Immunoglobulin Resistance in Kawasaki Disease

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Background: The aim of this study was to identify risk factors for immunoglobulin resistance, including clinical symptoms such as arthritis and the pH of intravenous immunoglobulin.

Methods: The data of children with Kawasaki disease who had received immunoglobulin were evaluated. Data regarding the brand of immunoglobulin administered were abstracted from the pharmacy records.

Results: Eighty consecutive children with Kawasaki disease were evaluated ($Mdn_{age} = 28$ months, 66% male). The prevalence of immunoglobulin resistance was 30%. Arthritis was a presenting symptom in the acute phase of Kawasaki disease in 8% (6/80, all male) and was seen in significant association with immunoglobulin resistance in comparison to those without arthritis (16.7% vs. 0.2%, $p = 0.008$). Next, the immunoglobulin brand types were divided into two groups: the relatively high pH group ($n = 16$), including Carimune (pH 6.6 ± 0.2), and the low pH group ($n = 63$), including Gamunex (pH 4–4.5) or Privigen (pH 4.6–5). Overall, no significant difference in immunoglobulin responsiveness was found between the low pH and the high pH groups (73% vs. 56%, $p = 0.193$), although the low pH group showed a trend toward a larger decrease in erythrocyte sedimentation rate ($p = 0.048$), lower steroid use ($p = 0.054$), and lower coronary involvement ($p = 0.08$) than those in the high pH group.

Conclusions: Children presenting with arthritis in the acute phase of Kawasaki disease may be at risk for immunoglobulin resistance.

Introduction

IMMUNOGLOBULIN RESISTANCE with persistent disease process and fever in Kawasaki disease is a more serious condition with a need for earlier detection and management.¹

Initial treatment with high-dose intravenous gammaglobulin (immunoglobulin) along with oral acetylsalicylic acid has been reported to reduce the risk of coronary artery sequelae. In the acute phase of Kawasaki disease, the response to treatment is considered abatement of fever.¹ However, some children do not respond to the initial dose of immunoglobulin (2 g/kg) and present with refractory or recurrent fever. This phenomenon is described as immunoglobulin resistance and is reported in 10–30% of Kawasaki disease patients.^{2,3}

Immunoglobulin resistance has been linked to a higher degree of overall inflammation as determined by higher levels of inflammatory markers, including erythrocyte sedimentation rate (ESR), C-reactive protein, and serum interleukin 6.⁴ Further, higher C-reactive protein levels have been linked to worse cardiac sequelae in Kawasaki disease.⁵ Often, a repeat dose of immunoglobulin leads to resolution of fever and other symptoms; otherwise treatment with

immunomodulators such as steroids, infliximab, methotrexate, cyclophosphamide, or plasmapheresis is needed for the alleviation of symptoms.^{1,6} Currently, there remains a need for early detection of immunoglobulin resistance, and various predictors such as risk factors, biomarkers, or scoring systems have been reported.^{3,4} However, there is still much to know about this group of resistant patients, and they warrant further investigation in order to determine factors that contribute to their resistance. Arthritis has previously been reported in Kawasaki disease in 7.5–45% of cases, in both acute or subacute phases,^{7–9} and although determined to be a transient finding,^{1,7} it has also been reported after immunoglobulin therapy.^{10,11} It was hypothesized that arthritis would be associated with a higher degree of inflammation and thus immunoglobulin resistance.

Difference in outcomes after Kawasaki disease based on different immunoglobulin brands has been reported in the literature.^{12,13} Immunoglobulins are human pooled immunoglobulin (IgG) that on exposure to low pH (pH 4, acid buffer treated preparation) results in increased binding to self-antigens, to inflammatory cytokines, and to foreign antigens, thus improving its efficacy.¹⁴ Low pH-treated immunoglobulin preparations have been shown to have a

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stronger inhibiting effect on proliferation of phytohemagglutinin-stimulated peripheral blood mononuclear cells and a higher antigen-binding capacity.¹⁴ It was hypothesized that immunoglobulin resistance may be related to the pH of the commercial brands of immunoglobulin.

The specific aims for this study were to determine: (a) clinical and laboratory risk factors for immunoglobulin resistance in both complete and incomplete Kawasaki disease, and (b) whether incidence of immunoglobulin resistance is related to the pH of the commercial brands of immunoglobulin.

Materials and Methods

A retrospective chart review of medical records was performed of patients diagnosed with Kawasaki disease (ICD 9 diagnostic code 446.10) over a 10-year period, from 2001 to 2011, at the Children's Memorial Hermann Hospital in Texas Medical Center after obtaining approval from the Institutional Review Board at the University of Texas Health Science Center at Houston (HSC-MS-07-0226).

