Management and outcome of intravenous gammaglobulin-resistant Kawasaki disease

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ABSTRACT

Introduction: This study aimed to determine the prevalence and risk of intravenous gammaglobulin (IVIG)-resistant Kawasaki disease (KD) and report the outcome of treatment in patients with persistent or recurrent fever.

Methods: 70 KD patients, who received IVIG treatment (2 g/kg) at a tertiary care hospital from January 1995 to June 2004, were retrospectively reviewed.

Results: Nine (13 percent) of the 70 patients failed to respond to initial treatment with IVIG. The patients who did not respond to IVIG had higher erythrocyte sedimentation rate (ESR) (104 versus 74 mm/h; p-value is 0.003), longer total days of fever (14.4 +/- 3.8 versus 9.2 +/- 2.3 days; p-value is 0.003) and higher initial coronary artery lesions (CAL) (7 of 9 [77.7 percent] versus 10 of 61 [16.3 percent]; p-value is 0.001) than those who responded to initial treatment. Seven of the nine patients who were retreated with IVIG (2 g/kg) responded to the second dose. The remaining two patients (two of nine, 22 percent) had persistent fever, which subsided after two to three doses of pulse intravenous methylprednisolone. At two months follow-up, IVIG-resistant patients had higher CAL by echocardiogram than IVIG-responsive patients (33 percent versus 3.2 percent, p-value is less than 0.05). Two IVIG-resistant KD patients had delayed diagnosis and developed giant aneurysms.

Conclusion: Patients with high ESR had increased risk of IVIG-resistant KD. IVIG-resistant Kawasaki patients had a higher prevalence of CAL at the acute phase and two months after onset.

Keywords: coronary artery lesion, gammaglobulin refractory Kawasaki disease, gammaglobulin resistance, intravenous immunoglobulin therapy, Kawasaki disease, methylprednisolone pulse therapy

Singapore Med J 2006; 47(9):780-784

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INTRODUCTION

Kawasaki disease (KD) is a systemic vasculitis of unknown aetiology. Intravenous gammaglobulin (IVIG) and high-dose aspirin are effective in rapidly resolving fever and reducing the prevalence of coronary aneurysms[1,2]. However, approximately 10-20% of patients have persistent or recurrent fever after initial IVIG treatment and are considered to have a higher risk of developing coronary aneurysms[3-5]. Different doses of IVIG and/or various types of corticosteroids or immunosuppressive drugs have been reported for additional treatment of IVIG-resistant KD patients[3,4,6,7]. Until now, there has been no large randomised controlled trial of treatment in IVIG-resistant KD because of an inadequate number of patients in each centre.

In current practice, most experts recommend retreatment with 2 g/kg of IVIG[8]. For those who remain febrile after two doses of IVIG, pulse methylprednisolone is recommended. This may be partly based on a randomised study by Hashino et al[9], who compared the efficacy of additional IVIG at 1 g/kg with pulse methylprednisolone in IVIG-resistant KD patients. Patients in the steroid group had a shorter duration of fever and no significant difference in incidence of coronary artery aneurysm. However, according to the report by Kato et al[10] on coronary artery aneurysm and thrombosis in KD patients, after treatment with prednisolone, most physicians were reluctant to use steroid as an initial treatment in IVIG-resistant KD.

We report the treatment results, with IVIG at 2 g/kg plus ASA and pulse methylprednisolone, in this particular group of patients, with the aim to increase information, especially in the Southeast Asian ethnic community. The long-term coronary

Table I. Baseline demographics and clinical characteristics.

	Group 1 (n=61)	Group 2 (n=9)	p-value
Age ± SD (months)	19.4 ± 14.7	16.4 ± 8.8	0.55
Age <1 year, n (%)	27 (44.4)	3 (33.3)	0.73
Male:female ratio (%)	31:30 (51)	4:5 (44)	1.0
Weight ± SD (kg)	10.5 ± 3.2	10.4 ± 2.7	0.9
Conjunctivitis, n (%)	56 (91.8)	8 (88.8)	0.57
Lymphadenopathy, n (%)	23 (37.7)	3 (33.3)	1.00
Mucositis, n (%)	61 (100)	9 (100)	1.00
Rash, n (%)	60 (98.3)	9 (100)	1.00
Extremity changes, n (%)	49 (80.3)	7 (77.7)	1.00
Incomplete criteria, n (%)	7 (11.4)	2 (22.4)	0.32

Table II. Laboratory results, treatment, and outcome of IVIG-responsive and IVIG-resistant KD patients.

