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Original Article

Prediction of responsiveness or non-responsiveness to treatment of acute Kawasaki disease using 1 gram per kilogram of immunoglobulin – an effective and cost-saving schedule of therapy

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Abstract Standard treatment of acute Kawasaki disease involves giving 2 grams per kilogram of immunoglobulin intravenously along with aspirin. More than half of the patients with acute Kawasaki disease, nonetheless, can be cured by giving only 1 gram per kilogram of immunoglobulin, thus reducing this aspect of the cost of treatment by half. Our purpose was to predict those patients with acute Kawasaki disease who would respond to treatment with 1 gram per kilogram of immunoglobulin given intravenously on the basis of their clinical profiles and laboratory findings prior to the initial treatment. We performed a retrospective review of the clinical records of consecutive patients with acute Kawasaki disease treated in our hospital with intravenous immunoglobulin from January, 2001, to December, 2005.

During this period, we treated in this fashion 98 patients with acute Kawasaki disease. 65% of these needing immunoglobulin therapy were cured by giving 1 gram per kilogram. The neutrophil count and the percentage of white blood cells representing neutrophils, along with aspirate aminotransferase, alanine aminotransferase, bilirubin and C reactive protein, were all significantly lower, and sodium was significantly higher, in those responding to 1 gram per kilogram of immunoglobulin when compared to those who did not respond. The days of illness at the first intravenous treatment was later in those responding than in those failing to respond. We generated a score for prediction, assigning a point for each of C reactive protein equal to or greater than 10 mg/dl, sodium equal to or lower than 133 meq/l, alanine aminotransferase equal to or greater than 110 IU/l, and 2 points for the percentage of white blood cells representing neutrophils equal to or greater than 70%. Using a cut-off point of a score less than 2, we were able to identify those responding with 60% sensitivity, and 91% specificity.

Thus, we are now able to predict those patients with acute Kawasaki disease who will respond to immunoglobulin given intravenously at 1 gram per kilogram using laboratory data, with a potential saving in medical costs.

Keywords: Mucocutaneous lymph node syndrome; prediction score; stratified therapy; cost performance

KAWASAKI DISEASE, AN ACUTE MULTISYSTEM vasculitis in small-medium arteries of unknown aetiology that primarily affects infants and children, is a major cause of acquired cardiac disease in Japan.[1,2] Standard therapy for the acute disease involves giving immunoglobulins at high dosage intravenously along with aspirin. The most common schedule for initial treatment is 2 grams per kilogram of immunoglobulin.

In our hospital, the patients received 1 gram per kilogram of intravenous immunoglobulin when they scored 4 or more in the system devised by

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Harada,[3] receiving an additional dose of 1 gram per kilogram of immunoglobulin if they showed fever, with temperatures exceeding 38 degrees centigrade, within 48 hours. The advantages of the reduced dosage are its low cost, and the possibility of reducing the incidence of side effects. Its disadvantages are its potential reduced effectiveness, with prolongation of hospitalization and the subsequent need for additional intravenous treatment with immunoglobulin. Of the patients with acute Kawasaki disease, nonetheless, two-thirds can be cured by administering only 1 gram per kilogram. If it proved possible to identify those likely to respond to the lower dose prior to its administration, this would reduce the cost of treatment, since those identified as non-responders could be given 2 grams per kilogram per day as the initial therapy.

The aim of our present study, therefore, was to seek to predict those patients with acute Kawasaki disease who would respond to 1 gram per kilogram of immunoglobulin given intravenously on the basis of their clinical profiles and laboratory findings prior to the initial treatment.

Materials and methods

We performed a retrospective review of the clinical records of consecutive patients with acute Kawasaki disease treated in our hospital with intravenous immunoglobulin from January, 2001, to December, 2005. We diagnosed the disease according to the guidelines used in Japan.[4] The first day of the illness was defined as the first day of fever. Patients were excluded when clinical or laboratory evidence suggested any other disease known to mimic acute Kawasaki disease, such as infections with the adenovirus, the Epstein-Barr virus, Streptococcus, or bacterial cervical lymphadenitis.

Prior to the initial treatment with immunoglobulin, we obtained details of the white blood cell count, the neutrophil count, the percentage of white blood cells representing neutrophils, haemoglobin, haematocrit, platelet count, the concentrations in the serum of total protein, albumin, sodium, asparate aminotransferase, alanine aminotransferase, aminotransferase per alanine aminotransferase, lactic dehydrogenase, total bilirubin, C reactive protein, and the erythrocyte sedimentation rate. If a laboratory test was performed twice or more prior to beginning treatment, the highest value was selected for analysis in the case of white blood cell count, neutrophil count, percentage of white blood cells representing neutrophils, serum asparate aminotransferase, alanine aminotransferase, lactic dehydrogenase, total bilirubin, C reactive protein and erythrocyte sedimentation rate, or the lowest value in the case of haemoglobin, haematocrit, platelet count, serum total protein, albumin, and sodium.

