Variability in Response to Intravenous Immunoglobulin in the Treatment of Kawasaki Disease

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Objectives To characterize the pattern of temperature response to intravenous immunoglobulin (IVIG) infusion in patients with Kawasaki disease (KD).

Study design Patients nonresponsive to IVIG (axillary temperature ≥37.5°C >24 hours after end of IVIG) were identified. Each patient with IVIG-nonresponsive KD was matched to a control patient with IVIG-responsive KD of the same age, sex, and duration of fever before IVIG. Hourly temperature profiles were obtained from immediately before the start of IVIG infusion until complete defervescence.

Results A total of 182 patients nonresponsive to IVIG were matched (total n = 364). Nonresponders were further classified as partial nonresponders (68%) (axillary temperature decreased to <37.5°C but fever recurred) and complete nonresponders (32%) (axillary temperature consistently ≥37.5°C throughout IVIG treatment). The temperature profile during IVIG infusion was similar between responders and partial nonresponders (EST: −0.061 [0.007]°C/h, $P < .001$ for responders vs EST: −0.027 (0.012)°C/h, $P = .03$ for partial nonresponders [responders vs partial nonresponders, $P = .65$]), where EST is the parameter estimate from the regression model, representing the change in degrees Celsius for each hour since start of IVIG. In complete nonresponders, IVIG was not associated with significant decreases in temperature (EST: −0.008 [0.010]°C, $P = .42$). Factors associated with complete (vs partial) nonresponse included laboratory-confirmed infection, greater C-reactive protein, and IVIG brand. Defervescence in partial nonresponders was achieved with a second IVIG dose for 72% of patients compared with 58% of complete nonresponders ($P = .001$). Complete nonresponders were more likely to develop coronary artery aneurysms vs partial nonresponders (OR: 2.4 [1.1-5.4], $P = .03$) or responders (OR: 3.2 [1.5-6.9], $P = .002$).

Conclusions Nonresponse to initial IVIG can be further characterized by temperature profile, and complete nonresponders may require more aggressive second-line therapy. *(J Pediatr 2016;179:124-30).*

Kawasaki disease (KD) is an acute pediatric vasculitis that can lead to the development of coronary artery aneurysms.[1] Treatment targeted toward the inflammatory process responsible for the clinical manifestations of KD with high-dose intravenous immunoglobulin (IVIG) is the established first-line therapy for children during the acute illness.[2-4] IVIG given within the first 10 days of illness has been shown to reduce the prevalence of coronary artery sequelae from 20%-25% in untreated patients to <5%.[4-6]

Approximately 10%-20% of patients with KD fail to respond to first-line therapy, marked by the persistence or recrudescence of fever.[7-9] These patients often receive second-line treatment, such as a second dose of IVIG or intravenous corticosteroids.[2] Nonresponsiveness to initial IVIG has been shown to result in greater risk for the development of coronary artery sequelae.[10,11]

Response to second-line therapy varies significantly between patients with nonresponse to IVIG.[12] Previous studies have not investigated the possible heterogeneity in nonresponsiveness; however, recognition of this possible heterogeneity may allow clinical prediction of the efficacy of second-line treatment and may inform therapeutic choice. We, therefore, sought to: (1) characterize the pattern of temperature changes in response to initial IVIG infusion; (2) determine whether there are distinct subpopulations of nonresponders based on patterns of temperature change after initial IVIG; and (3) determine whether response to subsequent second-line therapy is associated with a pattern of temperature change after initial therapy.

CRP	C-reactive protein
EST	Parameter estimate from the regression model, representing the change in degrees Celsius for each hour since start of IVIG
IVIG	Intravenous immunoglobulin
KD	Kawasaki disease

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Methods

Medical records of all patients diagnosed with KD at the Hospital for Sick Children, Toronto, Canada, between January 2001 and December 2013 were reviewed. The study was approved by the Hospital's research ethics board, and the requisite for individual consent was waived for the retrospective study design. Diagnosis of complete KD was defined as fever for ≥5 days in duration and the presence of at least 4 of the 5 clinical criteria: bilateral nonpurulent conjunctivitis, cervical lymphadenopathy of ≥1.5 cm, perioral edema, rash, and erythema and edema of extremities. Incomplete KD was defined as fever for ≥5 days in duration and ≤3 of 5 of the aforementioned criteria. All patients included in the study received standard first-line therapy for treatment of KD, which consisted of 2 g/kg IVIG and high-dose (80-100 mg/kg) acetylsalicylic acid. Lastly, study inclusion criteria specified that patients' temperature records were available beginning from start of initial IVIG infusion until complete defervescence.

