Demographic and Treatment Variability of Refractory Kawasaki Disease: A Multicenter Analysis From 2005 to 2009

abstract

OBJECTIVE: Approximately 10% to 15% of Kawasaki disease (KD) is refractory to treatment with initial intravenous immunoglobulin (IVIG). However, there is no consensus on pharmacologic treatment of refractory KD (rKD). Demographic characteristics of patients with rKD and regional variability in their treatment in the United States have not been reported on a large scale. The goal of this study was to describe the demographic and treatment variability in rKD by using a large multi-institutional database.

METHODS: Data were obtained for patients with KD from January 2005 to June 2009 by using the Pediatric Health Information System. Patients who received a single dose of IVIG were labeled as having standard KD (sKD) and those who required additional medications were labeled as having rKD.

RESULTS: Of the 5633 patients studied, 4818 (85.5%) received 1 dose of IVIG (sKD) and 815 (14.5%) received >1 medication (rKD). Median age was 30 months (interquartile range: 14–53) and 30 months (interquartile range: 15–54) for rKD and sKD patients, respectively (P = .438). No significant change was noted in the gender or ethnic distribution of patients between rKD and sKD groups. Seasonal distribution of rKD was comparable to sKD. IVIG was the most common (64.5%) initial medication chosen to treat rKD, followed by methylprednisolone (27.1%) and infliximab (8.3%); however, there was significant regional variability. Of patients with rKD, 81% required only 1 additional medication (after the initial IVIG) for treatment.

CONCLUSIONS: Patients with rKD have similar age, gender, ethnic, and seasonal distribution as sKD patients. IVIG is the most common (64.5%) initial medication chosen to treat rKD; however, there is regional variation.

INTRODUCTION

More than 3 decades have passed since the first description of Kawasaki disease (KD) in the United States in 1976.¹ Recently, the increasing incidence of KD has been reported in many countries.²⁻⁴ Overall, KD incidence in the United States has been stable (9–18 per 100,000 children <5 years of age) over the last decade according to a recent multicenter analysis.⁵ Intravenous immunoglobulin (IVIG) is the accepted first-line therapy for children with KD; however, there is no consensus for treatment of patients whose fever persists despite the initial dose of IVIG.⁶ These refractory cases represent about 10% to 15% of the entire KD population, and it has been shown that patients with refractory KD (rKD) are more prone to having coronary involvement than those with nonrefractory KD.⁷⁻⁸ Medications, including intravenous corticosteroids and infliximab, have been studied as potential...
therapies for patients with rKD; however, there is no agreement on their indications.8–13

In this study, we characterized the demographic characteristics and variability in treatment of rKD. We also identified the first medication used in the treatment of rKD; specifically, what is the first medication given when the disease is refractory to the initial dose of IVIG. The Pediatric Health Information System (PHIS) database was used to obtain administrative and pharmacy data for patients with KD from 40 free-standing children’s hospitals throughout the country from January 2005 to June 2009.

METHODS
Human Subjects Protections
The protocol for this study was reviewed and approved by the institutional review board of Children’s National Medical Center.

Data Source
Data for this study were obtained from PHIS, an administrative database that contains inpatient, emergency department, ambulatory surgery, and observation data from 43 nonprofit, tertiary care pediatric hospitals in the United States. These hospitals are affiliated with the Child Health Corporation of America (Shawnee Mission, KS), a business alliance of children’s hospitals. Data quality and reliability are assured through a joint effort between the Child Health Corporation of America and participating hospitals. The data warehouse function for the PHIS database is managed by Thomson Reuters (Ann Arbor, MI). For the purposes of external benchmarking, participating hospitals provide discharge/encounter data, including demographic characteristics, diagnoses, and procedures. Forty-two of these hospitals also submit resource utilization data (eg, pharmaceuticals, imaging, laboratory) into the PHIS. Data are de-identified at the time of data submission and are subjected to a number of reliability and validity checks before being included in the database. For this study, data from 40 hospitals were included based on completeness for analysis.

