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Infliximab Plus Intravenous Immunoglobulin (IVIG) Versus IVIG Alone as Initial Therapy in Children with Kawasaki Disease Presenting with Coronary Artery Lesions: Is Dual Therapy More Effective?

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Abstract

Background—We previously demonstrated that 80% of KD patients who develop coronary artery lesions (CALs) have them at diagnosis. We postulated that KD patients presenting with CALs represent a group that may benefit from more aggressive initial therapy. Infliximab has been shown to decrease inflammation in KD patients when added to standard therapy. We compared outcomes of KD patients with CALs initially treated with IVIG alone versus IVIG plus infliximab.

Methods—Medical records of KD patients from 1/2009 - 7/2016 were retrospectively reviewed. CALs were defined as a LAD or RCA z-score ≥ 2.5 . KD patients with CALs on initial echocardiogram (ECHO) treated with IVIG alone were compared with those treated with IVIG plus infliximab. Clinical characteristics were compared between groups using Wilcoxon rank-sum test, chi-squared test, and Fischer's exact tests; length of stay was analyzed using log-normal regression; and need for additional therapy using logistic regression. Effect of treatment on CALs between groups was assessed using linear mixed models.

Results—Sixty-nine KD patients with CALs at presentation were included. Fifteen of 34 (44%) patients treated with IVIG alone required additional therapy compared to 4 of 35 (11%) patients treated with IVIG plus infliximab ($p = 0.003$). There were no significant differences between treatment groups for length of stay, CALs, or CRP fall.

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Conclusions—IVIG plus infliximab as initial therapy reduces the need for additional therapy in KD patients presenting with CALs. Intensified initial therapy, consisting of infliximab plus IVIG, could be considered for this group of KD patients.

Keywords

Kawasaki Disease; Infliximab; Coronary artery lesions

INTRODUCTION

Kawasaki's Disease (KD) is an acute vasculitis of unknown etiology that presents in children of all ages, but primarily occurs in children under the age of 5 years.¹ The primary blood vessels affected are the medium size arteries, most notably the coronary arteries, resulting in coronary artery lesion (CALs) in 25% of untreated patients.¹ KD is now the leading cause of acquired heart disease in children.¹ Standard therapy for patients with acute KD is treatment with intravenous immune globulin (IVIG) and aspirin which reduces the risk of CALs from 25% to 5%.² However, studies have shown that 10-38% of patients fail to respond or develop recrudescence fever; these patients are characterized as IVIG resistant and are at highest risk in developing coronary artery aneurysms and require additional therapy to interrupt the inflammatory process.^{3, 4}

In Japan, effective scoring systems have been developed to identify KD patients at high risk for IVIG resistance.⁵⁻⁷ Intensified therapy with prednisolone and IVIG in these high risk patients improved coronary artery outcomes in the study populations.^{8, 9} Efforts to identify a subset of "high risk" KD patients in more heterogeneous populations like the U.S., however, have been unsuccessful.^{4, 10} We previously demonstrated that 80% of children with KD who develop CALs have those lesions present at time of diagnosis.¹¹ We postulate that these patients likely represent a group that may benefit from more aggressive initial therapy.¹¹

Infliximab, a tumor necrosis factor (TNF) α antagonist, has been shown to be safe, well tolerated, and is used in some centers to treat IVIG resistant KD¹²⁻¹⁴. A prior study using infliximab plus IVIG as an intensification of initial therapy in KD patients has been shown to decrease fever duration, some markers of inflammation, and left anterior descending coronary artery z-scores.¹⁵ In this study, we compared KD patients with CALs at initial presentation treated with standard therapy with those treated with standard therapy plus infliximab to see if there was a reduction in IVIG resistance, decrease in length of stay, and differences in CALs changes between groups.

