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ORIGINAL RESEARCH

IVIG Resistance in Kawasaki Disease: Clinical and Laboratory Risk Factors and the Potential Role of Administration Timing

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Objective: Intravenous immunoglobulin (IVIG) resistance is associated with coronary artery abnormalities in Kawasaki disease (KD) and requires additional therapy. The purpose of this study was to determine independent risk factors for IVIG resistance, investigate the response to IVIG treatment at different time points and determine whether the time option of IVIG treatment altered IVIG resistance.

Methods: The clinical data of 6264 KD patients in southwest China were analyzed retrospectively. According to the response to IVIG treatment, the patients were divided into IVIG response group and IVIG resistance group. Multiple logistic regression model was used to identify independent risk factors for IVIG resistance, and trend chi-square test was used to examine the effect of IVIG timing on IVIG resistance.

Results: Multivariate analysis showed that IVIG time, WBC, PLT, HB, ALT and Na were independently associated with IVIG resistance, and IVIG time was a key variable for IVIG resistance. In addition, these data suggested that the rate of IVIG resistance was the lowest when treated with IVIG on the seventh and eighth day of initial fever.

Conclusion: IVIG timing is a key factor in IVIG resistance. Our data suggest a lower resistance rate when IVIG is administered on the seventh and eighth day of initial fever. However, the clinical implications of delaying treatment are uncertain, and early IVIG administration remains essential to prevent cardiovascular complications. Further research is needed to validate these findings and to guide clinical practice.

Keywords: Kawasaki disease, KD, intravenous immunoglobulin time, intravenous immunoglobulin resistance

Background

Kawasaki disease (KD) is an immune-mediated self-limited acute vasculitis that primarily occurs in children under 5 years of age and affects the medium-sized arteries, especially the coronary arteries.[1,2] Coronary artery abnormalities are several dreaded complications of KD. The continuous development of coronary artery abnormalities may lead to a series of cardiovascular complications and even death.[3,4] The underlying pathogenesis of KD remains unclear, but fortunately, standardized treatment can alter the natural course of the disease.[5] According to the American Heart Association (AHA) guidelines, the standardized

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treatment in the acute phase of KD is treatment with intravenous immunoglobulin (IVIG) combined with aspirin, which improves symptoms, reduces inflammation, and inhibits coronary artery lesions.[6] However, approximately 10–20% KD patients exhibit IVIG resistance and require additional therapy, which increases the risk of blood disease transmission, increases the financial burden of the patient, and more importantly, increased risk of coronary artery abnormalities.[7–9]

IVIG resistance should be considered if fever persists 36–48 hours or recurrences occur within 2 weeks after administration.[10] Currently, multiple studies have shown that therapy intensification strategies for high-risk patients with IVIG resistance, such as corticosteroid or infliximab combination with initial therapy, can shorten the time of fever and reduce the need for additional therapy.[11,12] Although Japan has developed a variety of scoring systems to predict IVIG resistance, this does not apply to other countries and regions.[13–15] Currently, multiple studies have shown that therapy intensification strategies for high-risk patients with IVIG resistance, such as corticosteroid or infliximab combination with initial therapy, can shorten the time of fever and reduce the need for additional therapy.[11,12] However, therapy intensification strategies have been associated with increased side effects and treatment costs. In addition, systemic inflammation, as indicated by prolonged fever duration, correlates with disease severity and endothelial dysfunction in KD. IVIG administration, by interrupting this inflammatory cascade, may improve therapeutic responsiveness, whereas delayed treatment risks overwhelming the anti-inflammatory effects of IVIG. Given this background, it is worth exploring how to gain benefits without therapy intensification strategies.

Therefore, this study aims to determine independent risk factors for IVIG resistance, investigate the response to IVIG treatment at different time points and determine whether the time option of IVIG treatment altered IVIG resistance.