Information on demographics and clinical course were abstracted from the medical records. Only those children who met the criteria for complete or incomplete Kawasaki disease¹ and who were treated with immunoglobulins in accordance with the published guidelines¹ at the Children's Memorial Hermann Hospital were included in the study. The diagnosis of arthritis was made upon identification of

joint swelling and/or limitation in the range of motion of the affected joint upon evaluation of a rheumatologist and/or other subspecialists based on joint swelling, or limitation in the range of joint movement along with joint pain or tenderness¹⁵ and clearly documented in the chart. Children with arthritis underwent serological tests for related infections. Diffuse swelling and erythema of the palms and soles with erythema was not considered arthritis. All Kawasaki disease children were initially treated with acetylsalicylic acid along with high-dose immunoglobulin 2 g/kg given as a single infusion over 10–12 h, and had laboratory testing done after completion of the infusion, including measurement of inflammatory markers. Any child who had persistence of fever beyond 48 h and/or required a second dose of high-dose immunoglobulin 2 g/kg after the first dose was labeled as immunoglobulin resistant¹ for this study. All Kawasaki disease children underwent serial echocardiograms with a focus on evaluating the coronary arteries. Coronary artery dilatation and aneurysms were reported based on z-scores as described by de Zorzi *et al.*¹ All clinical symptoms were assessed, including respiratory symptoms, arthritis, and mucosal and skin changes. Several clinical parameters were evaluated before the first immunoglobulin dose, along with the outcome of treatment in each patient. The days of fever and change in laboratory markers of inflammation (erythrocyte sedimentation rate [ESR] and C-reactive protein) after the first immunoglobulin dose were recorded. The data regarding the

TABLE 1. DEMOGRAPHIC AND CLINICAL FINDINGS IN CHILDREN WITH IMMUNOGLOBULIN RESPONSIVE VERSUS RESISTANT KAWASAKI DISEASE

	All	IgG responsive	IgG resistant	p-Value
Patients, <i>n</i>	80	56	24	
Age at onset, months (median, range)	27.5 (3–168)	25.5 (3–132)	37 (6–168)	0.225
Age < 6 months, <i>n</i> (%)	6 (8)	6 (11)	0 (0)	0.213
Age ≤ 6 months and < 1 year, <i>n</i> (%)	10 (13)	6 (11)	4 (17)	
Age ≥ 1 year, <i>n</i> (%)	64 (80)	44 (79)	20 (83)	
Gender, males, <i>n</i> (%)	53 (66)	37 (66)	16 (67)	0.959
Weight, kg (median, range)	13.6 (6.2–65.9)	12.3 (6.2–37.1)	14.6 (7.2–65.9)	0.084
Ethnicity, <i>n</i> (%)				0.657
African American	18 (22.5)	14 (25)	4 (17)	
Caucasian	18 (22.5)	11 (20)	7 (29)	
Hispanic	33 (41.2)	24 (43)	9 (37)	
Asian	11 (13.3)	7 (12)	4 (17)	
Fever				
Duration before IgG, days (median, range)	6 (2–35)	6.5 (2–31)	6 (3–35)	0.612
Patients with ≤ 4 days of fever before IgG (<i>n</i> , %)	7 (9)	5 (9)	2 (8)	0.650
Total duration, days (median, range)	7 (2–37)	6.5 (2–31)	9.5 (5–37)	0.017
Signs/symptoms, <i>n</i> (%)				
Fever	80 (100)	56 (100)	24 (100)	1.000
Rash	72 (90)	50 (89)	22 (92)	1.000
Adenopathy	36 (45)	27 (48)	9 (38)	0.377
Swollen hands and/or feet	34 (43)	24 (43)	10 (42)	1.000
Oral mucosal changes	59 (74)	42 (75)	17 (71)	0.698
Conjunctivitis	59 (74)	44 (79)	15 (63)	0.134
Coronary ectasia	14 (18)	4 (7)	10 (42)	0.001
Coronary aneurysm	3 (4)	0 (0)	3 (13)	0.025
Periungual desquamation	24 (30)	20 (36)	4 (17)	0.114
Respiratory distress	14 (18)	8 (14)	6 (25)	0.248
Arthritis	6 (8)	1 (2)	5 (21)	0.008
Patients with incomplete KD, <i>n</i> (%)	34 (42.5)	24 (43)	10 (42)	0.921

n, number; IgG, immunoglobulin; KD, Kawasaki disease.

brand of immunoglobulin administered were extracted from the pharmacy records for those patients.

Statistical analysis

Descriptive analysis was performed on the data using Stata v10 (StataCorp, College Station, TX). Contingency tests were used to compare categorical variables between groups. Comparison of continuous variables between groups was performed using a two-tailed *t*-test (for parametric data) and a Mann–Whitney *U*-test (for nonparametric data). Logistic regression models were fitted to evaluate the independent effect of different clinical and biochemical parameters on resistance to therapy. Statistical significance was assumed at $p < 0.05$.