PATIENTS AND METHODS

Patients

All children admitted to Children's Hospital Colorado (CHCO) from January 2009 to July 2016 and diagnosed with KD by pediatric infectious disease specialist were eligible for the study. Patients were included if they had CALs present at time of diagnosis on their first echocardiogram (ECHO) prior to treatment. Medical records were retrospectively reviewed using a standardized form to collect demographic data, clinical information, ECHO findings,

and laboratory test results. Coronary artery lesions (CALs) were defined as a Boston z-score ≥ 2.5 in the right coronary artery (RCA) or left anterior descending (LAD) coronary artery. Coronary artery aneurysms were defined as Boston z-score ≥ 5.0 . Day 1 of illness was defined as the first day of fever. IVIG resistance was defined as a recrudescence of fever (temperature $\geq 38.3^{\circ}\text{C}$) from 36 hours to 7 days after completion of IVIG infusion. In our institution from 2009 - 2013, standard initial therapy for treatment of all patients with KD was IVIG (2g/kg IV over 12 hours) and high dose aspirin (80-100mg/kg/day divided every 6 hours). After 2013, clinical practice gradually changed to treating KD patients who had CALs at presentation with IVIG, high dose aspirin, and infliximab (5mg/kg as a single dose infused intravenously over 2 hours) as first line therapy, due to concern that these patients needed intensification of therapy to try to limit worsening of their CALs. Study data were collected and managed using REDCap electronic data capture tools hosted at the University of Colorado School of Medicine and the study was approved by the Colorado Multiple Institutional Review Board.¹⁶

Statistical Analysis

Data cleaning and statistical analysis were conducted using R version 3.3.2. Linear mixed models were fit using the R package *nlme*. P-values in Table 1 are the result of t-tests when mean and standard deviation are reported, Wilcoxon rank-sum tests for median and inter-quartile interval, and chi-square or Fisher's exact test for counts and percentages depending on the minimum expected cell count. The effect of treatment on length of stay was assessed with log-normal regression. The effect of treatment on need for second therapy was assessed primarily for those needing additional therapy due to fever, and for all reasons as a sensitivity analysis. Logistic regression was used to assess these binary outcomes. The effect of treatment on CRP pre and post treatment was assessed using linear mixed models, with a random intercept to account for correlation between the two measures. CRP was log-transformed due to skewness. Finally, the effect of treatment on CAL in both the LAD and RCA arteries was assessed using linear mixed models. LAD and RCA CAL measures were collected at baseline and each patient follow-up visit, with an average of 4.8 measurements per patient. To account for variation in the timing of the CAL measurement and correlation between a patient's measurements, time was treated as continuous and a spatial exponential covariance structure was implemented using days from baseline ECHO as the distance measure. Additionally, we fit a combined model including both artery measures in one outcome, modeling correlation by nesting artery within patient. Coronary artery aneurysms were compared between two treatment groups at baseline, 2, and 6 weeks. All regression models were adjusted for age and gender. Due to the inclusion criteria being defined as RCA or LAD z-score of ≥ 2.5 , the CAL models were also adjusted for which artery was measured as abnormal (RCA, LAD, or both). A significance level of 0.05 was used for hypothesis tests.

RESULTS

During the study period, 429 patients were diagnosed with KD and treated at our institution. Sixty-nine (16%) of these patients had CALs present at diagnosis prior to treatment and were included in the study. There were 34 KD patients with CALs treated with IVIG and 35

KD patients with CALs treated with IVIG plus infliximab. All patients received aspirin. Thirty (89%) of the patients treated with IVIG and aspirin alone (IVIG alone group) were treated prior to 2014 and 32 (89%) of patients treated with IVIG, aspirin, and infliximab (IVIG plus infliximab group) were treated after 2014 (Figure 1). Except for the fact that patients in the IVIG alone group were more likely to have been diagnosed before 2014, there were no differences in demographic, clinical, or laboratory characteristics between groups (Table 1). Fifteen of 34 (44%) patients treated with IVIG alone required additional therapy compared to 4 of 35 (11%) patients treated with IVIG plus infliximab (Table 2). Two patients in each group received an additional therapy because of worsening CALs (not because of return of fever). Including these patients in the analysis did not significantly change the results. Overall, the odds of needing a second treatment due to persistence or recrudescence of fever was 8.1 times higher in the treatment group that only received IVIG and aspirin (95% CI 2.26, 37.55; $p=0.003$). This effect was independent of age and sex (data not shown). Of the 15 patients who received initial therapy with IVIG alone, 9 received a second dose of IVIG (6 responded and 3 required a 3rd therapy) and 6 received infliximab (4 responded, 1 required a 3rd therapy, and 1 required 2 additional [3rd and 4th] therapies). The one patient who required a 4th therapy was the only patient who received steroids. Of the 4 patients in the IVIG plus infliximab group who required a second therapy, 2 were treated with a second dose of IVIG and 2 were treated with infliximab; none of them required a 3rd therapy.

