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MINIREVIEWS

Use of corticosteroids during acute phase of Kawasaki disease

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Abstract

In spite of initial intravenous immunoglobulin (IVIG) treatment, a significant number of patients are unresponsive to it and are at a higher risk for coronary artery lesions. Corticosteroids have been used as a secondary drug or used in combination with IVIG. Three options of using corticosteroids for the treatment of patients during the acute phase of Kawasaki disease, have been considered. The first is their use exclusively for patients unresponsive to IVIG treatment. The second is their use in combination with IVIG as the routine first line therapy for all patients. The last is the use in the combination as the first line therapy for selected patients at a high risk being unresponsive to initial IVIG. However, it is uncertain that the corticosteroids as the second line treatment are better than the additional IVIG in patients unresponsive to initial IVIG. The combination of corticosteroids and IVIG as the routine first line therapy also have not enough evidences. The last option of using corticosteroids - the combination of corticosteroids and IVIG in patients at high risk of unresponsiveness, is a properly reasonable treatment strategy. However, there have been no globally standardized predictive models for the unresponsiveness to initial IVIG treatment. Therefore, future investigations to determine the best predictive model are necessary.

Key words: Kawasaki disease; Methylprednisolone; Corticosteroids; Coronary aneurysm; Immunoglobulins; Prednisolone; Fever

Core tip: In spite of initial intravenous immunoglobulin (IVIG) treatment, a significant number of patients are unresponsive to it and are at a higher risk for coronary artery lesions. Corticosteroids have been used as a secondary drug or used in combination with IVIG. There are several options of using corticosteroids for the treatment of patients with Kawasaki disease during the acute phase. A thorough review of the use of corticosteroids in acute phase Kawasaki disease was performed in this paper.

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INTRODUCTION

Kawasaki disease is an acute, self-limited systemic type of vasculitis which occurs predominantly in young children. Kawasaki[1] firstly reported it in 1967, and it is now acknowledged as a common acquired heart disease of children in many developed countries. The etiology of Kawasaki disease is currently unknown. It is a reasonable open hypothesis that Kawasaki disease is caused by an unidentified microorganism that induces striking immune perturbations in genetically susceptible individuals. Although the efforts to find a causative microorganism have failed[2-4], the suspicion of an association between some unidentified microorganism and Kawasaki disease remains[4-7]. Investigations to identify a genetic susceptibility locus in Kawasaki disease also have been performed recently[8-10]. Several institutes had cooperated and reported a result regarding the genetic susceptibility of Kawasaki disease[11]. A recent review[12] further explains the related genetic studies. The standard first line therapies during the acute phase are an intravenous infusion of immunoglobulin (IVIG) and the administration of a high dose of aspirin[13]. Corticosteroids were used as the first line therapy before Kato *et al*[14] suggested the possibility of an aggravation of coronary artery lesions caused by them. Another report[15] to the contrary was quieted because the strong therapeutic efficacy of IVIG was reported in 1984[16]. More than 10 years after the introduction of IVIG, there were reports of the successful therapeutic application of corticosteroids for children with Kawasaki disease unresponsive to initial IVIG treatment in whom neither significant aggravation of coronary artery lesions nor other adverse effects were found after the administration of corticosteroids[17-19]. In addition, a question about the study by Kato *et al*[14], in which an information about randomization methods was not provided, was raised[17-19].

According to the guidelines of American Heart Association (AHA) in 2004, corticosteroids treatment could be recommended for children in whom $\geqslant$ 2 infusions of IVIG have been ineffective in alleviating the fever and acute inflammation[13]. However, corticosteroids have been occasionally used more early as the second line therapy for patients unresponsive to initial IVIG treatment, as the routine first line therapy in combination with IVIG, or as the first line therapy in combination with IVIG for selected Kawasaki disease patients at a high risk of unresponsiveness to initial IVIG.

