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Usefulness of an Initial Single Intravenous Immunoglobulin Therapy for Kawasaki Disease

By Toshimasa Nakada
Aomori Prefectural Central Hospital, Japan

Abstract- Kawasaki disease is an acute systemic vasculitis of unknown cause that affects mainly infants and children. Coronary artery lesions (CAL) are one of the most important complications of this disease. An appropriate therapy during acute phase of Kawasaki disease to prevent large CAL has not been established. Recent studies disclosed that aspirin and flurbiprofen appeared to have a negative impact on the suppressive effects of initial intravenous immunoglobulin (IVIG) therapy on CAL development in the acute phase of Kawasaki disease and that an initial single IVIG therapy with delayed administration of anti-inflammatory drugs might be useful for prevention of large CAL. Furthermore, recent study disclosed that variable factors including IVIG resistance, responsiveness, and relapse of disease were associated with CAL complications and that an initial single IVIG therapy may be useful for the prevention of large CAL caused by different factors of Kawasaki disease.

Keywords: kawasaki disease, intravenous immuno-globulin therapy, coronary artery lesions, aspirin, flurbiprofen.

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I. Introduction

Kawasaki disease is an acute systemic vasculitis of unknown cause that affects mainly infants and children [1] . Coronary artery lesions (CAL) are one of the most important complications of this disease. During the acute phase (before day 30 from disease onset), coronary artery aneurysms develop. During the convalescent phase (after day 30), large aneurysms develop into subsequent stenosis and these stenotic lesions cause myocardial ischemia and even death. On the other hand, small aneurysms regress without leaving stenotic lesions. Long-term follow-up studies have shown that a maximum CAL size >5 mm was a statistically significant predictive risk factor for myocardial ischemia, and that all CAL≤5 mm in size regressed to normal size [2]. Another study reported that the threshold diameter for acute phase CAL that developed into subsequent stenosis was 6.0 mm [3]. Therefore, the prevention of CAL of >5 mm may be an important goal in the acute treatment of Kawasaki disease to prevent coronary artery stenosis in later stages of the disease [4].

Treatment with intravenous immunoglobulin (IVIG) therapy reduces the occurrence of CAL caused by Kawasaki disease [5,6]. The current standard therapy during the acute phase of Kawasaki disease is 2g/kg/day IVIG therapy [7]. Combination regimens of IVIG and other drugs including steroids and infliximab have been tried as the initial therapy for patients with Kawasaki disease [8,9]. However, the treatment for the prevention of large CAL has not been established, and not enough studies have been performed with regard to initial IVIG monotherapy in spite of the safety and effectiveness of this therapy [4,10].

II. Aspirin's Role in the Treatment of the Acute Phase of Kawasaki Disease

Currently, the standard therapy for pediatric patients with Kawasaki disease is the combination of IVIG and aspirin. Platelets are activated during the acute phase of Kawasaki disease, which provides biological plausibility for antiplatelet therapy in these patients [11]. However, the role and impact of anti-inflammatory drugs (ADs), including high or medium-dose aspirin on IVIG therapy during the acute phase of Kawasaki disease remain unclear. Previous study highlighted insufficient evidence for the addition of aspirin to IVIG therapy regarding suppression of CAL caused by Kawasaki disease [12].

Two studies have shown that ADs may be unnecessary in the acute phase of Kawasaki disease [13,14]. Another two studies disclosed that the prevalence of CAL differed between patients who received initial IVIG therapy without ADs and those who received concomitant ADs with initial IVIG [15,16]. In one of these studies [15], the regimen of IVIG was 400 mg/kg day over 5 days, which is not standard at present. Current initial IVIG protocol for Kawasaki disease is 2g/kg/day. Recent two studies using 2g/kg/day initial IVIG therapy showed that the prevalence of CAL was lower in the patients received initial IVIG therapy without concomitant ADs compared to those with concomitant ADs (Table 1). These studies showed that an initial IVIG therapy without concomitant ADs may be useful for suppression of CAL caused by Kawasaki disease.