	Group 1 (n=61)	Group 2 (n=9)	p-value
Haematocrit ± SD (vol%)	31 ± 3.8	30.6 ± 3.2	0.76
WBC ± SD (cells/mm^3)	17,321 ± 5,833	18,155 ± 3,190	0.67
PMN ± SD (%)	64.4 ± 12.4	66.7 ± 14	0.62
Platelets ± SD ($\times 10^3/mm^3$)	487 ± 189	512 ± 233	0.72
ESR ± SD (mm/h)	74 ± 27.5	104 ± 21.5	0.003*
IVIG (g/kg/dose)	1.9 ± 2.8	1.97 ± 0.08	0.46
ASA (g/kg/dose)	77.4 ± 16.3	80.00 ± 15.0	0.65
Initial CAL, n (%)	10 (16.3)	7 (77.7)	0.001*
CAL at 2 months, n (%)	2 (3.2)	3 (33)	0.013*
Fever before IVIG (days) ± SD	7.8 ± 2.4	7.8 ± 3.7	0.92
Total duration of fever (days) ± SD	9.2 ± 2.3	14.4 ± 3.8	0.003*

CAL: coronary artery lesion

outcome of these patients is rarely reported. A retrospective analysis of our KD patients was carried out in order to determine the prevalence and risk of IVIG-resistant KD, and report the outcome of treatment in patients with persistent or recurrent fever.

METHODS

All patients who fulfilled the criteria for acute KD at Chiang Mai University Hospital, a tertiary referral hospital, were studied between January 1995 and June 2004. The patients included had received a single dose of IVIG at 2 g/kg/dose within 12 hours and aspirin at 80-100 mg/kg/day. However, patients who had been treated with a regimen other than 2 g/kg of IVIG in a single dose plus aspirin were excluded.

All patients diagnosed as having KD were evaluated by laboratory investigations at the time of hospital admission and two months after diagnosis. The echocardiographical findings at the time of admission, at two months and at one year after diagnosis were reported. Resistant KD was defined as the persistence or recrudescence of fever (≥38.0ºC) at least 48 hours after the end of IVIG infusion[11]. Definitions of coronary dilatation and aneurysm were based on the following published criteria[11,12]: (1) dilated if the Z score was >2 and

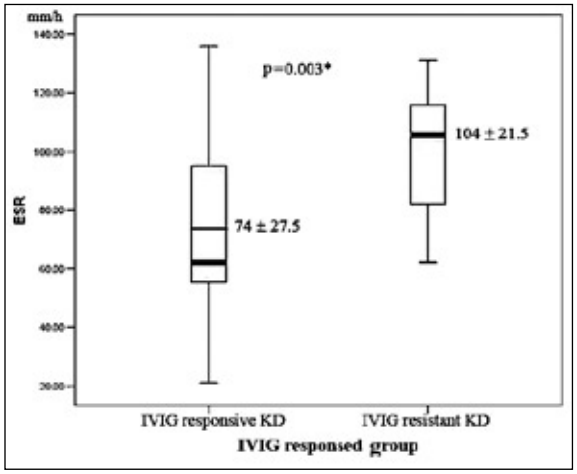

Fig. 1 Box plot of ESR level before initiation of IVIG treatment according to IVIG response. The thick horizontal line in the box represents the median value, and the bottom and top edges of the box are located at the sample 25th and 75th percentile, respectively. The thin horizontal line in the box (overlap with the thick line in the right box) represents the mean for measure variable.

<3, ectasia if the Z score was >3 with uniform dilatation, and aneurysm if the Z score was >3 with a focally dilated segment, or when the internal diameter of a segment was at least 1.5 times as large as that of the adjacent segment; or (2) clearly irregular lumen. Aneurysms were classified as giant (internal diameter of >8 mm), medium sized (internal diameter of 5-8 mm) and small (internal diameter of <5 mm)[13].

The descriptions of basic data were expressed as mean ± standard deviation and percentage. The difference in the number of patients between groups was analysed by the unpaired t-test or chi-square test. A p-value <0.05 was considered as statistically significant. All statistical tests were performed using the Statistical Package for Social Sciences (SPSS) version 11.0 for Windows (Chicago, IL, USA).