Study Design and Definitions
This retrospective, cross-sectional study included subjects who were discharged from the hospital between January 1, 2005, and June 30, 2009, with a principal diagnosis of KD (International Classification of Diseases, Ninth Revision code 446.1) and received at least 1 dose of IVIG. These dates were selected because the American Heart Association published revised guidelines6 for diagnosis and treatment of KD in 2004 and established IVIG as the standard of care for patients with KD, so we evaluated variability of treatment after the guidelines were published. To minimize coding errors, we excluded patients who did not receive IVIG and excluded patients who were transferred from other facilities.

Data were collected about patient demographic characteristics and treatment; specifically, age, gender, ethnicity, geographic region of the United States (Northeast, North-Central, South, and West), dates of admission and discharge, and number of doses of IVIG, methylprednisolone, and infliximab dispensed. Oral steroids were not included in our analysis because there are a number of indications for their use, including common conditions such as reactive airway disease, and parenteral methylprednisolone is considered the steroid of choice when treating KD.11 Drugs including cyclosporine and methotrexate were omitted as well, because it would be rare for them to be used after failure of a single dose of IVIG. We assumed that a medication associated with the encounter was administered to the patients.

KD was considered refractory if additional treatment was required after the initial dose of IVIG. Those who were treated with only 1 dose of IVIG were labeled as having standard KD (sKD). One of the aims of the study was to analyze the first medication chosen after failure of initial IVIG, so patients in whom it was not possible to decipher the order of medications were excluded from that analysis. A readmission was considered the same KD episode for the purpose of recording medications used if it occurred within 3 days of discharge. This choice was based on the assumption that a longer gap between 2 admissions might have influenced providers to choose IVIG over methylprednisolone or infliximab.

Data Analysis
Continuous variables were summarized as medians with interquartile ranges (IQRs). The Mann–Whitney U test was used for comparing central tendencies. We used the χ2 test or Fisher’s exact test for comparing proportions over time, as appropriate. A P value <.05 was considered to be significant. The results of the study were statistically analyzed with SPSS Statistics 17 for Windows (SPSS Inc, Chicago, IL).

RESULTS
A total of 5701 patients were identified during our study period. Nine patients were excluded because their disposition was not to home (8 transferred, 1 died). An additional 59 patients were
excluded because there was no IVIG associated with the encounter, yielding 5633 patients. A flowchart depicting distribution of the patient population is seen in Fig 1. Demographic characteristics are presented in Table 1. The median age of our study population was 2.5 years (range: 1 month to 19.5 years). Patients <6 months of age accounted for 8.2% of total KD patients (8.1% of sKD and 9.1% of rKD patients were <6 months age, \( P = .309 \)). The male to female ratio was 1.56:1 (1.55:1 in sKD and 1.59:1 in rKD groups; \( P = .71 \)). Seasonal distribution of rKD was similar to sKD, with a low incidence from July to September and high incidence in winter, with a peak in January (Fig 2).

Median length of stay was statistically shorter in patients with sKD (3 days; IQR: 2–4) compared with rKD (4 days; IQR: 2–6; \( P < .001 \)). A total of 304 (0.05%) patients had >1 admission during the study period for KD. Eighty-eight (28.9%) of these readmissions occurred within 3 days of discharge from initial admission. There were a total of 278 patients with 2 admissions, 24 with 3 admissions, and 1 each with 4 and 5 admissions.

Of the 5633 patients studied, 4818 (85.5%) received 1 dose of IVIG (sKD) and 815 (14.5%) received additional medications for KD treatment (rKD). Of the 815 patients with rKD, 93 were excluded from further analysis because the second KD medication given could not be identified. Of the remaining 722 patients, IVIG was the second drug of choice in 466 patients (64.5%), methylprednisolone in 196 patients (27.1%), and infliximab in 60 (8.3%) patients. Of all patients with rKD, 19% required >1 additional medication for treatment (Fig 1).