Author: Department of Pediatrics, Aomori Prefectural Central Hospital, Aomori City, Japan. e-mail: toshimasanakada@yahoo.co.jp

Table 1 : Comparison of the prevalence of coronary artery lesions between the patients who received 2g/kg/day initial IVIG therapy with and without concomitant ADs administration

Studies	patients without concomitant ADs	patients with concomitant ADs	P
Study A	1.5 % (2/134) (n = 134)	12.1 % (8/66) (n = 66)	0.003
Study B	3.9% (2/51) (n = 51)	7.8% (10/129) (n = 129)	0.514

IVIG: intravenous immunoglobulin, ADs: anti-inflammatory drugs (Aspirin or Flurbiprofen)
Study A: Clinical Medicine Research 2015;4:127-131
Study B: Korean Circulation Journal 2013;43:182-186

III. Effects of ADs on Intravenous Immunoglobulin Therapy in the Acute Phase of Kawasaki Disease

Recent study disclosed that aspirin and flurbiprofen appeared to have a negative impact on the suppressive effects of initial IVIG therapy on CAL development in the acute phase of Kawasaki disease [17].

It was previously reported that ADs, including aspirin, affected the immunological function of T-cells [18,19,20]. A recent study suggested that the pathway comprising T-cells may play a role in the mechanism of action of IVIG [21,22]. Furthermore, a recent immunological study highlighted that T cell activation in the early and middle stages was involved in the mechanism underlying cardiovascular injury in Kawasaki disease [23]. These findings suggest that ADs can alter the effects of IVIG on Kawasaki disease.

IV. An Initial Single ivig Therapy with Delayed Administration of ADs for Prevention of Large cal Caused by Kawasaki Disease

Recent study showed a usefulness of an initial single IVIG therapy with delayed administration of ADs (aspirin or flurbiprofen) for prevention of large CAL caused by Kawasaki disease [4]. In this study, all 132 patients received 2g/kg/day initial IVIG therapy. 74 patients received aspirin and 58 patients received flurbiprofen after completion of initial IVIG infusion. Initial IVIG therapy resistance occurred in 31 of 132 patients (23%), and 10 patients (8%) received additional IVIG. One patient received urinastatin and one patient received plasma exchange as third-line therapy. Before the 30th day, the prevalence of CAL was 2% (2/132); after 30 days, it was 1% (1/132). The maximal internal CAL diameters were 4.8mm (Z score = 6.3) among all patients.

Patients who received initial IVIG monotherapy with delayed administration of ADs may not receive a negative impact on the suppressive effects of ADs to IVIG therapy until the start time of ADs administration. However, patients who received initial IVIG therapy with concomitant use of ADs may receive a negative impact of ADs during IVIG therapy. This difference may be a mechanism that the combination order of initial IVIG therapy with administration of ADs may lead to the prevention of large CAL.

V. Background Factors Associated with the Complications of cal Caused by Kawasaki Disease

Recent study disclosed that variable factors including IVIG resistance, responsiveness, and relapse of disease were associated with CAL complications and that an initial single IVIG therapy may be useful for the prevention of large CAL caused by different factors of Kawasaki disease [10].

Another study showed that a patient who had received initial IVIG and prednisolone combination therapy developed large CAL after relapse [24]. This demonstrated the difficulties associated with administration of appropriate additional therapy after initial therapy with steroids. A single IVIG therapy does not modify the clinical course of Kawasaki disease. This characteristic permits clinicians to easily manage the treatment progress and to provide additional therapies at appropriate times during the clinical course. With these advantages and reported outcomes of CAL, initial single IVIG therapy may be superior to combination treatment with initial IVIG therapy and steroids.

VI. Conclusions

Aspirin and flurbiprofen appeared to have a negative impact on the suppressive effects of initial IVIG therapy on CAL development in the acute phase of Kawasaki disease. Patients who received initial IVIG monotherapy with delayed administration of these ADs may not receive a negative impact on the suppressive effects of ADs to IVIG therapy until the start time of ADs administration. Furthermore, a single IVIG therapy does not modify the clinical course of Kawasaki disease. This characteristic permits clinicians to easily manage the treatment progress and to provide additional therapies at appropriate times during the clinical course. An initial single IVIG therapy may be useful for the prevention of large CAL caused by different factors including IVIG-

resistance, -responsiveness, and relapse of Kawasaki disease.

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