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Patterns of Fever in Children After Primary Treatment for Kawasaki Disease

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Background: We sought to determine if fever in the early postintravenous immunoglobulin (IVIG) time period (first 36 hours after IVIG completion) for Kawasaki disease, with or without additional infliximab, can predict IVIG resistance and coronary artery abnormalities (CAA).

Methods: Acute Kawasaki disease subjects enrolled in a clinical trial of infliximab plus IVIG (n = 96) versus placebo/IVIG (n = 94) had temperatures recorded every 6 hours after completion of IVIG infusion. Fever was defined as temperature >38.0°C; patients with persistent or recrudescent fever >36 hours after completion of IVIG were classified as IVIG resistant. Multivariable logistic regression by fever pattern was performed to predict outcomes (IVIG resistance and CAA).

Results: There was no difference in the time to defervescence between the infliximab/IVIG group (n = 96) versus placebo/IVIG group (n = 94). There was no fever after completion of IVIG in the majority of subjects [66% of those with no CAA (n = 139) and 76.5% of those with CAA, (n = 51)]. Although subjects with at least 1 fever 24–36 hours post-IVIG had a higher probability of IVIG resistance [odds ratio = 30.6 (95% confidence interval: 6.7–139.8); $P < 0.0001$], fever at 24–36 hours was not associated with higher likelihood of CAA. There were also 11% (n = 19) of IVIG responders who had fever at 24–36 hours post-IVIG. The majority of subjects with CAA (43 of 51, 84.3%) were identified by the initial echocardiogram, so the effect of fever on development of CAA could not be assessed.

Conclusions: Fever in the first 36 hours after IVIG completion is not predictive of CAA. Our data support refraining from retreatment until 36 hours after completion of IVIG.

Key Words: Kawasaki disease, fever, infliximab, intravenous immunoglobulin

Treatment with a single dose of intravenous immunoglobulin (IVIG) and high-dose aspirin results in resolution of fever in 80–90% of Kawasaki disease (KD) patients and significantly reduces the rate of coronary artery aneurysms.[1,2] However, a subset of patients who have persistent or recrudescent fever after IVIG treatment are at increased risk of developing coronary artery abnormalities (CAA),[3] and the optimal timing for additional therapies for those who are resistant to initial treatment is unclear. The American Heart Association guidelines have suggested retreatment with a second IVIG infusion for patients with fever at 36 hours after completion of the first IVIG infusion, but the optimal timing for retreatment has not been studied and remains varied in the literature with several studies providing retreatment at 24 hours after completion of the IVIG infusion.[4–7]

We recently completed a randomized, placebo controlled trial of IVIG and either placebo or infliximab for primary treatment of KD[8] and systematically recorded temperatures during hospitalization for 196 children with acute KD. We postulated that fever patterns following treatment with IVIG and/or infliximab would identify patient subsets at risk for development of CAA and IVIG resistance.

METHODS

All patients met criteria for KD according to AHA guidelines.[4,8] As per study protocol, body temperature was measured by both axillary and either oral or rectal routes just before administration of the aspirin (80–100 mg/kg/d divided every 6 hours) on a 6 AM–12 PM–6 PM–12 AM schedule. Nurses were instructed to obtain additional temperature readings if fever was suspected clinically by any route of acquisition. Subjects with temperature ≥38°C were permitted to receive acetaminophen every 4 hours as needed for fever. All patient temperature measurements by any route of acquisition were entered into the case report forms. Thermometers were provided to the family during hospitalization, and primary caregivers were instructed to take the subject's temperature once daily for 72 hours after discharge (oral, axillary or rectal). A member of the study team contacted the family 72 hours after discharge to determine if the subject had had a temperature ≥38.0°C. Parents were instructed to call study personnel if any fevers occurred in the week after hospitalization. Temperatures utilized in this analysis were obtained by oral, rectal or axillary routes, and the highest temperature was used for analysis. As per study protocol, children with persistent or recrudescent fever ($T > 38.0$°C) without another likely source >36 hours after the end of the IVIG infusion received a second dose of IVIG (2 g/kg). For purposes of this analysis, children were defined as "IVIG resistant" if they developed persistent or recrudescent fever by oral or rectal measurement without a clear alternative diagnosis at 36 hours–7 days after primary treatment. As per study protocol, these IVIG-resistant subjects received a second dose of IVIG. This analysis evaluated temperatures starting from the time of completion of IVIG during the initial hospitalization. Time to sustained defervescence after completion of IVIG was calculated for patients by treatment arms. Patients were considered to have sustained defervescence if the temperature was less than 38.0°C and remained below that level for the remainder of the hospitalization. Among 196 patients enrolled in the initial study protocol, 1 patient was withdrawn from the study as previously described[8]; 2 patients had greater than 50% missing temperature data and were excluded from data analysis. Three children received

a second infusion of IVIG before the 36-hour time point, and were excluded from statistical analyses.