Results

A total of 80 consecutive multiethnic patients with Kawasaki disease were evaluated, and their demographic and clinical data are described in Tables 1–4. Using established definitions, the cases were stratified into “complete” or “incomplete” Kawasaki disease as well as by responsiveness to immunoglobulin therapy,¹ and immunoglobulin resistance was seen in 30% of these children (Table 1). The frequency of each symptom prior to immunoglobulin therapy

is reported in Table 1. The total duration of fever from the beginning of the disease until its alleviation after immunoglobulin therapy is also reported in Table 1.

The prevalence of immunoglobulin resistance in the children with Kawasaki disease was 30%. As expected, there was a significantly longer total duration of fever in the immunoglobulin-resistant versus -responsive children. No difference was found in the duration of fever prior to immunoglobulin therapy between responsive versus resistant children. Children with a fever lasting ≤ 4 days prior to immunoglobulin therapy did not differ between the two groups either. Comparisons of laboratory findings between the immunoglobulin responsive and resistant patients were also performed (Table 2). There was no significant difference between any of the laboratory findings between the two groups prior to therapy.

Arthritis was significantly more common among the immunoglobulin-resistant children (Tables 1 and 4). Overall, the presenting signs and symptoms prior to immunoglobulin therapy were quite similar between the two groups, except for arthritis, which was significantly higher in resistant children. Further, a significantly higher number of resistant children had coronary aneurysms (3/3, 100%) and coronary ectasia (10/14, 71%) prior to immunoglobulin therapy.

The response based on the pH of the immunoglobulin was analyzed (Table 3). The pharmacy record of specific

TABLE 2. TREATMENT AND LABORATORY FINDINGS IN CHILDREN WITH IMMUNOGLOBULIN RESPONSIVE VERSUS IMMUNOGLOBULIN RESISTANT KAWASAKI DISEASE PRIOR TO THERAPY

	All	IgG responsive	IgG resistant	p-Value ^a
Erythrocyte sedimentation rate, mm/h, $n = 71$				
Pre IgG, median (IQR), $n = 71$	70 (52–97)	72 (50–97)	68 (57–97.5)	0.730
Post IgG, median (IQR), $n = 32$	97.5 (76–115.5)	92 (68–111)	108 (77–118)	0.317
Change in ESR, median (IQR), $n = 29$	14 (–4 to 23)	0 (–15.5 to 18.5)	20 (12–36)	0.064
C-reactive protein, mg/dL				
Pre IgG, median (IQR), $n = 42$	7.2 (0.02–95.0)	7.2 (0.02–95)	7.3 (0.28–24.2)	0.911
Post IgG, median (IQR), $n = 13$	2.2 (0.07–57.6)	1.7 (0.07–57.6)	11.5 (1.17–23.6)	0.770
Change in CRP, median (IQR), $n = 13$	–5.95 (–7.1 to –2.6)	–6.4 (–15.0 to –3.0)	–4.4 (–5.95 to –2.6)	0.380
Serum sodium, mEq/L (mean, SD), $n = 63$	135 (3)	135 (3)	134 (2)	0.110
Serum sodium < 133 mEq/L, n (%)	56 (100)	4 (7)	4 (17)	0.232
Serum bicarbonate, mEq/L (mean, SD), $n = 64$	22.2 (3.4)	22.3 (3.3)	21.9 (3.8)	0.648
Lactate dehydrogenase, mg/dL, median (IQR), $n = 7$	239 (169–341)	239 (4–335)	275 (189–386.5)	0.480
Aspartate transaminase, mg/dL, median (IQR), $n = 61$	34 (28–62)	32 (25–57)	47.8 (31–85)	0.053
Alanine transaminase, mg/dL, median (IQR), $n = 62$	38 (20–91)	38 (16–87)	37 (27–138)	0.219
Albumin, mg/dL, (mean, SD), $n = 59$	2.9 (0.6)	3.0 (0.6)	2.7 (0.6)	0.119
Albumin ≤ 2.9 mg/dL, n (%)	29 (49)	18 (43)	11 (65)	0.128
White blood cell count, mm ³ , median (IQR), $n = 80$	15.1 (11.3–19.3)	15.4 (11.3–19.0)	14.7 (9–20.1)	0.466
Bands, mm ³ , median (IQR)	2 (0–7)	2 (0–6)	5 (0–11)	0.267
Eosinophils, mm ³ , median (IQR), $n = 80$	1.6 (1–4)	2.3 (1–4)	1 (0.8–3.3)	0.227
Platelets, mm ³ , median (IQR), $n = 80$	424 (282.5–536)	442.5 (319–541.5)	309.5 (236.5–480)	0.065
Platelets < 100,000 mm ³ , n (%)	3 (4)	1 (2)	2 (8)	0.213
Hemoglobin, g/dL (mean, SD), $n = 80$	10.9 (1.4)	10.9 (1.4)	10.9 (1.4)	0.870

All values are from tests performed prior to immunoglobulin therapy except for ESR and CRP as stated.