The geographic distribution of participating hospitals included 6 hospitals in the Northeast, 11 hospitals in the North-Central region, 14 hospitals in the South, and 9 hospitals in the West (regions were established in the PHIS database). There was a statistically significant (\( P = .039 \)) difference in the prevalence of rKD based on region; lowest prevalence of rKD was in the West (12.9%) compared with the highest prevalence in the South (17.2%; \( P = .039 \)) (Table 2). The most common second medication chosen for rKD was a second dose of IVIG in all regions except the Northeast, where there was a significantly higher use of methylprednisolone (55.3%; \( P < .001 \)). Also, infliximab was used at a significantly higher frequency in the

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**TABLE 1** Demographic Characteristics of the Study Population

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>sKD (n = 4818 [85.5%])</th>
<th>rKD (n = 815 [14.5%])</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male, %</td>
<td>60.8</td>
<td>61.38</td>
<td>.71</td>
</tr>
<tr>
<td>Length of stay, d (IQR)</td>
<td>3 (2–4)</td>
<td>4 (2–6)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Age, mo, median (IQR)</td>
<td>30 (15–54)</td>
<td>30 (14–53)</td>
<td>.438</td>
</tr>
<tr>
<td>Age group (% of total)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0–12 mo</td>
<td>20.3</td>
<td>22.0</td>
<td>.647</td>
</tr>
<tr>
<td>13–23 mo</td>
<td>18.8</td>
<td>19.0</td>
<td></td>
</tr>
<tr>
<td>24–59 mo</td>
<td>40.4</td>
<td>38.2</td>
<td></td>
</tr>
<tr>
<td>&gt;59 mo</td>
<td>20.4</td>
<td>20.8</td>
<td></td>
</tr>
<tr>
<td>Ethnicity (% of total)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-Hispanic white</td>
<td>38.3</td>
<td>42.1</td>
<td>.075</td>
</tr>
<tr>
<td>African American</td>
<td>20.4</td>
<td>21.2</td>
<td></td>
</tr>
<tr>
<td>Hispanic white</td>
<td>19.6</td>
<td>17.0</td>
<td></td>
</tr>
<tr>
<td>Asian</td>
<td>8.9</td>
<td>7.6</td>
<td></td>
</tr>
<tr>
<td>American Indian</td>
<td>0.2</td>
<td>0.1</td>
<td></td>
</tr>
<tr>
<td>Others</td>
<td>8.2</td>
<td>9.3</td>
<td></td>
</tr>
<tr>
<td>Missing data</td>
<td>4.4</td>
<td>2.6</td>
<td></td>
</tr>
</tbody>
</table>
West (29.2%; P < .001) compared with other regions (Fig 3).

DISCUSSION

In a recent publication, Son et al analyzed patients with KD from 2001 to 2006 from 27 hospitals by using the PHIS database; our study also used the PHIS database but included patients from 2005 to 2009 and included 40 hospitals. Son et al reported an overall increase in KD admissions from 2001 to 2006, as well as a significant increase in the use of infliximab for the treatment of KD. Similar to the current study, they reported that ~14% of patients with KD develop rKD. However, compared with the work by Son et al, our study focused on demographic and practice patterns of rKD. We characterized age, gender, ethnic, and seasonal distribution of rKD compared with sKD, and found similar characteristics. Although Son et al characterized overall trends in use of non-IVIG KD medications, we identified the first medication chosen by physicians when IVIG fails.

To the best of our knowledge, this is the first study to focus specifically on treatment variability in rKD on a large scale. We found no difference in the incidence of rKD with regard to gender, age, or ethnicity. Some of these findings are in accordance with results of studies by Do et al, Cha et al, and Durongpisitkul et al, who have reported similar age and gender distribution between rKD and sKD in Korea and Thailand. Our results contrast with other studies that have found younger age to be a predictor for rKD. We found higher prevalence of rKD in the southern region compared with the rest of the country; however, reasons for this variability are not known. Although failure to respond usually is defined as persistent or recrudescence fever >36 hours after completion of the initial IVIG infusion, there is no universal agreement on this definition. Variability in this definition may at least in part contribute to regional variation in prevalence of rKD.