RESULTS

70 patients who fulfilled the inclusion criteria of the study were classified into two groups. Group 1 consisted of 61 (87%) IVIG-responsive KD patients who initially improved after treatment with IVIG (2 g/kg) plus a high dose of aspirin. Group 2 consisted of the other nine (13%) IVIG-resistant KD patients who did not respond to the first dose of IVIG and were retreated with a second course at IVIG 2 g/kg. There was no significant difference in age, sex, weight and clinical characteristics between groups 1 and 2 (Table I).

Table II compares the laboratory results, treatment, and outcomes of the two groups. The IVIG-resistant group had a significantly higher erythrocyte sedimentation rate (ESR) level (104 ± 27.5 mm/h versus 74 ± 21.5 mm/h; p=0.003) (Fig. 1), coronary artery lesion (CAL) at initial echocardiogram (77.7% versus 16.3%; p=0.001) and CAL at two months (33% versus 3.2%; p=0.13) than the IVIG-responsive group. Although the initiation of IVIG therapy was the same (7.8 ± 2.4 days versus 7.8 ± 3.7 days), the duration of fever was 9.2 ± 2.3 days in Group 1 and 14.4 ± 3.8 days in Group 2 (p=0.003).

In IVIG-resistant patients, seven out of nine (78%) cases responded to an additional treatment with 2 g/kg of IVIG (Fig. 2). The remaining two (22%) cases had persistent fever, which subsided after two and three doses, respectively, of pulse intravenous methylprednisolone (30 mg/kg/dose) once daily. One patient had delayed diagnosis and IVIG treatment until Day 16 of the disease, when she already had a medium-sized aneurysm with pericardial effusion on an initial echocardiogram. Despite defervescence of fever after three daily doses of methylprednisolone, her medium-sized coronary aneurysm had progressed to a giant aneurysm (diameter 8 mm) at two months echocardiography follow-up, and persisted as a giant aneurysm up to the one year follow-up (reported elsewhere[14]).

In one IVIG-resistant patient, who responded to additional treatment, progressive change of coronary aneurysm also occurred from medium-sized aneurysm at initial echocardiography (Day 19 of illness) to a giant aneurysm at two months follow-up. At one year follow-up, the aneurysm regressed to 6 mm in diameter. Coronary dilatation commonly occurred in IVIG-resistant KD, but would eventually regress in both groups mostly at two months of echocardiography.

DISCUSSION

The prevalence of IVIG-resistant KD in this study is 13%, which is concordant with that in other reports[3-5]. Many authors suggested that on-going active vasculitis in resistant KD may lead to significant coronary artery abnormalities[15]. We found that a high ESR level and abnormal initial echocardiogram were the predictors for IVIG-resistant KD. These results probably reflect greater severity of coronary arteritis in addition to prolonged duration of inflammation in resistant KD patients.

The appropriate treatment for patients with persistent fever after the first dose of IVIG is uncertain. Although a second dose of