Although not statistically significant, there was a trend towards shorter length of stay in the IVIG plus infliximab group (Table 2). There were no significant differences between treatment groups in hospital costs (data not shown), fall in CRP 24 hours post treatment, nor in overall improvement of coronary artery z-scores at 2 and 6 weeks (Table 3).

Although not statistically significant, there were more adverse events noted in the IVIG group (Table 2). Two patients in the IVIG only group experienced infusions reactions, 2 develop aseptic meningitis, and 2 developed hemolytic anemia requiring blood transfusions. One of the cases of aseptic meningitis and both cases of hemolytic anemia developed after receipt of the second dose of IVIG. One infusion reaction occurred in the IVIG plus infliximab group. No patients presented with a serious bacterial or viral infection in the 3 months after treatment in either group.

DISCUSSION

Our study suggests that IVIG and aspirin plus infliximab as initial therapy for KD patients with CALs reduces the need for additional second line therapy, thus decreasing the number of patients who are IVIG resistant. This is important as previous studies have demonstrated that KD patients who are IVIG resistant and have prolonged inflammation are at higher risk for CALs and aneurysms.¹⁷ Furthermore, coronary artery dilatation or aneurysms may lead to stenosis or thrombosis as these patients for which there are currently no known treatments.¹⁸ Therefore, it is imperative that KD patients with CALs at presentation be treated with aggressive initial therapy to diminish the inflammation associated with this disease and improve outcomes in this population.

There have been many efforts to identify high risk KD patients who have a high likelihood of being IVIG resistant in order to treat these patients more aggressively and decrease the incidence of CALs. Prior studies from Japan have resulted in successful scoring systems including the Egami, Sano, and Kobayashi scores to predict IVIG resistance.^{6, 7, 19} Unfortunately, these scoring systems have low sensitivity in heterogeneous U.S. populations and efforts to identify “high-risk,” IVIG resistant patients in North American cohorts have been unsuccessful.^{4-8, 10, 19} Our present study demonstrates that children with KD who have CALs at diagnosis have a high likelihood of IVIG resistance, as almost half of those in the IVIG alone group required a second therapy. Furthermore, a recent US study found that having a z-score ≥ 2 at presentation was predictive of future development of coronary artery aneurysms.²⁰ Our data combined with this recent study supports targeting this group of patients (those with CALs present at diagnosis) for more aggressive initial therapy.

The first use of infliximab for the treatment of KD was reported in 2004 by Weiss et al and was subsequently used in 1% of the 4811 IVIG resistant cases.^{21, 22} Infliximab is a chimeric monoclonal antibody that binds with high affinity to tumor necrosis factor (TNF)- α which is found in high levels in acute KD patients. Tremoulet et al demonstrated in a randomized double-blind, placebo-controlled trial that infliximab plus IVIG as initial intensified therapy resulted in shorter fever duration and faster normalization of inflammatory markers.¹⁵ They also demonstrated that infliximab as an intensification of initial therapy decreased LAD z-scores at week 2 but no differences were seen at week 5.¹⁵ Our findings differ as their study did not demonstrate a decrease in the number of IVIG resistant patients with use of infliximab.¹⁵ This may reflect a difference in the patient study populations. Our study was limited to patients who had CALs at initial presentation whereas Tremoulet’s study randomized all KD patients with or without CALs. As such, the Tremoulet study was likely underpowered to detect a difference in this important outcome. Together these studies support the use of infliximab as adjunctive therapy in patients with KD and provide an alternative option to the use of corticosteroids.

