Efficacy of Intravenous Immunoglobulin Combined with Prednisolone Following Resistance to Initial Intravenous Immunoglobulin Treatment of Acute Kawasaki Disease

Tohru Kobayashi, MD[1,2], Tomio Kobayashi, MD[3], Akihiro Morikawa, MD[1,4], Kentaro Ikeda, MD[1], Mitsuru Seki, MD[3], Shinya Shimoyama, MD[3], Yoichiro Ishii, MD[3], Takahiro Suzuki, MD[5], Kimiko Nakajima, MD[3], Naoko Sakamoto, PhD[6], and Hirokazu Arakawa, MD[1]

Objectives To determine the most effective first-line rescue therapy for intravenous immunoglobulin (IVIG) nonresponders, using IVIG, prednisolone, or both, to prevent coronary artery abnormalities (CAAs).

Study design We retrospectively reviewed the clinical records of 359 consecutive patients with Kawasaki disease who failed to respond to initial IVIG.

Results CAAs up to 1 month after treatment were less common in the IVIG+prednisolone group (15.9%) than in the IVIG group (28.7%, $P = .005$) and the prednisolone group (30.6%, $P = .01$). The IVIG+prednisolone group had significantly lower risks of failing to respond to first-line rescue therapy (aOR 0.16, 95% CI 0.09-0.31), CAAs up to 1 month (aOR 0.46, 95% CI 0.27-0.90), and CAAs at 1 month (aOR 0.40, 95% CI 0.18-0.91) than the IVIG group. In the prednisolone and IVIG+prednisolone groups, risk score, day of illness at first-line rescue therapy, prednisolone monotherapy, and resistance to first-line rescue therapy were independent risk factors for CAA. Sex and resistance to first-line rescue therapy were independent risk factors in the IVIG group.

Conclusions IVIG+prednisolone may be superior to IVIG or prednisolone as first-line rescue therapy in the treatment of IVIG nonresponders. To establish the efficacy of rescue therapy with IVIG+prednisolone following nonresponse to initial IVIG, a prospective randomized trial is warranted. *(J Pediatr 2013;163:521-6)*.

Kawasaki disease (KD) is an acute febrile illness of childhood characterized by clinical and histopathologic features of systemic vasculitis.[1] Treatment with intravenous immunoglobulin (IVIG) and aspirin is effective in resolving inflammation and preventing coronary artery abnormality (CAA) formation.[2-4] However, approximately 15%-20% of patients develop persistent or recurrent fevers after IVIG treatment completion and are considered to have a higher risk of developing CAAs.[5-7]

In these patients, the predominant clinical practice is to administer additional therapy, which may include retreatment with IVIG,[5-7] corticosteroids,[8-10] other cytotoxic agents,[11,12] infliximab,[13-15] or plasma exchange.[16] Most physicians select retreatment with IVIG as the first-line rescue therapy, as recommended by the American Heart Association in 2004.[17] The guidelines state that corticosteroids should be administrated as second-line rescue therapy for patients who fail to respond to a second dose of IVIG. However, no firm evidence for the efficacy of any rescue therapy in this group of children has been established because of the lack of randomized controlled trials and well-designed cohort studies. Over a number of years, patients with KD in our hospitals who failed to respond to primary IVIG therapy have been treated with regimens including corticosteroids and, especially, a standard dose of intravenous prednisolone followed by daily administration of oral prednisolone.

The aim of this study was to determine the most effective first-line rescue therapy, using IVIG, prednisolone or both, to prevent CAAs.

Methods

We retrospectively reviewed the clinical records of consecutive patients with KD from September 2000-December 2011, from 13 medical institutions in Gunma

CAA	Coronary artery abnormality
CRP	C-reactive protein
IL	Interleukin
IVIG	Intravenous immunoglobulin
KD	Kawasaki disease
mPSL	Methylprednisolone

From the [1]Department of Pediatrics, Gunma University Graduate School of Medicine, Maebashi, Gunma, Japan; [2]Division of Clinical Pharmacology and Toxicology, The Hospital for Sick Children, Toronto, Ontario, Canada; [3]Department of Cardiology, Gunma Children's Medical Center, Shibukawa, Gunma, Japan; [4]Kitakanto Allergy Institute, Midori, Gunma, Japan; [5]Department of Pediatrics, Saiseikai Maebashi Hospital, Maebashi, Gunma, Japan; and [6]Department of Health Policy, National Center for Child Health and Development, Setagaya, Tokyo, Japan

Supported by Ministry of Health, Labor, and Welfare Sciences Grant of Comprehensive Research on Practical Application of Medical Technology (Randomized Controlled Trial to Assess Immunoglobulin plus Steroid Efficacy for Kawasaki Disease; H20-Rinsho-Shiken-Ippan-08), and the Morinaga Foundation for Health and Nutrition. T.K. received a scholarship fund (Banyu Fellowship Program 2012). The authors declare no conflicts of interest.