To characterize the pattern of temperature changes in response to IVIG infusion, every recorded temperature beginning from immediately before the start of the initial IVIG infusion up until complete defervescence was obtained from the nursing flowsheet of each patient. Peak temperature before IVIG infusion, rate and timing of IVIG infusion, as well as timing and dosage of antipyretic medications also were obtained from the flowsheet. It was important to distinguish the temperature value immediately before the start of initial IVIG infusion (which we labeled as baseline temperature) from the peak temperature value before IVIG infusion because many patients had received antipyretic medications before the start of initial IVIG. Accordingly, patients' peak temperatures often decreased in response to receiving antipyretic medications, thereby lowering temperature values immediately before the start of IVIG (baseline temperature) below our definition of fever (≥37.5°C axillary measurement). Additional data that were abstracted from medical records included patient demographics, clinical features of presentation, laboratory values (immediately before initial IVIG infusion), IVIG brand, medical management, response to treatment, and coronary artery outcomes.

Patients were classified as nonresponders if they had an axillary temperature of ≥37.5°C for greater than 24 hours after the end of the initial IVIG infusion. This definition was established during collection of temperature data because nonresponsiveness often was evident at or before 24 hours after the end of initial IVIG. Although some studies suggest that axillary temperatures are less reliable than core temperatures,[13] axillary measurements are the standard at our institution and were well suited to our study objective of identifying temperature trajectories. Each IVIG nonresponder was then matched to a control patient with IVIG-responsive KD based on age, sex, and duration of fever before IVIG.

Measurement of coronary artery dimensions from echocardiography during the acute illness and then at 6- to 8-week follow-up were obtained. Patients were defined as having coronary artery abnormalities if the mean z score adjusted for body surface area was ≥2.5 in any coronary artery segment.[1] Coronary artery aneurysms were defined as body surface area-adjusted z score of +5 or more in any coronary artery branch.[14] The Pediatric Heart Network equations were used for the right coronary artery, left coronary artery, and left anterior descending artery; the Pediatric Heart Network equation for the left anterior descending branch also was used for the circumflex artery.[14] All 4 arteries were included in the maximum z-score calculation.

Continuous data are reported as means with SDs or median with IQR as appropriate depending on the variable distribution. Categorical data are reported as frequencies. Comparisons between groups were performed with linear (for continuous variables) or logistic (for binary variables) regression models with study group as an ordinal variable and IVIG responders as the reference category. The Wald χ^2 test was used to obtain the P value for the statistical significance of the differences between nonresponders and matched control patients (responders). Temperature profile over time was modeled in linear regression models adjusted for repeated measurements over time through an autoregressive covariance structure. Regression models were further adjusted for antipyretic medications, rate of IVIG infusion, and IVIG concentration. The slope of change in temperature per gram of IVIG per hour was then calculated for each group. All statistical analyses were performed with SAS, v9.3 (SAS Institute, Cary, North Carolina).

Results

A total of 1017 patients with a diagnosis of KD were seen at the Hospital for Sick Children between January 2001 and December 2013, of which 182 (18%) were nonresponsive to IVIG and met the inclusion criteria. Nonresponsive patients were then matched to 182 controls with IVIG response based on age, sex, and duration of fever before IVIG. Temperature profiles (~12 000 measurements included in the study) of response vs nonresponse over 36 hours after first IVIG shows that the responders had a statistically significant decrease in temperature per hour (−0.053 ± 0.007°C per hour, −1.9 ± 0.3°C over 36 hours, $P < .001$) and per 0.1 g/kg IVIG (−0.078 ± 0.016°C per 0.1 g/kg IVIG, −2.8 ± 0.6°C over 2 g/kg IVIG, $P < .001$), but the nonresponders did not (−0.007 ± 0.007°C per hour, −0.3 ± 0.2° over 36 hours, $P = 2.6$ and −0.031 ± 0.019°C per 0.1 g/kg IVIG, −1.3 ± 0.7°C over 2 g/kg IVIG, $P = .07$, respectively).

During collection of temperature data, 2 distinct subpopulations of nonresponders were identified on the basis of their respective temperature profiles: partial nonresponse was defined as axillary temperature decreasing to <37.5°C during IVIG infusion but then recurring, and complete nonresponse was defined as axillary temperature remaining ≥37.5°C during and after IVIG infusion. Identification of patients' subtype of nonresponse was made during collection of temperature data from the nursing flowsheets.