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Early Immunoglobulin Therapy and Outcomes in Kawasaki Disease

A Nationwide Cohort Study

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Abstract: Kawasaki disease is the leading cause of acquired heart disease among children in most industrialized countries; however, only few descriptive studies have discussed the pros and cons of early immunoglobulin therapy. This study aimed to see the effect of early immunoglobulin therapy on Kawasaki disease outcomes.

Patients who received immunoglobulin therapy for the first time were enrolled. Basic data were analyzed for descriptive epidemiology. If there was no prescription of antipyretics 4 to 12 days before admission, those patients were regarded as early immunoglobulin therapy group. The risk for acute aneurysm, requiring long-term anticoagulant therapy and recurrence rate were compared.

Of 5235 patients with first attack of Kawasaki disease, 1156 received early immunoglobulin therapy. The odds ratios for acute aneurysm and needing long-term anticoagulant therapy were 0.99 (95% confidence interval [CI], 0.75–1.29) and 1.06 (95% CI, 0.86–1.31), respectively. The recurrence rate was higher for the early immunoglobulin therapy group, with an adjusted hazard ratio of 1.38 (95% CI, 1.29–1.47).

Early immunoglobulin therapy might not be beneficial for the coronary outcomes of children with Kawasaki disease in this observational study. On the contrary, it might be associated with higher recurrence rate. A randomized controlled study comparing early and late intravenous immunoglobulin therapy would have probably brought relevant results.

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Abbreviations: ATC = anatomical therapeutic classification, IVIG = intravenous immunoglobulin, NHIRD = National Health Insurance Research Database, NHRI = National Health Research Institutes.

INTRODUCTION

Kawasaki disease is now the leading cause of acquired heart diseases among children in most industrialized countries.[1–9] It is a systemic vasculitis that predominantly involves the coronary arteries. It can cause coronary aneurysms in the acute phase and induce long-term sequelae-like coronary stenosis or obstruction.[10–12]

For the treatment, most physicians follow the guidelines endorsed by the American Heart Association and American Academy of Pediatrics.[13] In the guidelines, intravenous immunoglobulin (IVIG) is considered the most effective therapy for acute Kawasaki disease. As regards the timing of IVIG therapy, the guidelines suggest that ''therapy should be instituted within the first 10 days of illness and, if possible, within 7 days of illness. However, treatment of Kawasaki disease before day 5 of illness appears no more likely to prevent cardiac sequelae than does treatment on days 5 to 7, but it may be associated with an increased need for IVIG retreatment.''[13] This recommendation is based on 2 observational studies. One is a questionnaire study from Japan,[14] whereas the other is a single-institution research in Hong Kong.[15] Nevertheless, there is still 1 study concluding that early IVIG therapy was associated with better coronary outcomes.[16]

Although several more studies with similar conclusions have been published in recent years,[17–19] a nationwide longitudinal cohort study is still lacking. This study aimed to elucidate from a nationwide perspective the associations between early IVIG therapy and outcomes of Kawasaki disease.

METHODS

This nationwide retrospective cohort study used data from the National Health Insurance Research Database (NHIRD). Although the National Health Insurance program was started in 1995 in Taiwan, the NHIRD for 1995 and 1996 are incomplete. Thus, data from 1997 to 2008 were analyzed. The claims data of in-patient expenditure by admissions (DD files), details of in-patient orders (DO files), ambulatory care expenditure by visit (CD files), and details of ambulatory care orders (OO files) were retrieved. The registries for contracted medical facilities (HOSB) and for beneficiaries (ID) files were also acquired.

