Use of adjunctive therapy in acute Kawasaki Disease in Latin America

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Keywords

kawasaki disease, Latin America, Steroids, infliximab, Adjunctive therapy

Abstract

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The objective was to characterize the use of adjunctive therapy in Kawasaki disease (KD) in Latin America between January 1st, 2009 and May 31st, 2017. Of these patients, 1152 received only a single dose of IVIG and 266 received additional treatment. Age at onset was similar in both groups (median 2 vs 2.2 years, respectively); the majority were male (58% vs 63.9%) and were hospitalized with the first 10 days of fever (85.1% vs 84.2%). The most common adjunctive therapy administered was steroids for IVIG-resistance, followed by additional doses of IVIG. The use of biologics such as infliximab was limited. KD patients who received adjunctive therapy were more likely to have a lower platelet count and albumin level as well as a higher Z score of the coronary arteries. This is the first report of adjunctive therapies for KD across Latin America. Future studies should address the barriers to therapy in children with acute KD throughout Latin America.

Contribution to the field

This is the first report of adjunctive therapies for KD across Latin America. This manuscript helps us to know the treatments that are used in Latin America, since they weigh without the resources, if IVIG is available, however, this study also shows the little use of biological therapy or other adjuvant treatments. Future studies should address the barriers to therapy in children with acute KD throughout Latin America

Ethics statements

Studies involving animal subjects

Generated Statement: No animal studies are presented in this manuscript.

Studies involving human subjects

Generated Statement: The studies involving human participants were reviewed and approved by ethics committee of each referral hospital. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

Inclusion of identifiable human data

Generated Statement: No potentially identifiable human images or data is presented in this study.

Data availability statement

Generated Statement: The datasets presented in this article are not readily available because only the co-authors of the different hospitals in Latin America. Requests to access the datasets should be directed to atremoulet@health.ucsd.edu.

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Keywords: Kawasaki disease, Latin America, Steroids, Infliximab, Adjunctive Therapy.

Abstract

Objective: To characterize the use of adjunctive therapy in Kawasaki disease (KD) in Latin America.

Methods: The study included 1418 patients from the Latin American KD Network treated for KD between January 1st, 2009 to May 31st, 2017.

Results: Of these patients, 1152 received only a single dose of IVIG and 266 received additional treatment. Age at onset was similar in both groups (median 2 vs 2.2 years, respectively); the majority were male (58% vs 63.9%) and were hospitalized with the first 10 days of fever (85.1% vs 84.2%). The most common adjunctive therapy administered was steroids for IVIG-resistance, followed by additional doses of IVIG. The use of biologics such as infliximab was limited. KD patients who received adjunctive therapy were more likely to have a lower platelet count and albumin level as well as a higher Z score of the coronary arteries.

Conclusion: This is the first report of adjunctive therapies for KD across Latin America. IVIG continues to be the initial and resistance treatment, however, steroids are also used; to a lesser extent, biological therapy such as infliximab. Future studies should address the barriers to therapy in children with acute KD throughout Latin America.

Introduction

Kawasaki disease (KD) is an acute systemic vasculitis in children. Recent studies have implicated inflammatory cytokines and abnormalities in immune regulation as part of the pathophysiology in KD, creating new targets for adjunctive therapy (4,5, 8, 15).

Publications about the epidemiology and even more, available drugs and treatment schedules for children with acute KD in Latin America are scarce. In one of the largest summaries of cases reported in the literature of children with KD in Mexico, only 250 children were reported in a 32 year period (17). Ulloa Gutierrez et al. found in Central America (Guatemala, El Salvador, Honduras, Nicaragua, Costa Rica, and Panama) from 2000 to 2010, only 11 reports from 4 countries, mostly consisting of single case reports and small series (18). Of all countries, Costa Rica contributed the highest number of cases (124 cases over 13 years). However, no cases were reported for Nicaragua or Guatemala. (18). The Latin American KD Network (Red de la Enfermedad de Kawasaki en America Latina, REKAMLATINA) is a standardized registry where data is retrospectively and prospectively collected from patients with acute KD throughout Latin American countries since January 2009. Demographics, clinical characteristics, laboratory evaluation, response to treatments and outcomes are gathered.

The initial and standard treatment for KD has been the use of high dose IV immunoglobulin (IVIG) in combination with aspirin (19). However, in some parts of Latin America, IVIG is not available for first line treatment of KD, and even when available it may be difficult to acquire or administer early.