^a*p*-Values for nonparametric data obtained using Mann–Whitney *U*-tests and for parametric data using *t*-tests unless otherwise stated. IQR, interquartile range; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; SD, standard deviation.

TABLE 3. THE pH OF IMMUNOGLOBULIN USED IN TREATMENT OF CHILDREN WITH KAWASAKI DISEASE

	Low pH (4.0–5.0)	High pH (6.2–7.6)	p-Value
Patients, <i>n</i>	63	16	
IgG responsive	46 (73)	9 (56)	0.193
Duration of fever prior to first IgG (IRV), days	6 (5–8)	6.5 (5–9.5)	0.602
Duration of fever prior to first IgG (IR), days	6 (4–8)	6 (5–9)	0.542
Duration of fever after first IgG (IRV), days	0 (0–1)	0 (0–1)	0.871
Duration of fever after first IgG (IR), days	3 (1–4)	2 (1–3)	0.375
Total dose of IgG, g/kg	2 (2–2.2)	2 (2–2.1)	0.712
Steroids, <i>n</i> (%)	2 (3)	3 (19)	0.054
Serum bicarbonate prior to IgG, mEq/L	22.1 (3.5)	22.5 (3.2)	0.661
Peak ESR prior to first IgG, mm/h	70 (52–106)	66 (50–92)	0.371
Change in ESR after IgG, mm/h	4 (–4 to 20)	21.5 (18.5–35)	0.048
Peak C-reactive protein, mg/dL	8.1 (3.6–12.1)	5.0 (2.1–7.8)	0.195
Coronary ectasia/aneurysm	10 (15.9)	6 (37.5)	0.080

Values in median (interquartile range) for all continuous (except serum bicarbonate, which is mean (*SD*)) or *n* (%) for categorical variables.

IRV, immunoglobulin responsive patients; IR, immunoglobulin resistant patients.

immunoglobulin brands was available for all 80 Kawasaki disease patients, along with the pH of each brand, as reported by the manufacturer. The brand types used during the 10-year study varied based on price and availability and were divided into two groups: high pH group, including Carimune (pH 6.6, *SD* 0.2, immunoglobulin A, IgA, 720 µg/mL) in 16 patients; and the low pH group, including Gamunex (pH 4–4.5, IgA 46 µg/mL) or Privigen (pH 4.6–5, IgA ≤25 µg/mL) in 63 patients.

Frequencies of symptoms and signs and distributions of biochemical parameters were compared after stratification by the pH of the immunoglobulin used for therapy. Overall, no difference was found between the two groups, although after the first dose of immunoglobulin (2 g/kg), the

low pH group showed a trend toward a larger decrease in erythrocyte sedimentation rate ($p=0.048$), a lower steroid use ($p=0.054$), and lower coronary involvement ($p=0.08$) than those in the high pH group. Furthermore, while 37.5% of the patients on high pH treatment had coronary involvement, only 15.9% of patients on low pH treatment had coronary involvement.

Finally, a multivariate logistic regression was performed to assess the independent effect of specific factors (initial ESR, initial C-reactive proteins, pH group of immunoglobulin, presence of arthritis, coronary ectasia and aneurysm, and presenting with Kawasaki disease). Results from the model showed a significant effect of coronary ectasia, where the odds of dilatation were nearly 10 times higher in patients

TABLE 4. KAWASAKI DISEASE CHILDREN WITH ARTHRITIS

Age, years	Gender	Race	Complete Kawasaki disease	Arthralgia/arthritis before Ig	Cardiac findings	ESR	Ig resistance
2	M	Hispanic	Yes	Left knee pain with limitation of motion (no swelling or redness of palms or soles)	None	50	Yes ^{a,b}
4	M	Caucasian	No	Pain and stiffness in joints (bilateral knees and shoulders, hip, neck)	Pericardial effusion (pericarditis confirmed by Gallium scan), coronary ectasia	94	Yes
4	M	Caucasian	Yes	Leg and ankle pain with limitation of motion (bilateral knee and ankles)	Coronary artery ectasia	140	Yes
4	M	Hispanic	Yes	Swollen knuckles with limitation of motion (no swelling or redness of palms or soles)	None	78	No
6	M	African American	Yes	Pain and stiffness in joints in legs and hands (no swelling or redness of palms or soles)	Coronary ectasia	65	Yes ^b
12	M	Hispanic	No	Wrist and ankle pain with limitation of motion (no swelling or redness of palms or soles)	Coronary ectasia	23	Yes

^aRe-admission for persistence of symptoms; ^btreated with steroids.
M, male.

who were resistant to therapy compared to those who were responsive (odds ratio, OR=9.97 [95% confidence interval, CI=1.37–72.32]). A second model was fitted that combined the presence of coronary dilatation or aneurysm into a single “any coronary involvement” category. The odds of “any coronary involvement” were nearly 15 times higher in patients who were resistant to therapy compared to those who were responsive (OR=5.6 [95% CI 2.1–115.9]).

