21]	67	0	0	0	None	Done	25	Not done	0
			69	400	3	1200	Divided	Done	11	Not done	0
9	USA	Newburger[10]	252	400	5	2000	Divided	Done	14	Done	10
			254	2000	1	2000	Single	Done	6	Done	6
10	USA	Newburger[22]	84	0	0	0	None	Done	15	Done	11
			74	400	4	1600	Divided	Done	5	Done	2
11	Japan	Ogawa[23]	52	0	0	0	None	Done	9	Done	6
			58	400	3	1200	Divided	Done	5	Done	3
12	Japan	Ogino[24]	51	0	0	0	None	Done	17	Done	1
			62	400	4	1600	Divided	Done	11	Not done	0
13	Japan	Okuni[25]	75	0	0	0	None	Done	15	Done	11
			77	100	1	100	Single	Done	17	Done	14
			66	100	1	100	Single	Done	14	Done	10
			99	0	0	0	None	Done	50	Done	30
			96	100	5	500	Divided	Done	42	Done	18
			100	100	5	500	Divided	Done	36	Done	18
14	Japan	Onouchi[26]	27	0	0	0	None	Done	8	Done	3
			24	200	3	600	Divided	Done	4	Done	3
			34	400	3	1200	Divided	Done	5	Done	4
15	Japan	Onouchi[27]	46	100	5	500	Divided	Done	7	Done	5
			44	200	5	1000	Divided	Done	3	Done	2
			52	400	5	2000	Divided	Done	2	Done	2
16	Japan	Tomita[28]	33	400	5	2000	Divided	Done	6	Done	2
			22	300	5	1500	Divided	Done	7	Done	1
			84	200	5	1000	Divided	Done	17	Done	5
17	Japan	Yabiku[29]	32	0	0	0	None	Done	3	Done	2
			44	1000	1	1000	Single	Done	5	Done	2
Total			4020						643		350

IVGG, intravenous gamma globulin; CALS, coronary artery lesions

Table 2. Total IVGG dose and outcome of coronary artery lesions

Total dose (mg/kg)	Total no. of pts.	No. of CAL(+)	Odds ratio	95% CI	*P*
At 30 days					
0	810	238 (29.4%)	1		
<1000	889	192 (21.6%)	0.662	0.519–0.815	0.00015*
1000 to <2000	1005	109 (10.8%)	0.292	0.222–0.371	0.00001*
≥2000	1016	104 (10.2%)	0.274	0.207–0.349	<0.00001*
	3720	**643**			
At 60 days					
0	826	143 (17.3%)	1		
<1000	889	123 (13.8%)	0.767	0.585–1.005	0.0548**
1000 to <2000	652	38 (5.8%)	0.296	0.200–0.436	0.00001**
≥2000	947	46 (4.9%)	0.244	0.170–0.349	<0.00001**
	3314	**350**			

The Cochran-Armitage test was used to examine whether the incidence of CALs decreased in a dose-dependent manner. All odds ratio were presented with 95% confidence interval (CI), and two-tailed $P < 0.05$ was considered to indicate statistical significance
* $P < 0.001$ (Cochran-Armitage test: chi-square = 144.2 > 10.8)
** $P < 0.001$ (Cochran-Armitage test: chi-square = 91.8 > 10.8)

Table 3. Method of administration of ≥1000 mg/kg of IVGG and outcome of coronary artery lesions

Method of administration	Total no. of pts.	No. of CAL(+) pts.	Odds ratio	95% CI	*P*
At 30 days					
1000–2000 mg/kg					
Divided	939	102 (10.9%)	1		
Single	66	7 (10.6%)	0.974	0.395–2.287	1.000
	1005	**109**			
≥2000 mg/kg					
Divided	762	98 (12.9%)	1		
Single	254	6 (2.4%)	0.164	0.064–0.393	<0.00001
	1016	**104**			
At 60 days					
1000–2000 mg/kg					
Divided	586	34 (5.8%)	1		
Single	66	4 (6.1%)	1.047	0.304–3.229	1.000
	652	**38**			
≥2000 mg/kg					
Divided	593	36 (6.1%)	1		
Single	354	10 (2.8%)	0.450	0.206–0.956	0.03645
	947	**46**			