For this research, children who were admitted for IVIG therapy for the first time with the main diagnosis of Kawasaki disease were enrolled. Main diagnosis of Kawasaki disease was defined as the first or second diagnosis code of International Classification of Diseases, 9th Revision, Clinical Modification 446.1. Patients were regarded as receiving IVIG therapy if medications of anatomical therapeutic classification (ATC) code J06BA02 were found in their in-patient order. Children
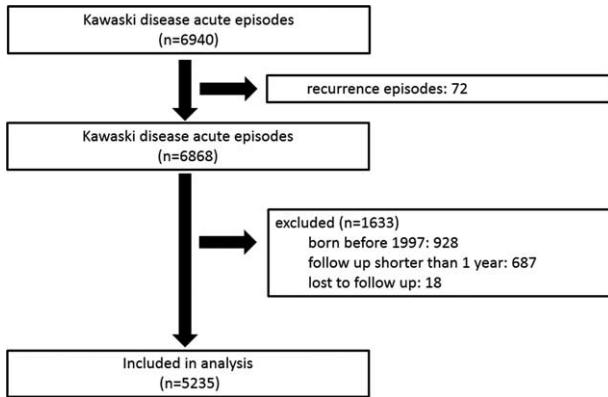
FIGURE 1. The composition of study cohort.

TABLE 1. Demographic Data of the Patients

	Short Fever Duration (<5 Days) (%)		Ordinary Fever Duration (≥5 Days) (%)		P Value
n	1156		4079		
Age group (y)					
0–1	633	54.8	1644	40.3	<0.001
1–2	282	24.4	1257	30.8	
2–3	126	10.9	627	15.4	
3–4	59	5.1	262	6.4	
4–5	33	2.9	144	3.5	
>5	23	2.0	145	3.6	
Sex					
Female	427	37.0	1532	37.6	0.76
Male	726	63.0	2543	62.4	
Congenital heart disease					
With	33	2.9	106	2.6	0.61
Without	1123	97.1	3973	97.4	
Hospital levels					
Medical centers	738	63.8	2631	64.5	0.68
Regional hospitals	418	36.2	1448	35.5	

born before 1997 were excluded because whether or not they received IVIG for the first time could not be clarified. Patients who were not followed up until the end of 2008 were regarded as censored cases and were not included in the data analysis. Children who were followed up for <1-year were also excluded.

The febrile duration was defined as the date of prescribing acetaminophen (ATC code N02BE) or nonsteroidal anti-inflammatory drugs (ATC code M01A) and the date of admission. Information regarding age, sex, hospital levels, and congenital heart disease were also collected as covariates. If there was no prescription of antipyretics 4 to 12 days before admission, those patients were regarded as patients with fever duration <5 days and were grouped as early IVIG therapy group.

Outcome analysis included recurrence, acute coronary aneurysms, long-term anticoagulant use, and IVIG nonresponsiveness. Patients were defined as Kawasaki disease recurrence if they received IVIG therapy for Kawasaki disease again >30 days after the first admission. Acute coronary aneurysm was defined if the diagnostic codes included International Classification of Diseases, 9th Revision, Clinical Modification 414.11. Because there was no chart information in the insurance claims data, IVIG nonresponsiveness was analyzed in a subset of patients who were <2 years old, considering the clarity of outcome definition, and defined as total dosage of IVIG >30 g in 1 admission or readmission for IVIG therapy within 30 days after the first admission. This definition method has been published for claims data analysis previously.[20]

Chi-square tests were applied for categorical data comparison. For categorical outcomes, crude odds ratio with confidence intervals were calculated first. Then, multiple logistic regression models were applied to adjust for possible confounding factors. The Kaplan–Meier method was used to compare the recurrence rate and the Cox regression model was then applied for covariate adjustments for the time-dependent outcomes. The SAS version 9.3 for Windows (SAS Institute, Inc., Cary, NC) was applied for data analysis, whereas the SPSS version 18.0 for Windows (SPSS, Inc., Chicago, IL) was used for survival curves. Statistical significance was set at $P < 0.05$.

According to the NHIRD, data that could be used to identify patients or care providers, including medical institutions and physicians, were scrambled before being sent to the National Health Research Institutes (NHRI) for database construction, and further scrambled before being released to individual researchers (http://nhird.nhri.org.tw/en/Data_Protection.html). The Taiwan's computer-processed personal data protection law and related regulations of the National Health Insurance Administration

and the NHRI of Taiwan were strictly followed. The protocol was reviewed and approved by the NHRI before data release. The institutional review board of Taichung Veterans General Hospital approved the study protocol.