Intravenous immunoglobulin was given at a dose of 1 gram per kilogram per day in those patients scoring 4 or more using the system devised by Harada.[3] Patients also received aspirin at 30 milligrams per kilogram. Additional intravenous immunoglobulin was given to those patients whose temperature exceeded 38 degrees centigrade and lasted more than 48 hours, and to those with recrudescent fever associated with acute Kawasaki disease symptoms after an afebrile period. We considered these patients to have failed to respond to the initial treatment with 1 gram per kilogram.

The coronary arteries were assessed by cross-sectional echocardiography performed at the initial treatment, and then between 6 and 8 days, 12 and 14 days, and 25 to 30 days. The coronary artery was defined as abnormal when its luminal diameter exceeded 3.0 millimetres in children under 5 years old, or 4.0 millimetres in children 5 years old or more, when the internal diameter of a segment was at least 1.5 times that of the adjacent segment, or when the luminal contours were clearly irregular.[5]

Data are presented as the mean plus or minus standard deviations for continuous variables. For all analyses, a 2-sided probability value below 0.05 was considered to indicate statistical significance. Univariate analysis using unpaired t-test was performed to determine whether the data could be used to discriminate between those responding or failing to respond to immunoglobulin given intravenously at 1 gram per kilogram.

Results

During the chosen period, we treated 98 patients with acute Kawasaki disease with intravenous immunoglobulin. Their baseline characteristics and clinical outcomes are shown in Table 1. Univariate analysis identified laboratory variables as significant predictors of failure to respond to immunoglobulin given intravenously at 1 gram per kilogram (Table 2). Neutrophil count, percentage of white blood cells representing neutrophils, serum asparate aminotransferase, alanine aminotransferase, and total bilirubin were all significantly lower, and the concentration of sodium in the serum was significantly higher in those responding compared to those who failed to respond. The number of days of illness at the time of the initial treatment was significantly larger in those responding.

We noted transient dilation of the coronary arteries within 1 month in 2 of the 64 responders, and in none of those who failed to respond. A coronary arterial abnormality at 1 month was seen

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Table 1. Baseline characteristics and clinical outcomes of the patients.

	Responders (n = 64)	Non-responders (n = 34)	Statistical analysis
Male/Female	43/21	23/11	Not significant
Age (years)	2.4 ± 1.6	2.1 ± 1.4	Not significant
Harada's score	4.6 ± 1.1	5.1 ± 0.8	$p < 0.05$
Days of illness at initial intravenous immunoglobulin	5.9 ± 1.2	5.4 ± 0.9	$p < 0.05$

Table 2. Laboratory variables between 1 gram per kilogram intravenous immunoglobulin responders and non-responders.

	Responders (n = 64)	Non-responders (n = 34)	Statistical analysis
White blood cell ($\times 10^3$/square millimetre)	14.9 ± 4.9	17.0 ± 6.5	Not significant
Neutrophil ($\times 10^3$/square millimetre)	9.7 ± 4.7	14.1 ± 6.5	$p < 0.005$
Percentage of white blood cells representing neutrophils	64.8 ± 13.2	76.4 ± 14.1	$p < 0.0005$
Haemoglobin (gram per decilitre)	11.1 ± 1.1	11.0 ± 0.8	Not significant
Haematcrit (percent)	32.4 ± 5.9	33.6 ± 2.9	Not significant
Platelet ($\times 10^4$/square millimetre)	34.1 ± 10.0	35.6 ± 17.1	Not significant
Total protein (gram per decilitre)	6.6 ± 0.5	6.5 ± 0.7	Not significant
Albmin (gram per decilitre)	3.6 ± 0.4	3.6 ± 0.5	Not significant
Sodium (milliequivalent per litre)	133 ± 2	132 ± 3	$p < 0.05$
Asparate aminotransferase (interunit per litre)	103 ± 220	213 ± 304	$p < 0.05$
Alanine aminotransferase (interunit per litre)	80 ± 134	149 ± 136	$p < 0.05$
Asparate aminotransferase per Alanine aminotransferase	1.70 ± 0.90	1.42 ± 0.86	Not significant
Lactic dehydrogenase (unit per litre)	545 ± 306	678 ± 527	Not significant
Total bilirubin (milligram per decilitre)	0.76 ± 0.69	1.39 ± 1.25	$p < 0.05$
C reactive protein (milligram per decilitre)	7.7 ± 4.1	10.4 ± 4.4	$p < 0.05$
Erythrocytic sedimentation rate (mm per hour)	78 ± 20	78 ± 19	Not significant

in 4 patients in those failing to respond, but in none of those responding to the initial treatment. Mild dilation was noted in 2 patients, and the other 2 had aneurysms of 4 millimetres and 7 millimetres, respectively. None of the patients had giant aneurysms with internal diameters equal to or more than 8 millimetres. Of the patients, 4 failed to respond to 2 courses of intravenous therapy. We administered immunoglobulin at 4 grams per kilogram on 3 occasions to 3 patients, while the other patient was given immunoglobulin four times, receiving 6 grams per kilogram. Of the 4 patients failing to respond to 2 courses of intravenous immunoglobulin, 2 had coronary arterial aneurysms.