Discussion

Kawasaki disease children who are resistant or refractory to initial immunoglobulin therapy with recrudescence of fever are thought to be a “hyperinflammatory phenotype” and are considered to be at a higher risk for coronary artery aneurysms^{3,16–19} and other complications.^{20,21} Several factors have been reported to be associated with refractory cases, including younger age,²² male gender,²³ earlier presentation,³ initial treatment before day 4 of fever, lower platelets,^{3,22} lower hemoglobin,^{3,24} higher white blood cell²⁵ and bands counts,³ elevated C-reactive protein^{3,19,22,24,26,27} and erythrocyte sedimentation rate,¹⁸ elevated lactate dehydrogenase,^{19,24} abnormal liver function,^{3,19,22,23,26,27} lower serum albumin^{23,28,29} and certain biomarkers,^{30–33} among others.³ Thus, failure to reduce inflammation and fever after immunoglobulin therapy are markers for immunoglobulin resistance in Kawasaki disease. Various scoring systems have been developed to detect the immunoglobulin-resistant phenotype early, but these are not interchangeable amongst different ethnic and regional backgrounds,^{5,4,22,23,34–37} possibly due to the genotypic heterogeneity. Higher transcript abundance along interleukin-1 pathway genes has been seen with immunoglobulin resistance, which may be a host-specific response.³⁰ Steroid therapy has been recommended, more so in the immunoglobulin-resistant phenotype, to reduce the incidence of coronary artery aneurysms.^{38–42} Infliximab, a monoclonal antibody against tumor necrosis factor α associated with signaling pathways of inflammation in Kawasaki disease,⁴³ has been reported to control fever in immunoglobulin-resistant children.⁴⁴

The immunoglobulin-resistant phenotype in the patients in the current study was similar to that described in previously published literature with a similar prevalence, and there were associations with a significantly longer duration of fever and a higher coronary artery involvement, signifying a hyperinflammatory status in resistant children. The prevalence of immunoglobulin resistance may differ between regions and at different time intervals.³ Similar to other studies,³ a prevalence of immunoglobulin resistance at 30% was found in the children with Kawasaki disease, without any gender or racial predilection. Several previously described risk factors in the literature associated with this phenotype were evaluated (see Tables 1 and 2). A significant association of immunoglobulin resistance with coronary artery ectasia or aneurysm was found, whereby the odds of any coronary involvement were nearly 15 times higher in patients who were resistant to therapy compared to those who were responsive. Arthritis in the acute phase and therapy with relatively higher pH immunoglobulin may be novel risk factors associated with a persistence of inflammation and possibly resistance in Kawasaki disease as seen in the present study.

Arthritis was significantly more common among immunoglobulin-resistant compared with -responsive children

(16.7% vs. 0.2%, $p=0.008$). A prevalence rate of arthritis of 6.3% was found in the acute phase of Kawasaki disease in patients in the current study, similar to a previously published report where it was 7.5%.⁷ In patients in the present study, arthritis was seen in the acute phase of Kawasaki disease prior to any immunoglobulin therapy, all in male gender, usually involving large joints, and was both oligoarticular and polyarticular (one child also had cervical arthritis). This may be explained by the fact that a higher degree of “leaky” vessels⁴⁵ would lead to more joint effusions and edema in children with immunoglobulin-resistant Kawasaki disease. Furthermore, involvement of bradytrophic cartilage within joints may represent worse inflammation that may be less responsive to immunoglobulin. An association of Kawasaki disease and arthritis is also seen in a case report in a child with coronary ectasia who had arthritis of the temporomandibular joint and cervical joint and was reported to be resistant requiring a second course of immunoglobulin and indomethacin with resolution of symptoms.⁴⁶ Arthritis in Kawasaki disease has been found to be associated with significantly increased inflammatory markers,⁷ a phenomenon that is also seen with immunoglobulin resistance, a “hyperinflammatory phenotype” as described above. Thus, the presentation of Kawasaki disease along with arthritis should alert a clinician for increasing vigilance for immunoglobulin resistance.