Echocardiograms were obtained during the initial hospitalization and at the week 2 and 5 visits per study protocol. Patients younger than 3 years were sedated with chloral hydrate for the echocardiogram. A single echocardiographer, blinded to study arm, interpreted all echocardiograms from both centers and reported coronary artery dimensions as Z scores. Patients were classified as having normal (Z score <2.5), dilated (Z score ≥2.5) or aneurysmal (focal dilation of an arterial segment ≥1.5 times the diameter of the adjacent segment) coronary arteries based on the maximum internal diameters of the proximal right coronary artery or left anterior descending coronary artery. CAA was defined as a Z score ≥2.5 for either the right coronary artery or left anterior descending at any time point.

Statistical Analysis

Categorical data were compared between the groups by using likelihood ratio χ^2 test or Fisher exact test as appropriate. Continuous data were compared between the groups by Wilcoxon 2-sample test. The Kaplan–Meier analysis with log-rank test was used to compare time to defervescence within 36 hours following the end of the IVIG infusion between groups. Multivariable logistic regression was used to test whether subject fever patterns could predict IVIG resistance. Two-tailed P value < 0.05 was considered significant. All tests were conducted in SAS 9.3 (by SAS Institute Inc., Cary, NC).

RESULTS

Overall Fever Patterns

Patterns of fever by time point after completion of IVIG among all children (n = 190) are shown in Table 1. After completion of IVIG, 131 subjects (68.9%) had no fever after completing IVIG. Of the 190 subjects, 18 (9.5%) had fever between 0 and 12 hours after IVIG, 37 (19.5%) had fever between 12 and 24 hours and 29 (15.3%) had fever 24–36 hours after the end of IVIG. Those with no fevers after completion of IVIG were younger than those with fever after completion of IVIG [median 2.5 years (interquartile range (IQR) 1.4–4.5) vs. 3.4 (IQR 2.3–5.3)]. There was no significant difference in CAA between afebrile subjects and those with fever [39 of 131 (29.7%) vs. 12 of 59, (20.3%); P = 0.2173] in the first 36 hours post-IVIG completion.

Fever Pattern in Infliximab Versus Placebo Groups

Among the 190 subjects included in the statistical analyses, 96 children received infliximab (5 mg/kg) and 94 received placebo treatment followed by IVIG. Seventeen children [9 (53%) in the infliximab group and 8 (47%) in the placebo group] were IVIG resistant. Although subjects treated with infliximab had fewer calendar days of fever when including time during study drug and IVIG

infusion,[9] there was no significant difference in time to sustained defervescence *post-IVIG* infusion between the infliximab/IVIG and the placebo/IVIG groups [mean 11.63 ± 16.5 hours vs. 13.5 ± 21.3 hours; P = 0.8). Kaplan–Meier analysis showing probability of fever (defined as temperature >38.0°C) over time after completion of IVIG is depicted in Figure 1. There were no significant differences by arm of treatment in the frequency of patients with at least 1 fever 0–12 hours, >12–24 and >24–36 hours after completion of IVIG (data not shown).

IVIG Responder Versus IVIG Resistant Groups

There were neither significant age or gender differences between the responder and nonresponder groups nor differences in the median day of fever at time of treatment (median of 5 days in both groups). Multivariable logistic regression controlling for age, treatment arm, gender and time period of fever in the first 36 hours (0–12, 12–24, 24–36 hours) after IVIG completion was performed to test whether IVIG resistance could be predicted by fever pattern. Subjects who had at least 1 fever during the 24- to 36-hour time period post-IVIG had a higher probability of IVIG resistance [P < 0.0001, odds ratio = 36.4 (95% confidence interval: 7.9–167.8)]. Presence of fever during the 24- to 36-hour time period was not associated with a higher likelihood of CAA [odds ratio = 1.07, 95% confidence interval: 0.36–3.2; P = 0.9].