Methods

Study Design and Participants

This study was a multi-center retrospective cohort study that retrospectively analyzed all hospitalized patients in 6 hospitals in southwest China: Children's Hospital of Chongqing Medical University, Kunming Children's Hospital, Guiyang Maternal and Child Health Care Hospital, Chongqing University Three Gorges Hospital, Chengdu Women's and Children's Central Hospital, Dazu Hospital of Chongqing Medical University. Data on all patients with KD from 2015 to 2019 at these hospitals were initially screened based on the following criteria: 1) were treated with IVIG; 2) age<18 years old; 3) confirmed diagnosis of KD. According to the AHA guidelines, in addition to persistent fever, KD is also accompanied by principal clinical features such as mucosal changes, conjunctivitis, polymorphous rash, extremity changes and lymphadenopathy. Classic KD is diagnosed when patients meet 4 or more principal clinical features, and incomplete KD is diagnosed in patients with fewer than 4 principal clinical features but with corresponding laboratory examination and echocardiography changes.[6] Patients with incomplete clinical data or with other cardiovascular disease were excluded from this study. This study was approved by the Ethics Committee of Children's Hospital of Chongqing Medical University and each individual participating center, and informed consent was obtained from the guardians of all participants.

Data Collection

From the electronic medical records system, we collected demographics and medical treatment data (age, sex, IVIG time and IVIG resistance). For each participant, the following laboratory variables were collected before IVIG treatment: white blood cells (WBC), platelets (PLT), hemoglobin (HB), neutrophil to lymphocyte ratio (NLR), erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), albumin (ALB), alanine aminotransferase (ALT), aspartate aminotransferase (AST) and sodium (Na). Baseline time was defined as the first day of fever.

Statistical Analysis

For categorical variables, data are presented as numbers (proportions) and compared using chi-square tests, for continuous variables, data were presented as mean ± SD or median (interquartile) and compared using Student's *t* test (for normal distributions) or the independent Mann–Whitney *U*-test (for non-normal distributions). When IVIG time was a continuous variable, Multiple logistic regression model was used to identify independent risk factors for IVIG resistance. When IVIG time was a categorical variable, trend chi-square test was used to examine the effect of IVIG

timing on IVIG resistance. All statistical analysis was performed using SPSS 26.0 software (SPSS, Inc., Chicago, USA) and P<0.05 was considered statistically significant.

Result

Patients' Characteristics

A total of 6264 patients with KD were included in this study. The basic characteristics of the patients were similar in each individual participating center. There were 3897 male patients with an average age of 2.54 years (standard deviation=2.01). Among these, 325 patients developed IVIG resistance, and the rate of IVIG resistance was 5.19%.

Independent Risk Factors Associated with IVIG Resistance in KD Patients

As shown in Table 1, when IVIG time was used as a continuous variable, there were significant differences in the following variables between IVIG response group and IVIG resistance group, including IVIG time, WBC, PLT, HB, NLR, CRP, ALB, ALT, AST and Na ($P < 0.05$). To identify independent risk factors associated with IVIG resistance, the variables with obvious differences in univariate analysis were further subjected to multiple logistic regression analysis. Multivariate logistic regression analysis revealed that IVIG time, WBC, PLT, HB, ALT and Na were independently associated with IVIG resistance. IVIG time (odds ratio 0.894; 95% confidence interval 0.834–0.959), WBC (odds ratio 1.025; 95% confidence interval 1.006–1.045), PLT (odds ratio 0.998; 95% confidence interval 0.997–0.999), HB (odds ratio 0.975; 95% confidence interval 0.966–0.984), ALT (odds ratio 1.001; 95% confidence interval 1.001–1.002) and Na (odds ratio 0.895; 95% confidence interval 0.865–0.926) were significantly associated with IVIG resistance after adjusting for confounders (Table 2).

Association between the Time Option of IVIG Treatment and IVIG Resistance in KD Patients

Table 3 showed the relationship between IVIG treatment at different time points and IVIG resistance. The time distribution of IVIG treatment was as follows: 9 cases on the second day, 84 cases on the third day, 312 cases on the fourth day, 1432 cases on the fifth day, 1619 cases on the sixth day, 1061 cases on the seventh day, 653 cases on the eighth day, 359 cases on the ninth day, 263 cases on the tenth day and 472 cases after the tenth day. The rate of IVIG

Table 1 Comparison of Clinical Variables Between IVIG Response and IVIG Resistance Group