Although no significant difference was found in immunoglobulin responsiveness between those treated with low pH versus high pH (73% vs. 56%, $p=0.193$), a trend was found toward persistent inflammation and possibly immunoglobulin resistance (a smaller decrease in ESR, higher steroid use, and higher coronary involvement) in children treated with a relatively higher pH in comparison to low pH immunoglobulin. While 37.5% of patients on high pH treatment had any coronary involvement, only 15.9% of patients on low pH treatment had any coronary involvement. In the present study, the high pH group included Carimune (pH 6.6, *SD* 0.2, IgA 720 $\mu\text{g/mL}$) and the low pH group included Gamunex (pH 4–4.5, IgA 46 $\mu\text{g/mL}$) or Privigen (pH 4.6–5, IgA $\leq 25 \mu\text{g/mL}$). Therefore, it is possible that treatment with a relatively high pH immunoglobulin (pH >6.2) maybe associated with a higher degree of inflammatory state after therapy.

Other studies in the literature have demonstrated (although not reported as such) that a relatively higher pH immunoglobulin was associated with more immunoglobulin resistance. One study found significantly higher immunoglobulin resistance (53% vs. 20%, $p=0.001$) with Intralobulin F (pH 5.2, IgA $\leq 2,500 \mu\text{g/mL}$) in comparison to three other brands.¹² In that study, the resistance was lowest in the Gamimune-N-treated group (pH 4–4.5, IgA 270 $\mu\text{g/mL}$).¹² The investigators attributed this to the beta-propiolactone-treated immunoglobulin G, which may have low monocyte Fc receptor inhibitory activity compared to other methods of preparation.^{12,47} In another study, Iiveegam, an immunoglobulin preparation with a higher pH (pH 6.4–7.2, IgA 10 $\mu\text{g/mL}$) was shown to be associated with more resistance when compared to Gamimune-N, an immunoglobulin preparation with lower pH.¹³ Thus, therapy with a relatively higher pH immunoglobulin may be associated with persistent inflammation and possibly resistance.

Besides the pH, there may be other differences in the immunoglobulin preparations, which might affect their efficacy

in Kawasaki disease. Since the immunoglobulin brand with a high pH also had a higher IgA content relative to the low pH brands in the present study, the effect of higher incidence of coronary ectasia and an increase in erythrocyte sedimentation rate after immunoglobulin therapy could also be attributed to a higher IgA content in the immunoglobulin. A similar trend of increased immunoglobulin resistance with a higher IgA content was seen in other studies described above although not reported as such.^{12,47} More recently, a significant association between the IgG–Fc region receptor genotype and immunoglobulin response has been detected in Kawasaki disease, indicating that the responses may also be genetically mediated.⁴⁸

This study had all the limitations of a retrospectively conducted chart review study. Furthermore, the power to detect any difference in response between various pH of immunoglobulin was small due to the study's limited sample size. Other factors that may be different between different brands of immunoglobulins were not evaluated, limiting the study to the pH alone based on the hypothesis. The study also lacked longitudinal follow-up of the Kawasaki disease children after discharge. Furthermore, the significant associations that were identified with coronary involvement and arthritis were based on small samples that yielded significant yet imprecise point estimates. A multicenter trial with a sufficiently large sample size is recommended to study the incidence of refractory or resistant cases, as well as factors contributing to the resistance.

In summary, children presenting with arthritis in the acute phase of Kawasaki disease may be at risk for immunoglobulin resistance.

Acknowledgments

The project described was partially supported by Grant Number K23HL089391 (PI Monesha Gupta, MD) from the National Heart, Lung, and Blood Institute. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Heart, Lung, and Blood Institute or the National Institutes of Health.

Author Disclosure Statement

No competing financial interests exist.

References

1. Newburger JW, Takahashi M, Gerber MA, et al. Diagnosis, treatment, and long-term management of Kawasaki disease: a statement for health professionals from the Committee on Rheumatic Fever, Endocarditis and Kawasaki Disease, Council on Cardiovascular Disease in the Young, American Heart Association. *Circulation* 2004;110:2747–2771.
2. Burns JC, Capparelli EV, Brown JA, Newburger JW, Glode MP. Intravenous gamma-globulin treatment and retreatment in Kawasaki disease. US/Canadian Kawasaki Syndrome Study Group. *Pediatr Infect Dis J* 1998;17:1144–1148.
3. Tremoulet AH, Best BM, Song S, et al. Resistance to intravenous immunoglobulin in children with Kawasaki disease. *J Pediatr* 2008;153:117–121.
4. Sato S, Kawashima H, Kashiwagi Y, Hoshika A. Inflammatory cytokines as predictors of resistance to intravenous