Portions of the study were presented as a poster at the American Health Association's Scientific Sessions in Los Angeles, California (November 3, 2012).

 http://dx.doi.org/10.1016/j.jpeds.2013.01.022

and Saitama prefectures, Japan. Patients with KD who were administered IVIG combined with prednisolone as primary therapy were excluded from the study. The initial IVIG dose was 2 g/kg/d for 1 day or 1 g/kg/d for 2 days consecutively. Patients also received aspirin (30 mg/kg/d). The dose of aspirin was decreased to 5 mg/kg/d after normalization of C-reactive protein (CRP) levels. KD was diagnosed using the Japanese Diagnostic Guidelines for Kawasaki Disease (5th revised edition).[18] The first day of the illness was defined as the first day of fever. Patients were considered afebrile when their body temperature at the axilla remained below 37.5°C for more than 24 hours. Laboratory data were obtained before initial IVIG treatment. We also estimated a risk score[19] with point scores and cut-off values for each variable as follows: 2 points each for sodium 133 mmol/L or less, initial treatment given on day 4 of illness or earlier, aspartate aminotransferase 100 IU/L or more, and neutrophils at least 80%; and 1 point for platelet count $30.0 \times 10^4/mm^3$ or less, CRP at least 10 mg/dL, and age 12 months or less. If a laboratory test was performed twice or more before initial IVIG treatment, the highest value was chosen for analysis in the case of white blood cell count, percentage neutrophils, serum total bilirubin, aspartate aminotransferase, alanine aminotransferase and CRP, or the lowest value in the case of platelet count, hematocrit, serum sodium, and albumin. Missing data were counted as 0 points. The presence of CAAs was assessed using two-dimensional echocardiography without blinding. CAA was defined as an internal lumen diameter ≥3 mm in a child less than 5 years old or ≥4 mm in a child 5 years of age or older, if the internal diameter of a segment was at least 1.5 times that of an adjacent segment or the lumen appeared irregular. In addition, we classified a CAA that was normalized within 1 month as transient dilation and a CAA that remained at 1 month as an aneurysm. This retrospective cohort study was approved by the local review board of Gunma University Graduate School of Medicine.

We defined patients who failed to respond to the initial IVIG as those who had persistent fever that lasted for more than 24 hours (nonresponse to the initial IVIG) or recrudescent fever associated with KD symptoms after an afebrile period (relapse). These patients were considered candidates for first-line rescue therapy. Patients who failed to respond to the initial IVIG were divided into 3 groups on the basis of their first-line rescue therapy, as follows: IVIG, prednisolone, and IVIG+prednisolone. The therapeutic methods used for these rescue therapies were selected in an arbitrary manner by pediatric doctors. Patients in the IVIG group received IVIG (1 g/kg or 2 g/kg single infusion) only. Patients in the prednisolone group received prednisolone sodium succinate (2 mg/kg/d in 3 divided doses) given by intravenous injection until the fever had resolved and then orally until CRP was normalized (<0.5 mg/dL), after which the dose was tapered over 15 days in 5-day steps (2 mg/kg/d for 5 days, 1 mg/kg/d for 5 days, and 0.5 mg/kg/d for 5 days). If the patient relapsed during the tapering of the prednisolone, increasing the dose or prolonging the duration of prednisolone was permitted. Patients in the IVIG+prednisolone group received both IVIG and prednisolone regimens. Second-line rescue therapy was considered in patients who did not become afebrile 24-48 hours after initiation of the first-line rescue therapy or in whom recrudescent fever occurred. These patients were defined as unable to respond to the first-line rescue therapy. Similarly, third- and fourth-line rescue therapies were considered if necessary.

Statistical Analyses

All analyses were conducted using the IBM SPSS statistical software package, v. 19.0J (IBM SPSS Japan, Tokyo). $P < .05$ was considered statistically significant in two-sided tests. The baseline characteristics and laboratory data of the 3 groups of first-line rescue therapy were compared using the χ^2 test with post hoc multiple comparison adjusted by Holm method for categorical data and by one-way ANOVA with a post hoc Dunnett test for continuous variables.

To compare the effect of clinical and coronary outcomes between the IVIG group and the 2 groups given corticosteroid, multiple logistic regression analysis was performed and ORs with 95% CIs were adjusted for age in months, sex, reason for rescue therapy (nonresponse to initial IVIG or relapse), and risk score. To identify independent risk factors for CAA in patients who received prednisolone as a first-line rescue therapy (the IVIG+prednisolone and prednisolone groups) and those who did not (the IVIG group), multivariable logistic regression models were constructed using sex, risk score, reason for first-line rescue therapy, day of illness at first-line rescue therapy, and resistance to first-line rescue therapy. The first-line rescue therapy regimen (IVIG+prednisolone or prednisolone monotherapy) was also included in the multivariable logistic regression model for regimens including prednisolone.

Results

During the study period, 1947 consecutive patients with KD were admitted and treated at our hospitals. One hundred and eighty-five patients who received IVIG+prednisolone as primary therapy and 17 who were treated with aspirin only were excluded from the study. Of the remaining 1745 patients, 375 (21.5%) failed to respond to initial IVIG treatment. One patient who already had CAA before first-line rescue therapy and 15 patients who had a past history of KD were excluded from the study. Thus, 359 patients with KD were analyzed.

Table I shows the baseline characteristics of the 3 treatment groups. Patients in the prednisolone group were significantly older than those in the IVIG group ($P < .001$). The incidence of relapse was higher in the IVIG group than in the prednisolone group ($P < .001$) and the IVIG+prednisolone group ($P = .017$). The day of illness at first-line rescue therapy was later in the IVIG group than in the prednisolone and IVIG+prednisolone groups (both $P < .001$). Patients in the prednisolone group had significantly higher white blood cell counts than the IVIG+prednisolone group ($P = .024$), greater neutrophil