Discussion

The Japan Research Committee on Kawasaki Disease has conducted nationwide surveys since 1970. The data of the 19th survey, covering the period from 2005 to 2006, showed that 67% and 18% of all cases receiving intravenous immunoglobulin therapy were treated at doses of 2 grams per kilogram per day immunoglobulin and 2 grams per kilogram immunoglobulin for 2 days, respectively. Only 10% of cases received intravenous immunoglobulin at 1 gram per kilogram per day. In our hospital, we used intravenous immunoglobulin therapy at a dose of 1 gram per kilogram per day, and not 2 grams per kilogram per day, because we considered the lower dose to be effective, less expensive, and safer. In this study, we found that two-thirds of the patients who needed intravenous immunoglobulin were cured at doses of 1 gram per kilogram per day. We found 4 patients to have coronary arterial abnormalities at 1 month, with 2 patients having coronary arterial aneurysms. It is well recognized, nonetheless, that around one-twentieth of children with Kawasaki disease, even when treated with high-dose intravenous immunoglobulin in the first 10 days of illness, develop at the least transient coronary arterial dilation, and 1% develop giant aneurysms,[6–8] so our study is not out of step with recognized findings. It has been suggested, nonetheless, that an initial daily dose of immunoglobulin of less than 1 gram per kilogram is a risk factor associated with the need for subsequent re-treatment.[9] Taking into account this possibility, it would be advantageous if we could predict those patients likely to fail to respond to 1 gram per kilogram, and give them 2 grams per kilogram.

Several scoring models have previously been developed to predict the likelihood of development of coronary arterial abnormalities. The first of these, reported by Asai[10] in 1983, was useful in determining indications for cardiac catheterization at a time before cross-sectional echocardiography

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Table 3. Percentage of neutrophils in responders and non-responders.

	Responders (n = 64)	Non-responders (n = 34)
Score ⩽1	39	3
Score >2	25	31

was used in Japan. A subsequent model devised by Iwasa[11] proved unduly complicated. It is the score devised by Harada[3] that is used by many Japanese physicians to decide whether intravenous immunoglobulin therapy should be given. Fukunishi et al.[12] reported that patients with C reactive protein more than 10 milligrams per decilitre, lactic dehydrogenase more than 590 interunits per litre, and/or haemoglobin less than 10 grams per decilitre prior to the initial treatment were likely to fail to respond to intravenous immunoglobulin. Sano et al.[13] reported that patients with at least two of three predictors, namely C reactive protein equal or more than 7.0 milligram per decilitre, total bilirubin equal or more than 0.9 milligram decilitre, or asparate aminotransferase equal or more than 200 interunit per litre, were likely to fail to respond. Kobayashi et al.[14] reported that their predictive models based on demographic and laboratory variables accurately predicted those failing to respond to the initial treatment of the acute disease.

Our predictive score assigns 1 point for C reactive protein equal or more than 10 milligrams per decilitre, sodium equal or less than 133 milliequivalent per litre, and asparate aminotransferase equal or more than 110 interunits per litre, as well as 2 points for the percentage of white blood cells representing neutrophils equal or more than 70. We assigned 1 point to those laboratory variables for which statistical analysis revealed a p value of less than 0.05, and 2 points for the one which statistical analysis showed to have a p value of 0.0005. Using a cut-off point of a score of less than 2, we could identify those responding to a dose of 1 gram per kilogram with 60% sensitivity and 91% specificity (Table 3). Specificity is more important than sensitivity, because it is important that those failing to respond should be treated with 2 grams per kilogram, and it is not harmful that those who do respond are treated with this increased dose.

In Japan, the nationwide survey showed that the annual number of patients with acute Kawasaki disease is about 10,000, and five-sixths of these patients were treated with intravenous immunoglobulin. Our data showed that patients with scores of less than 2, accounting for about two-fifths of the patients treated with intravenous immunoglobulin, should be treated with 1 gram per kilogram intravenous immunoglobulin. The cost of 2.5 grams immunoglobulin is about 30,000 Japanese Yen. If 3,440 patients, two-fifths of those treated with immunoglobulin, and weighing 10 kilograms, are treated at a dose of 1 rather than 2 grams per kilogram, this can result in a saving of 412,800,000 Yen, equivalent to 3,894,000 United States dollars, or 2,472,000 Euros each year.

In conclusion, our data shows that patients with acute Kawasaki disease scoring less than 2 in our system can be considered to be responsive to immunoglobulin given intravenously at 1 gram per kilogram, and should be treated at this lower dose.

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