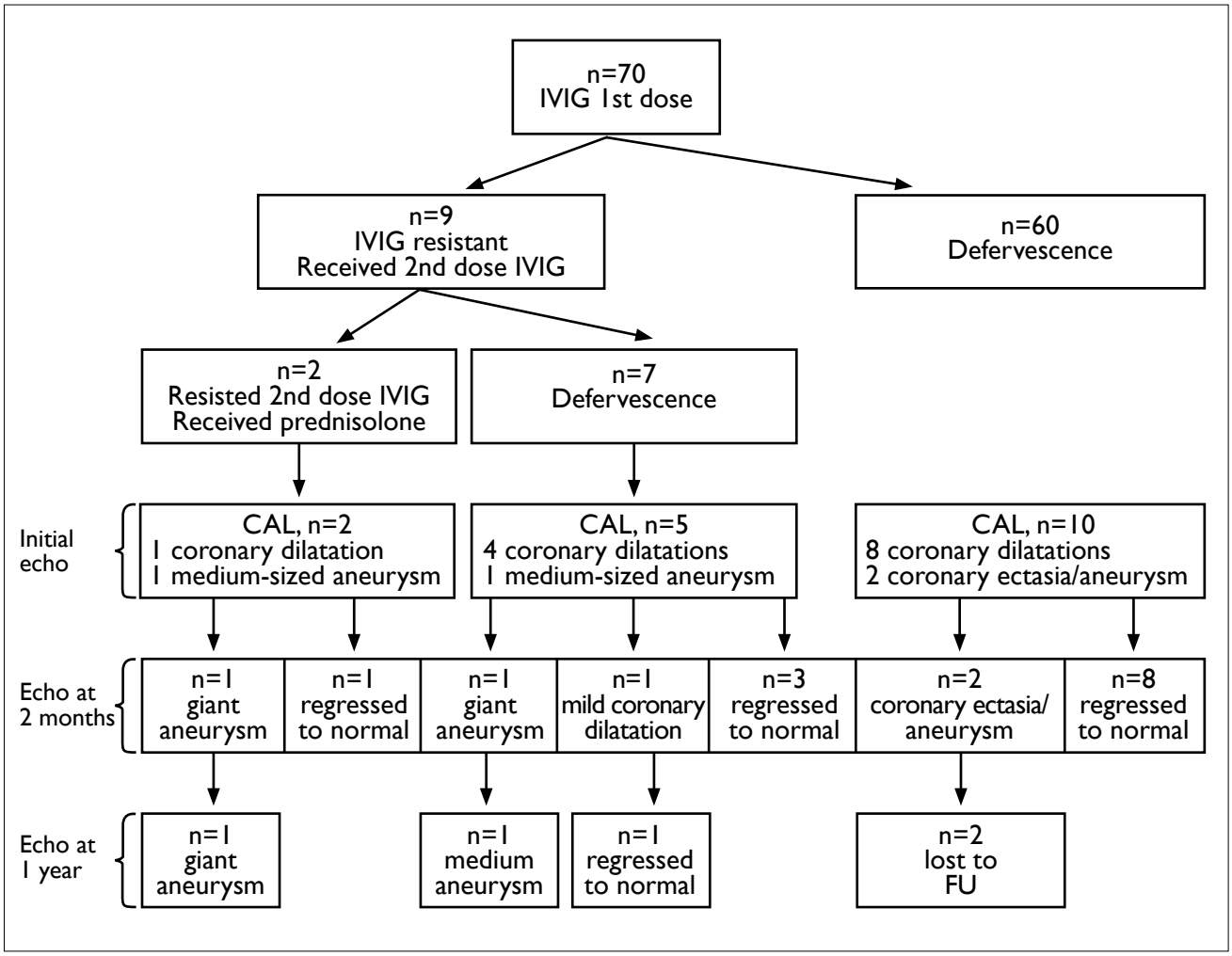

Fig. 2 Overview of treatment and coronary outcome of IVIG-resistant KD patients.

IVIG is safe and recommended by experts, one-third of patients still had persistent or recrudescent fever[3-5]. In our study, the response rate was 22% for IVIG retreatment, which is comparable to other studies[3-5]. In contrast, corticosteroids seem to be more effective in the resolution of fever[9], but the coronary artery outcome is still uncertain. Both our patients responded well to pulsed methylprednisolone but one of them had the progressive coronary artery abnormality from medium-sized to giant aneurysm. The delay in IVIG treatment and retreatment was probably the cause of giant aneurysm in this patient.

Several small case series have described children with IVIG-resistant KD, in whom the administration of steroid therapy was associated with an improvement in symptoms and the absence of a significant progression in coronary abnormalities or adverse effects[4,6,16]. Although the present recommendation of pulsed steroid treatment in IVIG-resistant KD failed after two infusions of IVIG, a multicentre controlled study is needed if steroids are to be used as first-line drugs.

The incidence of coronary artery aneurysm in IVIG-resistant KD was higher than that of IVIG-responsive KD at both two months and one year after the onset of the disease. We had two IVIG-resistant KD children with delayed IVIG treatment (more than ten days) who eventually developed giant aneurysm. There was a limitation in interpreting this data because the two patients received late IVIG treatment and retreatment. Prolonged duration of fever either before IVIG treatment or between IVIG treatment and retreatment may increase the risk of giant aneurysm. The long-term outcome of small coronary aneurysms or ectasia was no different among IVIG-resistant and IVIG-responsive KD patients.

The limitations of this study were that it was retrospective, with a small number of IVIG-resistant KD patients, and was not randomised to receive methylprednisolone. A large prospective multicentre randomised trial of IVIG-resistant patients for methylprednisolone compared to IVIG and infliximab would be essential for better treatment in this group of KD patients. In conclusion, patients with high ESR have an increased risk of IVIG-resistant KD. IVIG-resistant KD patients had a higher prevalence of CAL at the acute phase. Late retreatment with IVIG and the long duration of fever may increase the risk of giant aneurysm. Small CAL had a tendency to regress to normal in both IVIG-resistant and IVIG-responsive KD patients.

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