The chi-square test with Yates' correction for 2 × 2 tables was used to compare the incidence of CALs among some treatment groups. All odds ratio were presented with 95% confidence interval (CI), and a two-tailed $P < 0.05$ was considered to indicate statistical significance

Discussion

The present study was based on a meta-analysis of previously published articles of randomized controlled studies concentrating on the effectiveness of IVGG therapy for reducing the incidence of CALs in patients with KD.[4,10,14–29] The results indicated that the administration of IVGG at higher doses and, especially ≥2000 mg/kg, in a single infusion rather than in divided doses on five consecutive days was more effective for the prevention of CALs evaluated during both the subacute and convalescent phases of the disease.

Kawasaki disease primarily affects children younger than 5 years of age, and it has a recurrence rate of less than 2%. More than 140 000 cases were reported in Japan during the last 30 years. The pathophysiologic mechanism of the disease is still unknown. However, immune activation and generalized vasculitis are two central features of KD, and one of the major characteristics is the development of CALs as a result of inflammation of medium-sized arteries, affecting up to 25% of untreated patients.[2,3] However, the administration of IVGG improved clinical status, and the incidence of CALs decreased from 25% to 5%.[8,9,11]

The effectiveness of IVGG in preventing CALs in active KD is believed to be dose-dependent, and the doses of IVGG were gradually increased as the frequency of administration was gradually decreased: The first dosage method suggested that IVGG administration of 200 mg/kg per day for five consecutive days[4] was more effective than that of aspirin alone. Then, a divided dosage of IVGG at 400 mg/kg per day for 5 days proved to be superior for preventing CALs in patients with KD in a multicenter randomized controlled trial in Japan.[26] Newburger et al. compared a

single IVGG infusion of 2000 mg/kg with a 5-day infusion of 400 mg/kg per day and found that the former dosage method led to a significantly lower incidence of CALs 2 weeks after IVGG administration.[10] However, the optimal schedule for administering IVGG has not yet been established in a study with a large number of KD patients.

So far, we found two important reports on meta-analysis results regarding IVGG treatment of CALs in KD patients. One was that by Durongpisitkul et al.,[30] who found that high-dose IVGG was superior to low-dose IVGG with respect to the development of CALs and that high-dose aspirin and low-dose aspirin groups had similar outcomes. In the other report, Terai and Shulman[11] stated that from their study of 1629 patients with KD they concluded that the prevalence of CALs was inversely related to the total dose of IVGG and was independent of the aspirin dose. In our analysis, we first showed that the higher doses of IVGG administered in a single infusion were more effective in preventing CALs, and we confirmed that the higher IVGG dose ($\geq$1000 mg/kg total dose) clearly inhibited CALs, as previously shown. Ultimately, our present meta-analyses indicated strongly that the administration of IVGG of $\geq$2000 mg/kg in a single infusion could be recommended as a highly effective therapeutic regimen, as mentioned lately in the Cochrane Review.[31]

Although the mechanism of action of IVGG on vasculitis in KD is obscure, many investigators have speculated that gamma globulin may block or modulate Fc receptors expressed on the activated lymphocytes or macrophages (or both) by providing a specific antibody against etiological agents or toxins or by providing an anti-idiotypic antibody resulting in suppression of exaggerated immune function. However, recent observations in our laboratory and others have demonstrated that the anti-inflammatory effects of IVGG attributed to a reduction in increased proinflammatory cytokines and their soluble receptors may induce endothelial cell activation and intimal injury during the active phase of KD, thereby triggering systemic vasculitis.[7,8] The increased serum cytokines levels – interferon-γ interleukin-6 (IL-6), tumor necrosis factor-α (TNFα) – and their soluble receptors (soluble IL-6 and soluble TNFα receptors) were abruptly down-regulated after IVGG administration,[5,6] resulting in alleviation of the clinical manifestations and laboratory abnormalities. Moreover, the cases refractory to IVGG administration repeatedly showed increased serum cytokine levels as well as inflammatory reactions reflected in the laboratory data and in clinical findings, such as high fever and mucocutaneous manifestations. Thus, future strategies for the treatment of KD may be more specific than merely stabilizing the action of proinflammatory cytokines and preventing cytokine production from activated lymphocytes or macrophages (or both) by IVGG administration.

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