In addition, although rates of IVIG resistance are unknown in Latin America, 10-20% of KD patients throughout the United States, Europe and Asia have IVIG-resistant KD, increasing the risk of developing coronary artery abnormalities (CAA) (20). It is this population in particular who may benefit from adjunctive therapy, as was recently recommended in the revised 2017 American Heart Association KD guidelines (11) . In addition, certain populations like infants with KD have a higher risk of developing CAA and thus may warrant additional adjunctive therapy (14, 21). A number of therapies exist for treating IVIG-resistant KD and those at high risk of CAA, including second dose of IVIG, steroids, infliximab, or other immunomodulatory therapies (7, 9, 22). However, treatment options are

limited in some regions of the world, including Latin America. Furthermore, as no study has determined which treatment is best for treating IVIG resistant KD or high-risk KD patients, the treatment choice is left to the treating physician. The aim of this study was to report the adjunctive therapies used to treat IVIG-resistant and high risk KD patients in Latin America.

Material and Methods

Subjects and Clinical Data

Data from patients with KD in the REKAMLATINA registry between January 1st, 2009 and May 31st, 2017 were considered for this analysis. This analysis included data from the first two multicenter studies of the network, REKAMLATINA-1 and REKAMLATINA-2. The latter retrospective study included patients who had a discharge diagnosis of classic or incomplete KD (according to the2004's AHA diagnostic criteria) and were admitted from January 1, 2009 to December 31, 2013 at each of the participant referral pediatric or general hospitals. Similarly, the REKAMLATINA-1 study enrolled KD patients but prospectively and who were admitted at any of the participant centers from June 1, 2014 to May 31, 2017. Each patient was treated and followed according to the standard protocol in each referral hospital. Data collected included age at onset, gender, clinical criteria, administered medications, response to therapy, laboratory results, echocardiographic findings, and clinical outcomes.

The internal dimension of the coronary arteries were converted to Z-scores (standard deviations from the mean normalized for body surface area) (Dimensions as published by the American Heart Association). The maximal Z score (Zmax) of the left anterior descending artery (LAD) or right coronary artery (RCA) in the first 8 weeks was calculated.

Laboratories included white blood cells count (WBC), platelet count, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), albumin, alanine aminotransferase (ALT), gamma glutamyl transpeptidase (GGT), and hemoglobin concentration normalized for age (zHgb).

IVIG resistance was defined as fever (≥38C) more than 36 hours but not more than 7 days after completion of the IVIG without another cause. For assessing IVIG resistance, we included only patients who received IVIG within the first 10 days of fever onset.

Patients were classified into 2 groups for analysis: (1) a single dose of IVIG or (2) other therapies, Which included those treated with a combination of IVIG and adjunctive therapies or only steroids.

Statistical Methods

Continuous variables were summarized as median (interquartile range [IQR], 25th–75th percentile). Categorical variables were summarized as frequencies and percentages. Demographic, clinical laboratory data, and disease outcome among the two groups were compared using the Wilcoxon Mann-Whitney test. All statistical analyses were conducted in Graph Pad Prism version 8.1.2. (available at: (https://www.graphpad.com).

Ethics

The study received Institutional Review Board approval at the University of California, San Diego as well as at each individual institution enrolling subjects in the REKAMLATINA database.

Results

A total of 1855 patients diagnosed with KD in 18 countries of Latin America were included in the Registry (Table 2), of which 437 patients were excluded due to significant lack of demographic, laboratory, treatment or echocardiographic data. Of the remaining 1418 patients, 1152 received only IVIG (81.2%) and 266 (18.8%) either IVIG in combination with adjunctive therapy or steroids alone (Figure 1). Age at onset was similar in both groups (median 2 yrs vs 2.2 yrs, respectively), average days of illness at the time of hospitalization (median 7.2 days vs. 7.3 days); the majority were male (58% vs 63.9%) and were hospitalized in the first 10 days of illness (85.1% vs 84.2%) (Table 1). There were no significant differences in the number of leukocytes, hemoglobin concentration adjusted for age, erythrocyte sedimentation rate, C-reactive protein levels, alanine aminotransferase or gammaglutamyl transpeptidase at the time of diagnosis between the two groups. As compared to KD patients treated with a single dose of IVIG, those treated with adjunctive therapies had a lower platelet count (423 vs 375, P= <0.0001) and lower albumin levels (3.3 vs 3.1, P= <0.0001) (Table 1).