- immunoglobulin therapy in Kawasaki disease patients. *Int J Rheum Dis* 2013;16:168–172.
5. Koyanagi H, Yanagawa H, Nakamura Y, Yashiro M. Serum C-reactive protein levels in patients with Kawasaki disease: from the results of nation-wide surveys of Kawasaki disease in Japan. *Acta Paediatr* 1997;86:613–619.
6. Wallace CA, French JW, Kahn SJ, Sherry DD. Initial intravenous gammaglobulin treatment failure in Kawasaki disease. *Pediatrics* 2000;105:E78.
7. Gong GW, McCrindle BW, Ching JC, Yeung RS. Arthritis presenting during the acute phase of Kawasaki disease. *J Pediatr* 2006;148:800–805.
8. Kawasaki T. [Acute febrile mucocutaneous syndrome with lymphoid involvement with specific desquamation of the fingers and toes in children]. *Arerugi* 1967;16:178–222.
9. Baker AL, Lu M, Minich LL, et al. Associated symptoms in the ten days before diagnosis of Kawasaki disease. *J Pediatr* 2009;154:592–595.e2.
10. Lee KY, Oh JH, Han JW, Lee JS, Lee BC. Arthritis in Kawasaki disease after responding to intravenous immunoglobulin treatment. *Eur J Pediatr* 2005;164:451–452.
11. Duzova A, Topaloglu R, Keskin M, Ozelcik U, Secmeer G, Tokgozoglu AM. An unusual pattern of arthritis in a child with Kawasaki syndrome. *Clin Rheumatol* 2004;23:73–75.
12. Tsai MH, Huang YC, Yen MH, et al. Clinical responses of patients with Kawasaki disease to different brands of intravenous immunoglobulin. *J Pediatr* 2006;148:38–43.
13. Manlhiot C, Yeung RS, Chahal N, McCrindle BW. Intravenous immunoglobulin preparation type: association with outcomes for patients with acute Kawasaki disease. *Pediatr Allergy Immunol* 2010;21:515–521.
14. Djoumerska I, Tchorbanov A, Pashov A, Vassilev T. The autoreactivity of therapeutic intravenous immunoglobulin (IVIG) preparations depends on the fractionation methods used. *Scand J Immunol* 2005;61:357–363.
15. Petty RE, Southwood TR, Baum J, et al. Revision of the proposed classification criteria for juvenile idiopathic arthritis: Durban, 1997. *J Rheumatol* 1998;25:1991–1994.
16. Sauvaget E, Bonello B, David M, Chabrol B, Dubus JC, Bosdure E. Resistant Kawasaki disease treated with anti-CD20. *J Pediatr* 2012;160:875–876.
17. Miura M, Ohki H, Tsuchihashi T, et al. Coronary risk factors in Kawasaki disease treated with additional gammaglobulin. *Arch Dis Child* 2004;89:776–780.
18. Sittiwangkul R, Pongprot Y, Silvilairat S, Phornphutkul C. Management and outcome of intravenous gammaglobulin-resistant Kawasaki disease. *Singapore Med J* 2006;47:780–784.
19. Sano T, Kurotobi S, Matsuzaki K, et al. Prediction of non-responsiveness to standard high-dose gamma-globulin therapy in patients with acute Kawasaki disease before starting initial treatment. *Eur J Pediatr* 2007;166:131–137.
20. Tsuge M, Shigemitsu Y, Yano Y, et al. Immunoglobulin resistance in Kawasaki disease with chronic granulomatous disease. *Pediatr Int* 2012;54:e32–34.
21. Kanegaye JT, Wilder MS, Molkara D, et al. Recognition of a Kawasaki disease shock syndrome. *Pediatrics* 2009;123:e783–789.
22. Egami K, Muta H, Ishii M, et al. Prediction of resistance to intravenous immunoglobulin treatment in patients with Kawasaki disease. *J Pediatr* 2006;149:237–240.
23. Sleeper LA, Minich LL, McCrindle BM, et al. Evaluation of Kawasaki disease risk-scoring systems for intravenous immunoglobulin resistance. *J Pediatr* 2011;158:831–835.e3.