Prior studies have demonstrated the safety of one dose of infliximab in children with KD.^{12, 14, 15} Similarly, we did not observe any adverse events in our patients in the IVIG plus infliximab group. Nevertheless, infectious complications have been reported in patients with underlying autoimmune diseases who have been treated with infliximab, usually with multiple courses of therapy.²³ Furthermore, patients with autoimmune diseases are often treated with other immunosuppressive agents concurrently with infliximab. To date, infectious complications have not been reported in KD patients treated with one dose of infliximab in KD patients. In this study, more adverse events were noted in the IVIG group compared to the infliximab group.

Our study has several limitations. This study is a single center retrospective study. Although we used a standardized data collection form, clinical evaluations may have differed depending on the individual providers who were caring for these children. Despite efforts to standardize therapy with time, the treatment of KD patients was at the discretion of the treating providers. Most patients treated with IVIG alone presented in the earlier years of this study. Therefore, if there is an infectious KD agent, it is possible that a different strain of the KD etiological agent could have been circulating in the early versus later time period

resulting in different responses to the two therapies. Similarly, there may have been some difference between the two group that occurred during these two time periods not accountable for in our analysis. Finally, due to the relatively small sample size, the study was likely underpowered to detect differences in CALs outcomes between treatment groups and for this endpoint further investigations are needed.

In summary, in this retrospective, single-center study IVIG plus infliximab as initial therapy significantly reduced the need for additional second line therapy in KD patients presenting with CALs. A prospective, randomized controlled trial is needed to investigate the use of intensified initial therapies in this group of KD patients.

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Figure 1.
Use of IVIG and IVIG plus Infliximab as Initial Therapies in Treatment of KD Patients with CALs from 2009-2016 at Children's Hospital Colorado

Table 1

Demographic, Clinical, and Laboratory Evaluation of KD patients at diagnosis by initial treatment. Summary statistics are median (IQR) for continuous variables and count (%) for categorical variables. P-values are based on Wilcoxon rank sum tests and chi-square tests for continuous and categorical variables respectively, except for sterile pyuria where a Fisher's exact test was used. Missing observations ranged from 0 to 7 patients, except for GGT where data existed for 53 of 69 patients.

	IVIG N = 34	IVIG + infliximab N = 35	p value
Demographics			
Sex (male, %)	28 (82.4%)	26 (74.3%)	0.61
Age (median, IQR)	3.5 (1.3 - 6.1)	2.1 (0.7 - 4.5)	0.08
Age < 1 year (%)	6 (17.6%)	13 (37.1%)	0.07
Age < 6 months (%)	3 (8.8%)	8 (22.9%)	0.19
Laboratory Characteristics (median, IQR)			
CRP (mg/dL)	10.9 (5.8 – 15.2)	8.2 (5.9 – 19.8)	0.93
ESR (mm/hr)	61 (43.5 – 86.5)	59.5 (37.3 – 84.0)	0.39
WBC ($\times 10^3$ /uL)	14.7 (12.1 – 18.6)	15.9 (11.8 – 17.5)	0.91
Hg (g/dL)	11.5 (10.4 – 12.9)	10.9 (10.1 – 12.1)	0.12
Platelets ($\times 10^3$ /uL)	348 (302 – 456)	404 (318 – 468)	0.14
Albumin (g/dL)	3.3 (3.0 – 3.7)	3.4 (3.0 – 3.7)	0.92
AST (U/L)	37 (27 – 58)	48 (32 – 67))	0.18
ALT (U/L)	40 (28 – 61)	49 (23 – 74)	0.64
Bilirubin (mg/dL)	0.4 (0.3 – 0.7)	0.5 (0.3 – 0.7)	0.87
AP (U/L)	170 (135 – 228)	156 (138 – 211)	0.84
GGT (U/L)	77 (22 – 110)	46 (21 – 100)	0.96
Sterile pyuria (≥ 10 WBC/HPF, %)	3/31 (9.7%)	4/31 (12.9%)	1.00
Clinical Characteristics			
Day of Illness Treated (median, IQR)	6 (5 - 10)	7 (6 - 10)	0.37
Admit to PICU (%)	5 (14.7%)	6 (17.1%)	1.00
Complete KD (≥ 4 clinical symptoms, %)	21 (61.2%)	19 (54.3%)	0.70
LAD z-score at diagnosis (median, IQR)	3.37 (2.15, 5.41)	3.09 (2.54, 4.10)	1.00
RCA z-score at diagnosis (median, IQR)	2.89 (2.23, 4.63)	2.70 (1.19, 4.01)	0.21
Aneurysms (z-score ≥ 5 , %)	10 (28.5%)	12 (35.3%)	0.61