Timing of Development of CAA

The majority of children with CAA had an abnormal baseline echocardiogram obtained during the initial hospitalization (n = 43, 84.3%), making meaningful statistical association of fever pattern with the small number of remaining patients (n = 8) difficult. There were 33 patients with a baseline echocardiogram that showed dilation (with no further progression to aneurysm on subsequent studies), 9 patients with a baseline echocardiogram that showed aneurysm and 1 patient with a baseline echocardiogram showing coronary dilation that progressed to aneurysm on subsequent studies. Only 8 patients had a baseline normal echocardiogram; all developed subsequent coronary dilation but not aneurysm. Patients with CAA had a trend toward younger age (median 2.4 years vs. 2.9 in those without CAA; P = 0.059); there was no significant difference in median duration of fever at time of treatment [5 days (IQR 4–7) vs. 5 days (IQR 4–6) in those without CAA, P = 0.715]. Of 17 subjects with IVIG resistance, 3 (17.6%) had CAA at baseline and 2 (11.7%) developed new CAA.

DISCUSSION

We found no significant differences in time to sustained defervescence after completion of IVIG between subjects who received infliximab/IVIG and those who received placebo/IVIG.

TABLE 1. Fever Patterns in the First 36 Hours After Completion of Intravenous Immunoglobulin Infusion

| Total Number of Patients | Patient Status "0" = No Fever During Time Period | | No CAA n = 139 | CAA n = 51 | IVIG Resistant n = 17 |
	First 24 Hours	24–36 Hours	n (%)	n (%)	n (%)
131	0	0	92 (66.2)	39, (76.5)	5 (3.8)*
30	Febrile	0	24 (17.3)	6 (11.7)	3 (10)†
15	Febrile	Febrile	13 (9.3)	2 (3.9)	5 (33.3)‡
14	0	Febrile	10 (7.1)	4 (7.8)	4 (28.5)‡

"0" indicates that the subject had no fever during the time period and "febrile" indicates that the subject had at least 1 fever during that time point (38.0°C or higher).
*Time to recrudescence of fever post-IVIG was 38 hours, 44 hours; 3 patients required readmission for fever at 5 days, and 7 days after completion of IVIG (n = 2).
†Time to recrudescence of fever was 42 hours, 38 hours, and 7 days after completion of IVIG (readmission).
‡For IVIG-resistant subjects (n = 9), median time to fever requiring retreatment was 37 hours (IQR 36.5–39 hours post-IVIG).
CAA indicates coronary abnormalities (either coronary dilation or aneurysm); IVIG, intravenous immunoglobulin; IQR, interquartile range.
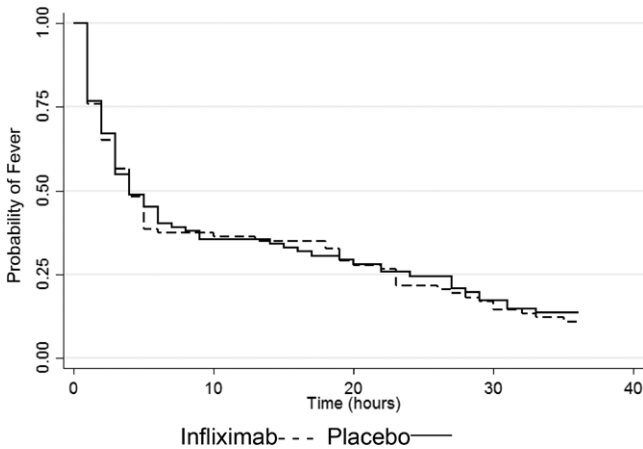
FIGURE 1. Kaplan–Meier curve showing probability of fever (defined as temperature >38.0°C by axillary, oral or rectal route) over the first 36 hours after completion of IVIG during *initial* hospitalization for treatment of KD. Resistant patients were those that developed persistent or recrudescent fever without a clear alternative diagnosis within 7 days after primary treatment and received a second dose of IVIG with or without further treatments. There was no significant difference between the infliximab (n = 96) and placebo (n = 94) groups in probability of having fever over time.

Fever during the 24–36 hours post-IVIG time period was associated with IVIG resistance; however, 11% of those who eventually responded to treatment also had fever during this time point. The majority of the children with CAA had abnormal baseline echocardiograms, so fever patterns after the completion of IVIG were less relevant as cardiac abnormalities were already apparent on the initial echocardiogram.

As per study protocol, discharge after treatment for KD was considered if there were no fevers for at least 24 hours after the completion of IVIG. We also instructed families to take the temperatures daily and called them 3 days after discharge from the hospital. Using this protocol, there were 4 patients who were readmitted for a repeat dose of IVIG. We recommend that families should be educated that it is possible that fevers may recur and that they should contact clinicians familiar with management of KD if fevers do recur within 7 days after treatment with IVIG for KD.