In regards to treatment, 1415 (99.7%) patients were treated with IVIG and 3 (0.2%) patients received only steroids (Figure 1). In total, 263 (18.6%) KD patients received more than a single medication for treatment of KD (N=198, steroids; N=60, additional IVIG; N=5, infliximab). In 1193 (84.3%), the response to IVIG was reported. Of these, 69 (5.8%) KD patients were noted to be IVIG-resistant and the majority (N=60, 87%) were treated with two doses of IVIG, with three of those patients getting a third dose of IVIG. In the remaining cases, patients were treated with either steroids (N=4, 6.2%) or infliximab (N=5, 7.2%) as rescue therapy. The IVIG response was unknown in 222 patients, 194 of whom received adjunctive therapy with steroids. Of these, 31 (16%) were less than 12 months old and 31 (16%) had CAA at the time of admission, which could have possibly led to the use of steroids. The rationale for giving only steroids without IVIG to three acute KD patients, specifically the availability of IVIG, is unknown.

In regards to coronary artery outcome, the Zmax of the coronary arteries was higher in KD patients treated with adjunctive therapy, especially those treated in the first 10 days of illness (0.73 vs 5.07, $P < 0.0001$, Table 1).

Discussion

This is the first multinational, multicenter study to report the use of adjunctive therapies in children with KD from Latin America. While the majority of KD patients only received a single dose of IVIG, nearly 20% of patients were treated with an adjunctive therapy after receiving an initial IVIG dose (20). This is similar to what has been reported in the United States and Japan (10). Although the rationale for such adjunctive therapy was unknown in all of these patients, the reasons for some adjunctive treatment were similar to those in other parts of the world, including IVIG-resistance, young age and CAA. While steroids were the most commonly reported adjunctive therapy, additional doses of IVIG were also administered relatively frequently. This is an interesting issue given the worldwide shortage that exists of IVIG and the risk of hemolytic anemia that has been reported with increasing doses of IVIG (13). In this particular study, we did not have sufficient data to assess whether the anemia seen in some KD patients was hemolytic and whether increasing doses of IVIG were associated with a higher risk for hemolytic anemia. However, currently there is a comparative effectiveness study of second dose of IVIG versus infliximab in IVIG-resistant KD patients that is evaluating the risk of hemolytic anemia further

in KD patients (13).

In this analysis, we had a low rate of IVIG-resistance, with only 5.8% of the total patients reported as such. This is likely an underestimation of IVIG-resistance in Latin America as the worldwide rate most likely ranges from 9 to 20% (10, 23). In previous reports from Latin America, IVIG resistance was reported to be 9% (6) and in multiethnic studies from the United States, IVIG-resistance in Hispanic KD patients was found to be 15% (16). If we were to assume that 132 KD patients received adjunctive treatment with steroids because they were IVIG resistance, the IVIG-resistance rate would be 14.2% (201/1415).

In this study, 14% of KD patients were treated with steroids as adjunctive therapy, a treatment that is commonly administered worldwide in KD patients. Dominguez et al. found 7.7% of KD patients were treated with corticosteroids for resistant after a first dose of IVIG at Children's Hospital of Colorado in the United States (3). Chen et al. reported 37.4% of Chinese KD patients were treated with steroids for resistance to the first dose of IVIG (2). In the most recent epidemiological survey of KD in Japan, 13% of KD patients were reported to have received steroids with initial IVIG given a high likelihood of IVIG-resistance (10).

In our study, only five KD patients were treated with infliximab in addition to IVIG. It may be that infliximab was not available in many centers or that there was limited experience in using the drug, thus it was not the adjunctive therapy of choice. By comparison, the use of adjunctive infliximab therapy has ranged from 1.4% in Spain to 6.5% in the United States (3). In this study there were also three patients, all of whom were diagnosed in the first 10 days of illness, who were treated only with steroids (methylprednisolone at 30 mg/kg/day). Although the reason is unknown for why these patients did not receive IVIG, difficulties to acquire this drug in some regions of Latin America exist, either because it is not readily available in a timely fashion or because the cost is notcovered by insurance and requires the family to pay out of pocket, which may not be feasible.

A lower albumin and platelet count were found in those treated with adjunctive therapy. It has been reported that low albumin and platelet count increase the risk for CAA, resistance, or recurrence in KD patients from other regions (11). The later median days of illness at the time of diagnosis in this cohort as compared to other countries may explain the lower albumin levels (1, 12). Thus, these patients were likely

sicker and thus warranted a higher rate of adjunctive therapies. Additionally, it is understandable that patients receiving adjunctive therapy had a higher Zmax, in line with the revised 2017 AHA KD guidelines that recommends high-risk KD patients receive more than just a single dose of IVIG (11). This study has both strengths and limitations. This is the largest data set to be analyzed for adjunctive treatment for the care of patients with acute KD in Latin America. Second, we analyzed KD patients attended at the main pediatric or referral countries in the region across 18 countries. The lack of some data that resulted in exclusion of patients is a limitation, and also absence of consensus as to when or how use adjunctive therapies. There was also a wide variability in reporting the response to IVIG therapy, which limited our ability to calculate the exact IVIG-resistance rate. Furthermore, the lack of long-term follow-up data of patients did not allow us to study the impact of adjunctive therapies.