RESULTS

There were 6940 acute episodes of Kawasaki disease in the NHIRD database between 1997 and 2008. Among them, 72 recurrent episodes, 928 children born before1997, 687 children with follow-up time <1 year, and 18 children lost to follow-up were excluded. Based on the demographic data of the 5235 children enrolled for analysis (Figure 1), those with short fever duration were significantly younger (Table 1).

Risk for Recurrence of Kawasaki Disease

The cumulative recurrence rate for children with short fever duration before immunoglobulin therapy was significantly higher (Figure 2). The estimated hazard ratio was 1.44 (95% confidence interval 1.35–1.54). After adjusting for possible confounding factors (eg, age, sex, level of hospital, and congenital heart diseases) using a multivariate Cox regression model, short fever duration before immunoglobulin therapy remained a significant risk factor for recurrence (Table 2).

Acute Aneurysm and Long-Term Anticoagulant

A multiple logistic regression model was applied to analyze the risk factors for requiring long-term anticoagulant treatment. Short fever duration did not significantly correlate with acute aneurysm formation, but treatment in a medical center had a significantly protective effect (Table 3). For requiring long-term anticoagulant treatment, treatment in a medical center, age <1-year old, female sex, and presence of congenital heart disease were significant factors on less
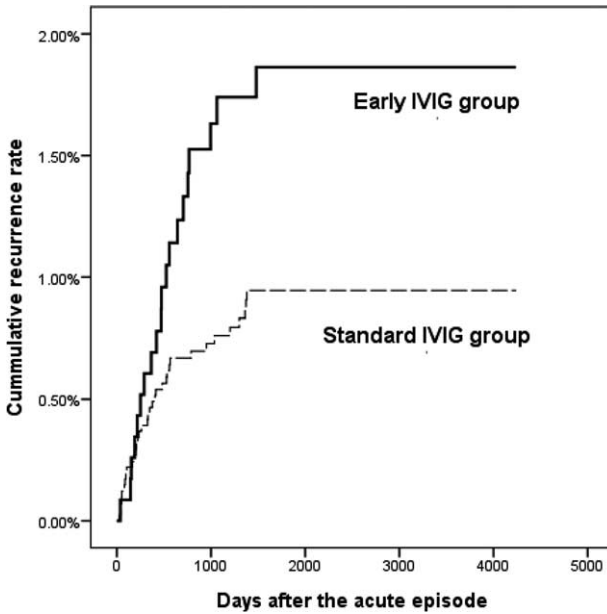
FIGURE 2. The cumulative recurrence rate for children with short fever duration before immunoglobulin therapy was significantly higher. The crude hazard ratio is 1.44 (95% CI 1.35–1.54).

long-term anticoagulants use. Fever duration did no significantly correlate with long-term anticoagulants use (Table 4).

Nonresponse to Immunoglobulin Therapy

Regarding the risk of immunoglobulin unresponsiveness, retreatment in a subgroup of children <2 years old were analyzed. Treatment in a medical center and female sex had significantly protective effects, but age <1-year old increased the risk. The association between fever duration and unresponsiveness was not significant (Table 5).

DISCUSSION

This is a nationwide longitudinal cohort study aimed to analyze the association between the timing of IVIG therapy and outcomes of Kawasaki disease. Based on the findings, the timing of IVIG therapy may not be associated with coronary outcomes; however, earlier IVIG therapy may be associated with a higher recurrence rate. Previous studies used data either from single institutions or a questionnaire survey.[14–19] This is

TABLE 2. Cox Regression Model for Survival Analysis

| | Hazard Ratio | 95.0% CI | | P Value |
		Upper	Lower	
Short fever*	1.38	1.29	1.47	<0.001
Infant (age <1 year)	1.50	1.42	1.59	<0.001
Medical center	1.07	1.01	1.14	0.017
Female	1.00	0.95	1.06	0.90
Congenital heart disease	1.03	0.87	1.22	0.74

CI = confidence interval.
* Crude hazard ratio: 1.44 (95% CI 1.35–1.54).