THE EXCLUSIVE USE OF CORTICOSTEROIDS IN PATIENTS UNRESPONSIVE TO IVIG TREATMENT

The best second line therapeutic methods for patients unresponsive to initial IVIG treatment is still uncertain. In an investigation of 5633 patients with Kawasaki disease in the United States, methylprednisolone was used as the second line therapy in 196 patients (27.1%) among the 722 patients unresponsive to initial IVIG[20]. IVIG was the second line drug of choice in 466 patients (64.5%) in this investigation. A nationwide survey in Japan showed that steroids were used exclusively in 2.0% of hospitals and that they were used with additional IVIG in 5.1% of hospitals as the second line therapy for patients unresponsive to initial IVIG[21]. Additional IVIG exclusive administration was the second line treatment of choice in 464 hospitals (44.1%) and a combination of additional IVIG and another drug was selected in another 26% of hospitals in this survey. Therefore, the most common second line treatment is additional IVIG administration currently.

Despite initial IVIG treatment, 6.8%-38.3% of patients are unresponsive to it[22-36] and are at a higher risk for coronary artery lesions[30-33,37]. A study based on the United States national database showed that the resistance rate to initial IVIG therapy was 16.3% (hospital range 8.0%-26.8%)[36]. Authors suggested that highly variable rates among pediatric hospitals are possibly associated with variable diagnostic and treatment patterns at individual hospitals[36]. The rate of resistance to second additional IVIG only treatment was 22.2%-48.6%[18,22,24-26,38], and was not lower than that to initial IVIG treatment. Therefore, a consideration of another therapeutic option in patients unresponsive to the initial IVIG treatment is reasonable, and corticosteroids have been considered as an alternative treatment. Several reports of the use of corticosteroids as a treatment in Kawasaki disease patients unresponsive to initial IVIG treatment are presented in Table 1. In these studies, 164-411 patients with Kawasaki disease were observed, and the rate of unresponsiveness to initial IVIG was 13.4%-18.0%. The definition of unresponsiveness is varied by institute. Persistent fever was used commonly as the definition, but the cut-off level of body temperature, the duration of observation for recrudescent fever, and whether or not the CRP level was used were different for each institute. The duration of observation for recrudescent fever is 36 h according to the definition of the AHA[13], and 24 h was suggested in the recent Japanese guideline[39]. Intravenous methylprednisolone pulse therapy for 3 d was applied in all studies[22-26,40]. The dose was 30 mg/kg per day in most of studies[22-24,26,40], except in one[25]. Oral administration of prednisolone was followed after pulse therapy in 3 studies[22,24,26]. In these studies[22-25,40], a comparative analysis between corticosteroid therapy and additional IVIG treatment was performed and showed no significant difference with respect to the occurrence of coronary artery aneurysms. The frequencies of adverse effects of corticosteroids seemed to be relatively higher in reports by Miura *et al*[26,40]. They defined hypothermia as < 35.0 ℃; bradycardia as a heart rate less than the second percentile of the normal standard; hypertension as a systolic/diastolic blood pressure > 95th percentile of normal standard; hyperglycemia as a fasting blood glucose > 6.99 mmol/L; and hyponatremia as a serum Na^+ level < 135 mmol/L[26]. Although any serious adverse

Table 1 Re-treatment with corticosteroids or additional intravenous immunoglobulin in Kawasaki disease patients unresponsive to initial intravenous immunoglobulin