Conclusion

This is the first report from the Latin American KD Registry focusing on adjunctive therapies in patients with acute KD. Understanding treatment trends in Latin America could help improve the standard of care for KD patients in this region.

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Table 1 Comparison of demographic, clinical characteristics and outcome among 1418 patients with Kawasaki disease in Latin America stratified by treatment

	IVIG alone (n=1152)	**IVIG and adjunctive therapy [(A)] (n=266)**	**P value***
Age in yrs at onset	2 (1.2 to 3.8)	2.2 (1 to 4.4)	0.5029
Sex, Male	58%	63.9%	0.0810
Illness day at diagnosis	7.2 (5 to 8)	7.3(5 to 9)	0.75
Illness, day at hospitalization ≤ 10 d >10 d	85.1% 13%	84.2% 15.7%	0.1799 0.2765
White blood cell count K×10^3	14.2 (11 to 18.14)	14.5 (10.55 to 19.02)	0.8866

zHgb	-1.2 (-2.38 to 0.14)	-0.94 (-2.16 to 0.51)	0.0639
Platelet count $K\times10^3$	423 (298 to 516)	375 (262 to 453)	<0.0001
ESR mm/h	45 (30 to 56)	47.5 (28 to 54)	0.6247
CRP mg/dL	6.7 (2.47 to 12.2)	7 (2.3 to 15.8)	0.4800
ALT IU/L	41 (22 to 87.5)	42 (24 to 101.8)	0.3716
GGT IU/L	48.5 (20 to 137.3)	77 (26.2 to 176)	0.0644
Albumin mg/dL	3.3 (2.9 to 3.7)	3.1 (2.7 to 3.4)	<0.0001
Overall coronary artery outcome (Zmax)	0.8 (-0.09 to 2.05)	1.5 (0.57 to 4.3)	<0.0001
Coronary artery outcome if diagnosed ≤10 days (Zmax)	0.73 (-0.14 to 1.84)	5.07 (1.82 to 11.22)	<0.0001

298 ALT, Alanine aminotransferase; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; GGT,
299 gamma glutamyl transpeptidase; zHgb, hemoglobin concentration normalized for age. Values are
300 median (IQR) unless otherwise noted.
301 (A) Patients were treated with the following treatment combinations: two doses of IVIG, three doses

of IVIG, steroids alone, steroids and IVIG, and infliximab.

*P value Wilcoxon-Mann-Whitney test for continuous variables to compare overall difference among the 2 groups.

Data were available for the following number of patients in each variable (IVIG only; IVIG+ adjunctive therapy): Age (n= 1152; n= 266); Sex (n=669; N= 170); Illness, day at hospitalization ≤ 10 d (n= 981; 319 n= 224) and >10 d (n= 150; n=42); White blood cell count K×10 ^{3} (n=1130; n=261); zHgb (n= 1127;n= 320 262); Platelet count K×10^{3} (n= 1113; n= 260); ESR (n= 715; n= 236); CRP (n= 1022; n= 219); ALT (n= 969; n= 252); GGT (n= 316; n= 108); albumin (n= 773; n= 219); overall coronary artery outcome (n= 590; n= 86); coronary artery outcome among diagnosed ≤ 10 days (n= 502; n= 20).

Table 2. Number of patients divided by each country (1,418 total patients).

Country	Number of patients contributed
Argentina	35
Brazil	31
Chile	82
Colombia	146
Costa Rica	215
Cuba	8
Dominican Republic	21
Ecuador	56
Guatemala	25
Honduras	27
Mexico	424
Panama	153
Paraguay	9
Peru	47
Puerto Rico	14
Salvador	92
Uruguay	31
Venezuela	2

Figure 1. Initial and subsequent treatments administered to 1418 patients with acute Kawasaki disease in Latin America.

Conflicts of Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Author Contributions

B.F-R, AHT, EVB and R.U-G were responsible for data analysis and writing of the manuscript. The rest of co-authors (principal investigators and coinvestigators) revised the manuscript and made intellectual contents to it.

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Figure 1.JPEG

Figure 1. Initial and subsequent treatments administered to 1418 patients with acute Kawasaki disease in Latin America.