Seasonal variation in incidence of KD has been described and is considered by many to be an important clue toward its etiology. Seasonality is a well-known characteristic of many infectious agents, including influenza, rotavirus, and respiratory syncytial virus in the winter and enteroviruses in the summer. Each of these occur with a predictable timing and duration every year. Our finding of identical seasonal trends in sKD and rKD perhaps points toward a common etiologic agent or a similar group of agents for these 2 conditions. In the recent years, a number of studies have shown host factors such as presence of specific genetic polymorphisms to be associated with KD. Shrestha et al have recently reported an association between IVIG refractoriness and the FCGR2B gene, which plays a role in the function of the Fc receptors, which in turn are integral to one of the proposed mechanisms of anti-inflammatory action of IVIG. A similar seasonality of rKD and sKD in our study reinforces the idea that host factors are more likely to be determinants of refractoriness of KD rather than agent factors.

This study found that most clinicians give a second dose of IVIG for cases

TABLE 2 Prevalence of rKD on the Basis of Region

<table>
<thead>
<tr>
<th>Region</th>
<th>No. of Patients (% of Study Population)</th>
<th>Prevalence of rKD, % (P = .039)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Northeast</td>
<td>679 (11.8)</td>
<td>14.6</td>
</tr>
<tr>
<td>North-Central</td>
<td>1467 (25.1)</td>
<td>14.3</td>
</tr>
<tr>
<td>South</td>
<td>1974 (39.5)</td>
<td>17.2</td>
</tr>
<tr>
<td>West</td>
<td>1513 (23.7)</td>
<td>12.9</td>
</tr>
</tbody>
</table>
of rKD; however, there was significant practice variability. Most patients with rKD (81%) required only 1 additional medication, and only 5% required >3 KD medications. We found significant regional practice variability with regard to medications used to treat rKD; specifically, increased methylprednisolone use in the Northeast and increased infliximab use in the West. This variation probably reflects opinions of experts in the region and their familiarity with use of either IVIG, infliximab, or methylprednisolone for the treatment of rKD. Data may also be influenced by previously conducted drug trials in those regions. Specifically, Burns et al. conducted a trial of infliximab for the treatment of IVIG-resistant KD and Newburger et al conducted a trial of methylprednisolone as a primary treatment of KD. The infliximab trial administered infliximab to 12 patients over 2 years, with the last enrollment being in September 2005, leading to 9 months of overlap with our study. Enrollment of methylprednisolone trial patients was concluded before the onset of our study period.

Our study must be viewed in light of some limitations. We used an administrative database, so authors did not have access to clinical features, physical examination findings, or laboratory values. Diagnosis and medication coding errors are also possible with a large database. This database includes only freestanding children’s hospitals, so results may not be truly representative of all inpatient pediatric facilities. The number of hospitals affiliated with PHIS varies from time to time, and admission rates to these tertiary care hospitals may be affected by a large number of variables. This variation makes it difficult to accurately calculate the incidence of rKD or analyze temporal trends in its management. In addition, the regional drug data might be biased secondary to medication preference in certain high-volume centers; however, PHIS prohibits analysis at an individual center level. Some patients in the study may have been transferred to these children’s hospitals after having received some form of therapy at another facility, which may introduce coding errors.

CONCLUSIONS

We described the demographic characteristics of patients with rKD in the United States by using a large multicenter database. Patients with rKD have the same age, gender, ethnic, and seasonal distribution as those with sKD. IVIG is the most common medication chosen to treat rKD (after administration of initial IVIG), although there is significant regional variation. Most patients with rKD require only 1 additional medication for treatment after the first dose of IVIG. We recommend a large multicenter prospective study to obtain more data to develop consensus for the treatment of rKD.

REFERENCES


Demographic and Treatment Variability of Refractory Kawasaki Disease: A Multicenter Analysis From 2005 to 2009
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