Ref.	No. of patients with KD	Definition of unresponsiveness: BT, obs period, other	No. of patients unresponsive to initial IVIG	Stage of CS Tx	Regimen	No. of patients re-Tx	Tx day after fever onset[1]	No. of patients with response	No. of patients with CAA	No. of patients with adverse effects
[22]	411	36 h after IVIG	63	2nd line	IVMP 30 mg/kg per day, 3 d Followed Pd	44	7 (6-8)	34	5	Hypertension 5, hypothermia 3, bradycardia 3, transient paralysis 1
					IVIG 1-2 g/kg	19	8 (5-11)	12	2	
[40]	NA	≥ 37.5 ℃, 48 h after IVIG	22	2nd line	IVMP 30 mg/kg per day, 3 d	11	NA	NA	2	Hypertension 10, hypothermia 1, bradycardia 9, hyperglycemia 6, aPTT↓ 3
					IVIG 2 g/kg	11	NA	NA	3	
[23]	164	≥ 37.5 ℃, 36-48 h after IVIG CRP↓ ≤ 50%	27	2nd line	IVMP 30 mg/kg per day, 3 d	13	7 ± 1.3	NA	0	Bradycardia 2
					IVIG 2 g/kg	14	8 ± 2.4	NA	3	
[24]	237	≥ 38 ℃, 36 h after IVIG 37.5 ℃-38 ℃ and CRP ↓ ≤ 50%	41	2nd line	IVMP 30 mg/kg per day, 3 d Followed Pd	14	7 (7-9)	7	5	Gastrointestinal bleeding 1
					IVIG 2 g/kg	27	8 (5-14)	21	7	
[25]	262	≥ 37.5 ℃, 48 h after IVIG CRP↓ ≤ 50%	35	3rd line	IVMP 20 mg/kg per day, 3 d	9	NA	NA	7	NA
					IVIG 1 g/kg	8	NA	NA	5	
[26]	412	48 h after IVIG	74	3rd line	IVMP 30 mg/kg per day, 3 d Followed Pd	21	8 (IQR 8-9)	21	2	Hypertension 17, hypothermia 3, bradycardia 17, hyperglycemia 7, serum Na↓ 4

[1]Median (range), median (IQR), or mean ± SD. IVIG: Intravenous immunoglobulin; KD: Kawasaki disease; BT: Body temperature; obs: Observation; Tx: Treatment; CS: Corticosteroids; CAA: Coronary artery aneurysm; NA: Not available; IVMP: Intravenous methylprednisolone pulse; Pd: Oral prednisolone; IQR: Interquartile range.

Table 2 Risk scoring systems for the selection of patients expected to have unresponsiveness to initial intravenous immunoglobulin treatment

	Cut-off	Points
Kobayashi score (≥ 4-5 points)[51,54,55]		
Age	≤ 12 mo	1
Days of illness at initial treatment	≤ 4	2
Platelet count	≤ 300×10^3/mm^3	1
Neutrophil	≥ 80%	2
CRP	≥ 10 mg/dL	1
AST	≥ 100 IU/L	2
Sodium	≤ 133 mmol/L	2
Egami score (≥ 3 points)[52]		
Age	≤ 6 mo	1
Days of illness at initial treatment	≤ 4	1
Platelet count	≤ 300×10^3/mm^3	1
CRP	≥ 8 mg/dL	1
ALT	≥ 80 IU/L	2
Sano score (≥ 2 points)[53]		
CRP	≥ 7 mg/dL	1
AST	≥ 200 IU/L	1
Total bilirubin	≥ 0.9 mg/dL	1

IVIG: Intravenous immunoglobulin; CRP: C-reactive protein; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase.

effects of corticosteroids inducing irreversible organ damage have not been reported in these studies[22-26,40], a close monitoring of vital signs, blood glucose level, and serum electrolytes level and supportive administration of medications – heparin infusion (15-20 units/kg per hour) and H2 blocker are needed in Kawasaki disease patients receiving corticosteroids. Meanwhile, a high incidence of adrenal suppression which had resolved within 6 mo was reported in patients treated with corticosteroids[41]. In the view of the reduction of fever, corticosteroids seem to be more effective than IVIG[23,25,42]. However, Furukawa *et al*[22] warned of a tendency for recrudescent fever in patients unresponsive to corticosteroids, which could potentially delay the therapeutic decision-making process. Although Miura *et al*[26] suggested increasing the dose of oral prednisolone following third line pulse therapy for the patients with recrudescent fever, whether this strategy could be applied to second line therapy is currently unclear. In addition, the usefulness of corticosteroids in the view of their medical cost is controversial[23-25], and this issue may be dependent on the therapeutic strategy of an institute and on the health system of a society.