Table 2

Clinical Outcomes by Initial Treatment. Retreatment and adverse events were tested with Fisher's exact tests. Length of stay was modelled with log-normal regression and CRP was log transformed and modelled with a linear mixed model.

	IVIG N = 34	IVIG + infliximab N = 35	p value
Required retreatment after initial therapy (%)	15 (44.1%)	4 (11.4%)	0.003
Length of stay (days, mean, 95% CI)	5.82 (4.17, 7.47)	3.90 (2.30, 5.50)	0.12
CRP post treatment as a proportion of pre-treatment	0.43 (0.31, 0.59)	0.37 (0.29, 0.47)	0.39
Adverse events (%)	6 (17%)	1 (3%)	0.06

Table 3

Changes in coronary artery z-scores from baseline by treatment group. Estimates, 95% confidence intervals, and p-values are based on linear mixed models allowing for a quadratic trends over time by treatment group. The difference estimates, CIs, and p-values result from linear contrasts testing differences in changes from baseline between the two groups at 2 and 6 weeks.

	IVIG alone	IVIG + infliximab	Difference	p-value
All patients	N=34	N=35		
Left anterior descending artery z-score				
change at week 2	-0.09 (-1.56, 1.37)	0.08 (-1.15, 1.31)	-0.17 (-2.09, 1.74)	0.8593
change at week 6	-1.43 (-3.32, 0.46)	-0.87 (-2.50, 0.76)	-0.56 (-3.06, 1.93)	0.6582
Right coronary artery z-score				
change at week 2	-0.54 (-1.60, 0.52)	-0.60 (-1.72, 0.53)	0.06 (-1.49, 1.60)	0.944
change at week 6	-1.56 (-3.04, -0.08)	-1.81 (-3.33, -0.29)	0.25 (-1.87, 2.38)	0.8145
Combined (patient level analysis)				
change at week 2	-0.36 (-1.25, 0.53)	-0.24 (-1.07, 0.60)	0.12 (-1.10, 1.34)	0.8492
change at week 6	-1.50 (-2.69, -0.30)	-1.27 (-2.38, -0.16)	0.23 (-1.40, 1.85)	0.7865
Patients with Aneurysms (z-score > 5)	N=10	N=12		
Left anterior descending artery z-score				
change at week 2	2.05 (-0.99, 5.09)	2.40 (0.27, 4.54)	-0.36 (-4.07, 3.36)	0.8504
change at week 6	0.58 (-3.37, 4.54)	0.84 (-2.10, 3.78)	-0.26 (-5.19, 4.67)	0.9182
Right coronary artery z-score				
change at week 2	1.42 (-1.66, 4.51)	1.70 (-0.27, 3.66)	-0.27 (-3.93, 3.39)	0.8844
change at week 6	0.60 (-3.34, 4.53)	-0.92 (-3.72, 1.88)	1.52 (-3.32, 6.35)	0.5387
Combined (patient level analysis)				
change at week 2	1.77 (-0.38, 3.92)	1.96 (0.51, 3.40)	-0.19 (-2.78, 2.41)	0.8883
change at week 6	0.57 (-2.20, 3.35)	-0.00 (-2.02, 2.01)	0.57 (-2.86, 4.00)	0.7427