Characteristics	IVIG Response Group (N=5939)	IVIG Resistance Group (N=325)	P value
Sex, male (%)	3685 (62.0)	212 (65.2)	0.246
Age (year)	2.54 ± 2.00	2.56 ± 2.15	0.869
KD classification, Classic KD (%)	4083 (68.7)	214 (65.8)	0.272
IVIG time (day)	6 (5–8)	6 (5–7)	< 0.001*
WBC (*10^9/L)	13.59 (10.35–17.40)	14.37 (10.75–19.01)	0.013*
PLT (*10^9/L)	408.25 ± 158.80	358.85 ± 166.63	< 0.001*
HB (g/L)	197.54 ± 13.60	104.78 ± 12.43	< 0.001*
NLR	2.52 (1.48–4.45)	4.57 (2.46–8.54)	< 0.001*
ESR (mm/1hr)	66.86 ± 22.99	67.10 ± 30.24	0.885
CRP (mg/L)	63.85 ± 50.54	76.74 ± 48.29	< 0.001*
ALB (g/L)	36.09 ± 5.14	34.46 ± 5.54	< 0.001*
ALT (U/L)	29.40 (19.40–51.50)	45.10 (25.00–109.95)	< 0.001*
AST (U/L)	28.80 (20.90–41.70)	37.00 (25.50–83.30)	< 0.001*
Na (mmol/L)	136.75 ± 3.20	135.16 ± 3.16	< 0.001*

Notes: *p < 0.05.

Abbreviations: IVIG, Intravenous immunoglobulin; WBC, White blood cells; PLT, Platelets; HB, Hemoglobin; NLR, Neutrophil to lymphocyte ratio; ESR, Erythrocyte sedimentation rate; CRP, C-reactive protein; ALB, Albumin; ALT, Alanine aminotransferase; AST, Aspartate aminotransferase; Na, Sodium.

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Table 2 Multiple Logistic Regression Analysis on Variables for the Prediction of IVIG Resistance

Variables	Odds Ratio	95% Confidence Interval	P value
IVIG time	0.894	0.834–0.959	0.002
WBC	1.025	1.006–1.045	0.010
PLT	0.998	0.997–0.999	< 0.001
HB	0.975	0.966–0.984	< 0.001
NLR	1.003	0.999–1.008	0.158
CRP	–	–	–
ALB	–	–	–
ALT	1.001	1.001–1.002	0.001
AST	–	–	–
Na	0.895	0.865–0.926	< 0.001

Abbreviations: IVIG, Intravenous immunoglobulin; WBC, White blood cells; PLT, Platelets; HB, Hemoglobin; NLR, Neutrophil to lymphocyte ratio; CRP, C-reactive protein; ALB, Albumin; ALT, Alanine aminotransferase; AST, Aspartate aminotransferase; Na, Sodium.

Table 3 The Association of Treatment Time with IVIG Resistance

Time Option of IVIG	IVIG Response (N=5939)	IVIG Resistance (N=325)
2nd	5	4
3rd	72	12
4th	279	33
5th	1322	110
6th	1551	68
7th	1035	26
8th	637	16
9th	344	15
10th	256	7
> 10th day	438	34

resistance was 0.444 on the second day of initial fever, and the lowest was 0.025 on the seventh and eighth days. Before fever for 7 days, the earlier treatment, the higher IVIG resistance rate, and after fever for 8 days, the IVIG resistance rate increased significantly after delayed treatment (Figure 1). On univariate analysis, the time option of IVIG treatment was

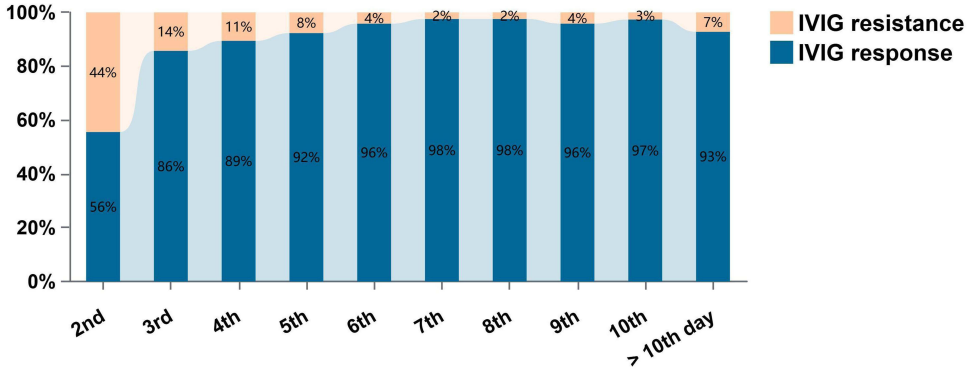

Figure 1 Temporal Dynamics of IVIG Resistance and Response.

a critical determinant of IVIG resistance ($P < 0.05$). IVIG resistance was funnel-shaped, and early or delayed IVIG treatment had a higher resistance rate.