Table 3 Clinical and laboratory variables associated with the unresponsiveness to initial intravenous immunoglobulin treatment

	Risk factors	Ref.
Age	≤ 6-12 mo	[51,52,58]
Sex	Male	[33,61]
Duration of fever	Long duration	[58,69]
Days of illness at initial treatment	≤ 4	[31,33,51,52,58,60,71]
Recurrent Kawasaki disease	Recurrent case	[33]
Principal features/symptoms	Early appearance	[72]
	Polymorphous exanthema	[60]
	Lymphadenopathy	[32]
Other physical findings	Changes around anus	[60]
Brand of IVIG	β-propiolactone	[65,66]
Neutrophil	≥ 80%, or increased	[51,58,60,69,72]
Band form	≥ 20%, or increased	[31,34]
Hemoglobin	Anemia by age, < 10 g/dL	[31,59]
Eosinophil count	High level – good response	[68]
Platelet count	≤ $300 \times 10^3/mm^3$, or decreased	[51,52,58,72]
	≥ $530 \times 10^3/mm^3$	[32]
ESR	≥ 75 mm/h, or increased	[32,37]
CRP	≥ 7-10 mg/dL, or increased	[51-53,58-60,69]
Albumin	Lower than normal	[34,61,67]
ALT	≥ 80-84 IU/L	[52,62]
AST	≥ 100-200 IU/L, or increased	[51,53,61,72]
Total bilirubin	≥ 0.9 mg/dL, or increased	[53,62,72]
γGlutamyl transferase	≥ 60 IU/L	[31]
Lactate dehydrogenase	> 590 IU/L	[59]
Sodium	≤ 133 mmol/L	[51]
Imaging studies	Sonographic GB abnormalities	[70]

IVIG: Intravenous immunoglobulin; ESR: Erythrocyte sedimentation rate; CRP: C-reactive protein; NT-proBNP: N-terminal fragment of B-type natriuretic peptide; GB: Gall bladder.

There has been no confirmative evidence of a better usefulness of corticosteroids as the second line treatment compared to additional IVIG. The combination of corticosteroids and additional IVIG as the second line therapy needs further study to confirm its efficacy, in spite of small group study[43] supporting it. By the way, this combination has been tried more frequently as the first line treatment instead.

THE USE OF CORTICOSTEROIDS IN COMBINATION WITH IVIG AS THE ROUTINE FIRST LINE TREATMENT

By about the year 2000, the combination of corticosteroids and IVIG as the first line therapy was reported shortening the duration of fever and/or reducing the severity of systemic inflammation[44-46]. Okada *et al*[46] reported that the levels of cytokines were lower, the duration of fever was shorter, and the C-reactive protein level decreased more quickly in the patient group who underwent the combination treatment than in the patient group who underwent IVIG treatment only. This result implicates a more rapid reduction of inflammatory reactions in the combination treatment. Wooditch *et al*[47] reported that the inclusion of corticosteroids in aspirin-containing regimens with or without IVIG for the first line treatment of Kawasaki disease reduces the incidence of coronary aneurysms in their meta-analysis. In addition, Inoue *et al*[48] reported that the combination of corticosteroids and IVIG as the first line therapy improved the clinical course and coronary artery outcome in their multicenter prospective study with 178 patients. However, the result of a multicenter randomized double-blind placebo-controlled study by Newburger *et al*[49], in which a single dose of methylprednisolone (30 mg/kg) was administrated did not agree with the result by Inoue *et al*[48] The result of another study of 216 patients in which dexamethasone (0.3 mg/kg per day for 3 d) was combined with IVIG showed no significant difference of coronary outcomes between groups[50]. Therefore, it is less likely that the administration of corticosteroids in combination with IVIG as the routine first line therapy in all Kawasaki disease patients reduces coronary artery lesions. However, further studies to determine the most appropriate regimen of corticosteroids should be needed, because the duration of the administration of corticosteroids (prednisolone was selected) including the period of tapering seems to be longer in studies which reported the efficacy of the combination therapy[45,46,48].

