Global Journals LaTeX JournalKaleidoscope™
Artificial Intelligence formulated this projection for compatibility purposes from the original article published at Global Journals. However, this technology is currently in beta. *Therefore, kindly ignore odd layouts, missed formulae, text, tables, or figures.*

Toshimasa Nakada[1]

[1] Aomori Prefectural Central Hospital

Received: 15 April 2015 Accepted: 1 May 2015 Published: 15 May 2015

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.

Index terms— kawasaki disease, intravenous immuno-globulin therapy, coronary artery lesions, aspirin, flurbiprofen.

1 Usefulness of an Initial Single Intravenous Immunoglobulin Therapy for Kawasaki Disease Toshimasa Nakada

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

2 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. 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.

3 Volume XV Issue IV Version I

Keywords: kawasaki disease, intravenous immunoglobulin therapy, coronary artery lesions, aspirin, flurbiprofen.

4 I. Introduction

awasaki 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 K during the acute phase of Kawasaki disease is 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.

5 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 30 th 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.

6 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.

7 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-Volume XV Issue IV Version I [1]

Figure 1:

[1]© 2015 Global Journals Inc. (US)Usefulness of an Initial Single Intravenous Immunoglobulin Therapy for Kawasaki Disease

1

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

Figure 2: Table 1 :

resistance, -responsiveness, and relapse of Kawasaki disease.

[Burns and Kawasaki Syndrome ()] , J C Burns , Glod , M P Kawasaki Syndrome . *Lancet* 2004. 364 p. .

[Ashida et al. ()] 'A case report of refractory Kawasaki disease with bilateral giant coronary aneurysms treated with intravenous immunoglobulin and prednisolone combination therapy'. A Ashida , N Ozaki , K Kishi , H Katayama , K Okasora , H Tamai . *Progress in Medicine* 2013. 33 p. .

[Inoue et al. ()] 'Activating Fc gamma receptors participate in the development of autoimmune diabetes in NOD mice'. Y Inoue , T Kaifu , A Sugahata-Tobinai . *J Immunol* 2007. 179 p. .

[Buckland and Lombardi ()] 'Aspirin and the induction of tolerance by dendritic cells'. M Buckland , G Lombardi . *Handb Exp Pharmacol* 2009. 188 p. .

[Nakada ()] 'Background factors associated with the complications of coronary artery lesions caused by Kawasaki disease'. T Nakada . *Clinical Medicine Research* 2015. 4 p. .

[Zhang et al. ()] 'Changes in CD69, CD25 and HLA-DR expressions in peripheral blood T cells in Kawasaki disease'. Y Y Zhang , X M Huang , M L Kang . *Zhonghua Er Ke Za Zhi* 2006. 44 p. .

[Nakada ()] 'Difference in the prevalence of coronary arterial lesions in Kawasaki disease according to the time of initiation of additional aspirin or flurbiprofen therapy'. T Nakada . *Med J Aomori* 2012. 57 p. .

[Ito and Kiyosawa ()] 'Effectiveness of aspirin therapy in acute phase of Kawasaki disease'. H Ito , N Kiyosawa . *Prog Med* 2002. 22 p. .

[Nakada ()] 'Effects of anti-inflammatory drugs on intravenous immunoglobulin therapy in the acute phase of Kawasaki disease'. T Nakada . *Pediatr Cardiol* 2015. 36 p. .

[Kobayashi et al. ()] 'Efficacy of immunoglobulin plus prednisolone for prevention of coronary artery abnormalities in severe Kawasaki disease (RAISE study): a randomized, open-label, blinded-endpoints trial'. T Kobayashi , T Saji , T Otani . *Lancet* 2012. 379 p. .

[Furusho et al. ()] 'High-dose intravenous gammaglobulin for Kawasaki disease'. K Furusho , T Kamiya , H Nakano . *Lancet* 1984. 2 p. .

[Tsuda et al. ()] 'Incidence of stenotic lesions predicted by acute phase changes in coronary arterial diameter during Kawasaki disease'. E Tsuda , T Kamiya , Y Ono , K Kimura , K Kurosaki , S Echigo . *Pediatr Cardiol* 2005. 26 p. .

[Tremoulet et al. ()] 'Infliximab for intensification of primary therapy for Kawasaki disease: a phase 3 randomised, double-blind, placebo-controlled trial'. A H Tremoulet , S Jain , P Jaggi . *Lancet* 2014. 383 p. .

[Lee et al. ()] 'Is high-dose aspirin necessary in the acute phase of Kawasaki disease?'. G Lee , S E Lee , Y M Hong . *Korean Circ J* 2013. 43 p. .

[Muller et al. ()] 'Long-term follow-up of acute changes in coronary artery diameter caused by Kawasaki disease: risk factors for development of stenotic lesions'. F Muller , W Knirsch , P Harpes , R Pretre , B E Valsangiacomo , O Kretschmar . *Clin Res Cardiol* 2009. 98 p. .

[Yahata et al. ()] 'Platelet activation dynamics evaluated using platelet-derived microparticles in Kawasaki disease'. T Yahata , C Suzuki , A Yoshikawa . *Circ J* 2014. 78 p. .

[Nakada ()] 'Prevention of large coronary artery lesions caused by Kawasaki disease'. T Nakada . 10.18103/mra.v0i3.138. http://dx.doi.org/10.18103/mra.v0i3.138 *Medical Research Archives* 2015.

[Research committee of the Japanese Scociety of Pediatric Cardiology; Cardiac Surgery committee for development of guidelines f 'Research committee of the Japanese Scociety of Pediatric Cardiology; Cardiac Surgery committee for development of guidelines for medical treatment of acute Kawasaki disease. Guidelines for medical treatment of acute Kawasaki disease: report of the Research committee of the Japanese Society of Pediatric Cardiology and Cardiac Surgery (2012 revised version)'. *Pediatr Int* 2014. 56 p. .

[Baumer et al. (2006)] 'Salicylate for the treatment of Kawasaki disease in children'. J H Baumer , S J Love , A Gupta . *Cochrane Database Syst Rev* 2006 Oct 18. (4) p. D004175.

[Newburger et al. ()] 'Single intravenous infusion of gamma globulin as compared with four infusion in the treatment of acute Kawasaki syndrome'. J W Newburger , M Takahashi , A S Beiser . *N Engl J Med* 1991. 324 p. .

[Yamamoto et al. ()] 'The inhibitory effects of intravenous administration of rabbit immunoglobulin G on airway inflammation are dependent upon Fcc receptor II b on CD11c(?) dendritic cells in a murine model'. M Yamamoto , K Kobayashi , Y Ishikawa . *Clin Exp Immunol* 2010. 162 p. .

[Huang et al. ()] 'The novel phospho-non-steroidal anti-inflammatory drugs, OXT-328, MDC-22 and MDC-917, inhibit adjuvantinduced arthritis in rats'. L Huang , G Mackenzie , N Ouyang . *Br J Pharmacol* 2011. 162 p. .

[Hsieh et al. ()] 'Treatment of acute Kawasaki disease: aspirin's role in the febril stage revisited'. K S Hsieh , K P Weng , C C Lin . *Pediatrics* 2004. 114 p. .

[Benammar et al. ()] 'Zizyphus lotus L. (Desf.) modulates antioxidant activity and human T-cell proliferation'. C Benammar , A Hichami , A Yessouufou . *BMC Complement Altern Med* 2010. 10 p. 54.