Discussion

KD remains a significant cause of acquired heart disease in children, particularly affecting the coronary arteries.[16] The standard treatment for KD involves IVIG combined with aspirin; however, approximately 10–20% of patients do not respond to IVIG, necessitating additional treatments. The objective of our study was to identify independent risk factors for IVIG resistance and to investigate the response to IVIG treatment at various time points for clinical reference.

The existing IVIG resistance risk scores exhibit limited generalizability across racial or ethnic populations and geographic regions, necessitating region-specific models to optimize predictive accuracy.[17] Our multicenter study in Southwest China identified six independent predictors of IVIG resistance: IVIG time (odds ratio 0.894; 95% confidence interval 0.834–0.959), WBC (odds ratio 1.025; 95% confidence interval 1.006–1.045), PLT (odds ratio 0.998; 95% confidence interval 0.997–0.999), HB (odds ratio 0.975; 95% confidence interval 0.966–0.984), ALT (odds ratio 1.001; 95% confidence interval 1.001–1.002) and Na (odds ratio 0.895; 95% confidence interval 0.865–0.926). These findings demonstrated substantial overlap with key predictors in established IVIG resistance models,[18,19] yet introduced a novel clinical dimension: the therapeutic timing window of IVIG administration.

Crucially, while WBC, PLT, Hb, ALT, and Na represent non-modifiable clinical parameters reflecting disease severity, IVIG time emerges as a modifiable treatment-related factor directly influencing outcomes. Statistical analysis revealed differential predictive power: the IVIG time-derived odds ratio (OR) exhibited greater discriminatory ability. Moreover, unlike laboratory parameters, IVIG time is a modifiable factor directly influenced by clinical decisions. Earlier treatment (<5 days) correlated with higher resistance rates (Figure 1), aligning with prior studies linking premature administration of IVIG to poor outcomes. Laboratory markers, such as elevated WBC, low PLT and low Na, reflect disease severity but lack actionable thresholds for optimizing IVIG timing. Additionally, for the first time, our findings revealed the therapeutic timing window of IVIG administration: the seventh and eighth day of initial fever to reduce IVIG resistance in Kawasaki disease. The large cohort strengthens this evidence, addressing variability in smaller studies.

IVIG treatment could effectively reduce inflammation. A retrospective study found that patients treated with IVIG within 10 days had a significantly lower risk of developing coronary artery abnormalities than those treated with IVIG after 10 days.[20] The AHA guidelines recommend timely IVIG treatment for KD patients within 10 days. IVIG time played an important role in the treatment of KD. In this study, we found that IVIG time was a key variable for IVIG resistance and the rate of IVIG resistance was the lowest when treated with IVIG on the seventh and eighth day of initial fever. We speculated that this observation may be related to the inflammatory dynamics of KD. Although the specific pathological mechanism of KD was still unclear at present, Lau et al established a KD coronary arteries mouse model to detect the effect of IVIG and demonstrated that IVIG inhibits inflammation in a dose-dependent manner.[21] The peak of KD inflammation is around 10 days, and early or late use of IVIG may not be effective.[6,22] Previous studies have also confirmed that the IVIG resistance rate in the early treatment group was significantly higher than that in the conventional treatment group.[23] However, it is crucial to emphasize that our findings are observational and should not be interpreted as a recommendation to delay IVIG treatment. Early IVIG administration remains crucial for reducing the risk of cardiovascular complications, as per current guidelines.

This study still has some limitations. First of all, this study is a retrospective study with selection bias. Second, this study mainly collected data on Kawasaki disease in southwest China, which may not serve as a population-wide risk assessment, and this needs to be supported by further big data.

Conclusions

IVIG timing emerged as a key variable influencing IVIG resistance. Our data suggest that the rate of IVIG resistance was lowest when treatment was administered on the seventh and eighth day of initial fever. However, it is crucial to interpret these findings with caution. Although the data indicate a lower resistance rate at these time points, it remains unclear whether actively delaying treatment in patients who meet criteria earlier would be beneficial or harmful. Therefore, we

advise against interpreting these results as a recommendation to delay IVIG treatment, and they should be considered preliminary and require further validation in different populations and scenarios.

Data Sharing Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Ethical Approval

This study was performed in line with the principles of the Declaration of Helsinki. Approval for this study was obtained from the Ethics Committee of the Chongqing Medical University Children's Hospital and each individual participating center.

Consent for Publication

Informed consent was obtained from the guardians of all patients.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare no conflicts of interest in this work.

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