THE USE OF CORTICOSTEROIDS IN COMBINATION WITH IVIG AS THE FIRST LINE TREATMENT IN SELECTED PATIENTS

Another strategy of a use of corticosteroids in Kawasaki

disease patients is their administration in combination with IVIG in selected patients who are expected to be unresponsive to initial IVIG treatment. Three risk scoring systems for the selection of patients were proposed in Japan (Table 2)[51-53]. The cut-off level of the sum of points in the Kobayashi scoring was changed from ⩾ 4 points[51] to ⩾ 5 points[39,54,55]. The sensitivity and the specificity for predicting initial IVIG unresponsiveness were 86% and 68% in the Kobayashi scoring model, 78% and 76% in the Egami scoring model, and 77% and 86% in the Sano scoring model, respectively, according to the reports by their respective creators[51-53]. There were following reports showing the efficacy of these three scoring systems[54-57]. The other predictive scoring systems have had no subsequent studies to show their usefulness, or are based on a small number of subjects[31,58-60]. Kobayashi *et al*[51] suggested four different points of their study from the study by Newburger *et al*[49]: the time to start a treatment was 2 d earlier in their study, a the longer duration of the administration of corticosteroids, the selection of patients with a high risk of unresponsiveness to initial IVIG treatment, and the ethnic homogeneity of their subjects[54]. The selection criteria of patients at a high risk have been the most hot issue until recently. The efficacy of the Japanese scoring systems has been tested in other institutes. However, satisfactory results have not been achieved, and an especially low sensitivity has been reported[43,60-63]. The sensitivity and the specificity of the Kobayashi scoring system were 33%-60% and 35%-87%[43,60-63], those of the Egami scoring system were 21.4%-57% and 77%-86.6%[60-62], and those of the Sano scoring system were 40%-60% and 85%-90%[61,62], respectively. These results suggest refinement of the Japanese scoring systems is needed before they can be used effectively. In addition, one recent study whose subjects were patients with incomplete Kawasaki disease, showed that the proportion of patients identified as being at high-risk for IVIG resistance using three Japanese scoring systems were not significantly different between the IVIG resistance group and the IVIG responsive group[64].

Many clinical/laboratory variables have been reported as the predictors of the unresponsiveness to initial IVIG treatment (Table 3)[31-34,37,51-53,58-62,65-73]. The diversity of predictors might be one reason of the low sensitivity of the proposed risk scoring systems. The biomarkers and the genetic variants also have been investigated as the predictors. However, there has been no report in which any aggressive therapy prevented coronary artery lesions in patients at high risk of unresponsiveness predicted by biomarkers and genetic variants. For more information about studies of biomarkers and genetic variants, two recent reviews are informative[74,75].

More-aggressive initial treatment for patients at a high risk of IVIG unresponsiveness after risk stratification using a predictive model has been recommended in the recently updated guidelines for the medical treatment of acute Kawasaki disease in Japan[39]. Future investigations to determine the best predictive model to use are necessary.

CONCLUSION

It is uncertain that the corticosteroids as the second line treatment are better than the additional treatment of IVIG in Kawasaki disease patients unresponsive to initial IVIG. It is also uncertain that the combination of corticosteroids and IVIG is better than the initial IVIG only treatment as the routine first line therapy during the acute phase. The therapeutic strategy that an aggressive treatment including the combination of corticosteroids and IVIG is needed in patients at high risk of unresponsiveness to initial IVIG treatment, is properly reasonable. Future investigations to determine the best predictive model for the unresponsiveness are necessary.

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