24. Fukunishi M, Kikkawa M, Hamana K, et al. Prediction of non-responsiveness to intravenous high-dose gamma-globulin therapy in patients with Kawasaki disease at onset. *J Pediatr* 2000;137:172–176.
25. Durongpisitkul K, Sangtawesin C, Khongphattthanayopthin A, et al. Epidemiologic study of Kawasaki disease and cases resistant to IVIG therapy in Thailand. *Asian Pac J Allergy Immunol* 2006;24:27–32.
26. Eladawy M, Dominguez SR, Anderson MS, Glode MP. Abnormal liver panel in acute Kawasaki disease. *Pediatr Infect Dis J* 2011;30:141–144.
27. Ichihashi K, Shiraishi H, Momoi M. 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. *Cardiol Young* 2009;19:224–227.
28. Kuo HC, Liang CD, Wang CL, Yu HR, Hwang KP, Yang KD. Serum albumin level predicts initial intravenous immunoglobulin treatment failure in Kawasaki disease. *Acta Paediatr* 2010;99:1578–1583.
29. Kuo HC, Yang KD, Liang CD, et al. The relationship of eosinophilia to intravenous immunoglobulin treatment failure in Kawasaki disease. *Pediatr Allergy Immunol* 2007;18:354–359.
30. Fury W, Tremoulet AH, Watson VE, et al. Transcript abundance patterns in Kawasaki disease patients with intravenous immunoglobulin resistance. *Hum Immunol* 2010;71:865–873.
31. Suzuki H, Suenaga T, Takeuchi T, Shibuta S, Yoshikawa N. Marker of T-cell activation is elevated in refractory Kawasaki disease. *Pediatr Int* 2010;52:785–789.
32. Ogata S, Ogihara Y, Nomoto K, et al. Clinical score and transcript abundance patterns identify Kawasaki disease patients who may benefit from addition of methylprednisolone. *Pediatr Res* 2009;66:577–584.
33. Minami T, Suzuki H, Takeuchi T, Uemura S, Sugatani J, Yoshikawa N. A polymorphism in plasma platelet-activating factor acetylhydrolase is involved in resistance to immunoglobulin treatment in Kawasaki disease. *J Pediatr* 2005;147:78–83.
34. Kobayashi T, Inoue Y, Takeuchi K, et al. Prediction of intravenous immunoglobulin unresponsiveness in patients with Kawasaki disease. *Circulation* 2006;113:2606–2612.
35. Sano T, Kurotobi S, Matsuzaki K, et al. Prediction of non-responsiveness to standard high-dose gamma-globulin therapy in patients with acute Kawasaki disease before starting initial treatment. *Eur J Pediatr* 2007;166:131–137.
36. Nakano H, Ueda K, Saito A, et al. Scoring method for identifying patients with Kawasaki disease at high risk of coronary artery aneurysms. *Am J Cardiol* 1986;58:739–742.
37. Fu PP, Du ZD, Pan YS. Novel predictors of intravenous immunoglobulin resistance in Chinese children with Kawasaki disease. *Pediatr Infect Dis J* 2013;32:e319–323.
38. Ayusawa M, Sonobe T, Uemura S, et al. Revision of diagnostic guidelines for Kawasaki disease (the 5th revised edition). *Pediatr Int* 2005;47:232–234.
39. Sundel RP, Baker AL, Fulton DR, Newburger JW. Corticosteroids in the initial treatment of Kawasaki disease: report of a randomized trial. *J Pediatr* 2003;142:611–616.
40. Wooditch AC, Aronoff SC. Effect of initial corticosteroid therapy on coronary artery aneurysm formation in Kawasaki disease: a meta-analysis of 862 children. *Pediatrics* 2005;116:989–995.
41. Kobayashi T, Saji T, Otani T, et al. Efficacy of immunoglobulin plus prednisolone for prevention of coronary artery abnormalities in severe Kawasaki disease (raise study): a randomised, open-label, blinded-endpoints trial. *Lancet* 2012;379:1613–1620.
42. Ogata S, Ogihara Y, Honda T, Kon S, Akiyama K, Ishii M. Corticosteroid pulse combination therapy for refractory Kawasaki disease: a randomized trial. *Pediatrics* 2012;129:e17–23.
43. Ogihara Y, Ogata S, Nomoto K, et al. Transcriptional regulation by infliximab therapy in Kawasaki disease patients with immunoglobulin resistance. *Pediatr Res* 2014;76:287–293.
44. Burns JC, Best BM, Mejias A, et al. Infliximab treatment of intravenous immunoglobulin-resistant Kawasaki disease. *J Pediatr* 2008;153:833–838.
45. Terai M, Honda T, Yasukawa K, Higashi K, Hamada H, Kohno Y. Prognostic impact of vascular leakage in acute Kawasaki disease. *Circulation* 2003;108:325–330.
46. Jen M, Brucia LA, Pollock AN, Burnham JM. Cervical spine and temporomandibular joint arthritis in a child with Kawasaki disease. *Pediatrics* 2006;118:e1569–1571.
47. Jungi TW, Santer M, Lerch PG, Barandun S. Effect of various treatments of gamma-globulin (IgG) for achieving intravenous tolerance on the capacity to interact with human monocyte Fc receptors. A comparative study. *Vox Sang* 1986;51:18–26.
48. Shrestha S, Wiener H, Shendre A, et al. Role of activating fcgamma gene polymorphisms in Kawasaki disease susceptibility and intravenous immunoglobulin response. *Circ Cardiovasc Genet* 2012;5:309–316.

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Received for publication August 22, 2014; accepted after revision November 9, 2014.