The AHA guidelines suggest using fever at ≥36 hours–7 days after completion of the initial IVIG infusion as the definition of IVIG resistance,[4] which was the definition chosen for our and for other recent KD clinical trials in KD.[8,10] Fever during this interval is generally assumed to reflect ongoing vasculitis, thus prompting clinicians to administer additional therapy. In Japan, scoring systems have been validated to predict IVIG resistance, but such scoring systems have had poor predictive value when applied to mixed ethnic populations of KD patients in the US.[3,11] Significant differences in definition of fever and definition of IVIG resistance may also account for some of these differences. Definition of IVIG resistance used in several scoring systems in Japan is persistent or recrudescent fever (axillary temperature >37.5°C) after 24 hours postcompletion of IVIG.[5,6] Retreatment rates in the US have varied among published reports.[12–14] Using the Pediatric Hospital Information System (PHIS) administrative database, IVIG retreatment in the US was estimated to occur in about 14.8%[12] of patients. However, the timing of retreatment is not available from PHIS. Previous reports have noted a wide variation in retreatment rates among US centers[15] and different intervals (24–72 hours after initial IVIG infusion) have been used to define IVIG resistance both in the US and in other countries.[5,15–17]

Because prolonged fever is a risk factor for development of CAA in KD,[3,11] it would seem desirable to administer treatments earlier than 36 hours based on fever patterns for those likely to require additional treatment. However, the majority of patients with CAA in this cohort had no fever at all after completion of IVIG, and although fever during the 24–36 hours post-IVIG time period was predictive of eventual nonresponse to treatment in this study, it was not associated with a higher likelihood of CAA. Furthermore, as noted in another US cohort, the majority of patients in this study with CAA (84%) had abnormalities present on the initial echocardiogram.[18] Our study lends support to the recommendation by the AHA to withhold additional therapy until 36 hours postcompletion of the IVIG infusion to prevent unnecessary retreatment. A decision to retreat based on fever at 24 hours after completion of the IVIG infusion would have led to unnecessary treatment of 19 of 172 (11%) of the responder group. The additional risk of hemolytic anemia after IVIG retreatment, which appears to be dose dependent and more common in those requiring 2 or more doses of IVIG, also favors waiting until 36 hours for retreatment.[19]

In our previous report of the clinical trial,[8] the median calendar days of fever in the infliximab group was 1 (range 0–4) compared with 2 days (range 0–6) in the placebo group (*P* < 0.0001). This reflected differences in fever duration from the time of enrollment in the trial, which also included the time before completion of IVIG and also included calendar days of fever in contrast to the more detailed temperature analysis presented here. Fever during the next calendar day after IVIG treatment in combination with laboratory testing has been identified as a risk factor for CAA, but this analysis did not include more specific time periods.[18] Due to the variability in time required to complete IVIG therapy, we did not analyze fever patterns before IVIG completion in this analysis. Thus, this analysis does not conflict with the results published with the clinical trial.

We recognize several strengths and limitations of this study. The randomized clinical trial with protocol-directed care afforded a unique opportunity to analyze fever and patient outcome in a large, well-curated dataset. The use of acetaminophen may have affected the fever patterns, although the protocol restricted its use only for children with a temperature of 38.0°C or higher. Fever is likely a surrogate for inflammation and our analysis did not include measurements of cytokines, particularly IL-1, that drives fever. Subsequent analyses of this cohort using transcript abundance and protein measurements for cytokines and their receptors may reveal more robust differences between the 2 treatment groups. To capture all data points, we included all routes of acquisition of temperature, including axillary temperatures, which tend to under-estimate fever versus core body temperatures.[20] However, the majority of axillary temperatures were obtained concomitantly with either oral or rectal temperatures as per the study protocol.

In conclusion, the majority of KD patients had no fever after completion of IVIG treatment, including those with CAA. We found that 11% of subjects who ultimately responded to the initial IVIG treatment had at least 1 fever between 24 and 36 hours post-IVIG; our findings support the current AHA recommendations to refrain from retreatment until 36 hours postcompletion of the initial IVIG infusion. Most patients with CAA had an abnormal initial echocardiogram. After discharge from hospital, parents of KD patients should be instructed to contact their physician if fever recurs within 7 days after completion of IVIG.

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