TABLE 3. Multivariate Logistic Regression for Acute Aneurysm Formation

| | Odds Ratio | 95% CI | | P Value |
		Lower	Upper	
Short fever*	0.99	0.75	1.29	0.91
Medical center	0.16	0.11	0.23	<0.001
Infant (age <1 year)	1.05	0.84	1.31	0.68
Female	0.88	0.70	1.11	0.28
Congenital heart disease	1.54	0.71	3.35	0.27

CI = confidence interval.
* Crude odds ratio 1.00 (0.77–1.31); P = 0.98.

the first nationwide cohort longitudinal study and it used the data from the NHI of Taiwan, which covers >98% of the population of Taiwan.[21,22]

Considering the association between the timing of IVIG therapy and outcomes of Kawasaki disease, the first study comes from the 15th to 16th nationwide survey of Kawasaki disease in Japan. Muta et al[14] found that earlier IVIG therapy correlated with higher retreatment rate. In a single-center case–control study from Hong Kong, Fong et al[15] made the same conclusion. In another single-center study from Japan, Egami et al[17] also reported short illness days as a risk factor for IVIG resistance. Using the 18th Japan nationwide survey, Uehara et al[19] reported increased IVIG resistance in earlier IVIG therapy. In Kobayashi's prediction model for IVIG unresponsiveness, short illness days were also listed as an important predicting factor[17,18]; however, a single-center study from Canada concluded that early IVIG therapy was associated with better coronary outcomes.[16]

The causal relationship about this phenomenon is actually unknown. A possible explanation is that physicians may tend to give IVIG earlier when they face more severe patients. More severe Kawasaki disease may have more severe clinical manifestations and the early presence of the 5 principal features.

In this study, early IVIG treatment is not significantly associated with IVIG unresponsiveness. IVIG unresponsiveness is associated with male sex, age <1 year, and treatment in regional hospitals. The discrepancy of results in this study from those of other studies may be due to different study methods, cohorts, and patients from different regions. Patients of refractory Kawasaki disease have more severe clinical course and

TABLE 4. Multivariate Logistic Regression for Long-Term Anticoagulants

| | Odds Ratio | 95% CI | | P Value |
		Lower	Upper	
Short fever*	1.06	0.86	1.31	0.56
Medical center	0.83	0.69	0.99	0.040
Infant (age <1 year)	0.69	0.58	0.82	<0.001
Female	0.70	0.58	0.84	<0.001
Congenital heart disease	0.49	0.32	0.74	0.001

CI = confidence interval.
* Crude odds ratio 1.01 (0.82–1.24); P = 0.95.

TABLE 5. Subset Analysis for Treatment Failure

		95% CI		
	Odds Ratio	Lower	Upper	P Value
Short fever*	1.08	0.78	1.50	0.63
Medical center	0.72	0.54	0.97	0.029
Infant (age <1 year)	1.93	1.48	2.53	<0.001
Female	0.71	0.53	0.95	0.020
Congenital heart disease	0.64	0.33	1.25	0.19

CI = confidence interval.
* Crude odds ratio 1.19(0.86–1.64); $P = 0.28$.

parameters than the other groups[18]; however, physicians in Taiwan may follow the guidelines of the American Heart Association and American Academy of Pediatric.[13] The real causes warrant more studies for elucidation.

Data of this study come from claims data of the National Health Insurance. Although it covers almost the entire population of Taiwan,[21,22] this study has certain limitations. First, for protecting the privacy, the data is anonymous. Thus, validation cannot be tested because of lack of individual data. Second, because the definition of illness days comes from prescription records, it carries certain degree of misclassifications. Third, the laboratory test results are not included in the claims data. As a result, the association between laboratory data and disease outcomes has not been analyzed. Moreover, the delaying of administration of IVIG could not be obtained from the insurance claims data. We regarded patients as being treated early if there were no antipyretics prescriptions 4 to 12 days before admission, it carries certain degree of misclassifications. The original purpose of this study was to analyze whether earlier therapy than recommended by the guideline endorsed by the American Heart Association and American Academy of Pediatrics is beneficial or harmful.[13] If patients are further divided into subgroups according to febrile durations, it will worsen the misclassifications and not the purpose of this study.

In summary, early immunoglobulin therapy might not be beneficial for the coronary outcomes of children with Kawasaki disease in this observational study. On the contrary, it might be associated with higher recurrence rate. A randomized controlled study comparing early and late IVIG therapy would have probably brought relevant results.

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