Effect of Intravenous Immunoglobulin for Fulminant Myocarditis on In-Hospital Mortality: Propensity Score Analyses

TOSHIAKI ISOGAI, MD, MPH,[1,2] HIDEO YASUNAGA, MD, PhD,[1] HIROKI MATSUI, MPH,[1] HIROYUKI TANAKA, MD, PhD,[2] HIROMASA HORIGUCHI, PhD,[3] AND KIYOHIDE FUSHIMI, MD, PhD[4]

Tokyo, Japan

ABSTRACT

Background: Fulminant myocarditis (FM) is a rare but life-threatening disease. Intravenous immunoglobulin (IVIG) is not recommended for acute or chronic myocarditis in Western nations owing to the lack of rigorous evidence, but it is widely used in other countries, including Japan. This nationwide retrospective cohort study focused on evaluating the effect of IVIG in FM patients.

Methods and Results: Using the Diagnosis Procedure Combination database in Japan, we identified 603 FM patients aged ≥16 years who received mechanical circulatory support within 7 days after admission. We performed propensity score analyses to compare the in-hospital mortality and total costs between IVIG users (n = 220; 36.5%) and nonusers (n = 383; 63.5%). Among propensity score−matched patients (164 pairs), there was no significant difference in in-hospital mortality between IVIG users and nonusers (36.6% vs 37.2%; $P = .909$). A multivariable logistic regression analysis showed no significant association between IVIG use and in-hospital mortality (adjusted odds ratio 0.91; 95% confidence interval 0.52 to 1.58; $P = .733$). The median total costs were significantly higher for IVIG users than for nonusers (US $44,226 vs $33,280; $P < .001$).

Conclusion: IVIG for FM was not significantly associated with a decrease in in-hospital mortality. (*J Cardiac Fail 2015;21:391−397*)

Key Words: Fulminant myocarditis, immunoglobulin, propensity score analysis, mortality.

Fulminant myocarditis (FM) is a life-threatening disease characterized by rapid progression of circulatory failure owing to an inflammatory myocardial injury.[1,2] Despite modern advances in mechanical circulatory support, the in-hospital mortality of FM remains high at 29%−42%.[3−7] Mechanical circulatory support is not a definitive therapy, but rather a bridging therapy until the cardiac function improves on its own.[8,9] If patients survive the critical phase of FM, the long-term prognosis is expected to be favorable.[6,10] Therapeutic options for FM are therefore needed to decrease the in-hospital mortality.

Intravenous immunoglobulin (IVIG), which has both antiviral and antiinflammatory effects,[11−13] is not generally recommended for the acute or chronic phases of myocarditis, but its effectiveness for FM remains uncertain. Because immune mechanisms are involved in the pathogenesis of myocarditis, several studies have been performed to evaluate the effect of IVIG for myocarditis. Although uncontrolled studies suggested that IVIG improved the left ventricular function,[14,15] a randomized controlled trial (RCT) in adult patients with presumed myocarditis showed no significant improvement in the ejection fraction with IVIG.[16] Based on the results of the RCT, IVIG for myocarditis is not recommended in review articles and guidelines published in Western countries.[17−21] However, the evidence from the RCT cannot be applied to FM, because the majority of the study subjects in the RCT were not FM patients and the measured outcome was not associated with the in-hospital prognosis. In fact, the statement of the European

From the [1]Department of Clinical Epidemiology and Health Economics, School of Public Health, The University of Tokyo, Tokyo, Japan; [2]Department of Cardiology, Tokyo Metropolitan Tama Medical Center, Tokyo, Japan; [3]Department of Clinical Data Management and Research, Clinical Research Center, National Hospital Organization Headquarters, Tokyo, Japan and [4]Department of Health Policy and Informatics, Graduate School of Medicine, Tokyo Medical and Dental University, Tokyo, Japan.

Manuscript received July 26, 2014; revised manuscript received December 31, 2014; revised manuscript accepted January 23, 2015.

Reprint requests: Toshiaki Isogai, MD, MPH, Department of Clinical Epidemiology and Health Economics, School of Public Health, The University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-0033, Japan. Tel: +81 3 5841 1887; Fax: +81 3 5841 1888. E-mail: toisogai-circ@umin.ac.jp

Funding: Grants from the Ministry of Health, Labour and Welfare, Japan (Research on Policy Planning and Evaluation grant number: H26-Policy-011).

See page 396 for disclosure information.

1071-9164/$ - see front matter

http://dx.doi.org/10.1016/j.cardfail.2015.01.004

Society of Cardiology Working Group on Myocardial and Pericardial Diseases[22] and the Japanese Circulation Society guideline[23] mention that IVIG may be used in myocarditis refractory to conventional heart failure therapy.

Small case series have shown successfully rescued FM patients who received IVIG,[24–26] but there are no rigorous studies demonstrating the benefit of IVIG for FM. In addition, data are lacking on the cost of IVIG treatment for FM. Evaluation of cost is crucial for determining the justifiability of using IVIG for FM, because IVIG is generally expensive.

At present, an RCT of IVIG for FM is considered to be practically infeasible because of the rarity of the disease as well as the widespread use of IVIG in Japan. Instead, a large-scale observational study can be a feasible alternative to an RCT. The objective of the present study was to investigate, with the use of a nationwide inpatient database in Japan, whether IVIG would decrease the in-hospital mortality in patients with FM.

Materials and Methods

Data Source

For this nationwide retrospective cohort study, we used the Diagnosis Procedure Combination (DPC) database in Japan. Details of the database were explained elsewhere.[27] Briefly, the DPC database includes administrative claims data and discharge abstracts. Data were collected for 6 months (from July 1 to December 31) each year from 2006 to 2010 by the DPC Study Group. In 2011, the duration of the survey each year was extended to 12 months. As of 2012, the number of participating hospitals was 1,057 and the number of patients included was 6.9 million per year, representing approximately 50% of all inpatient admissions to acute care hospitals in Japan. The database included data of 29 million inpatients for a total of 51 months from July 2007 to March 2013.

The available data include: unique identifiers of hospitals; patient age and sex; diagnoses recorded with text data in the Japanese language and *The International Classification of Diseases, Tenth Revision* (ICD-10) codes; drugs and devices; diagnostic and therapeutic procedures; discharge status (dead or alive); and total costs. The requirement for informed consent was waived owing to the anonymous nature of the data. This study was approved by the Institutional Review Board at The University of Tokyo.

Patient Selection and Data

In the present study, FM patients were defined as patients with acute myocarditis (ICD-10 codes I40.x and I41.x) who received mechanical circulatory support (intra-aortic balloon pump [IABP] alone or IABP plus extracorporeal membrane oxygenation [ECMO] or ventricular assist device [VAD]). We identified FM patients aged ≥16 years who received mechanical circulatory support within 7 days after admission from July 2007 to March 2013. To increase the accuracy of the diagnosis of FM and decrease the heterogeneity of patients' backgrounds, we excluded the following patients from this study: patients who (i) underwent percutaneous coronary intervention or coronary artery bypass grafting during hospitalization; (ii) had a previous history of myocardial infarction (ICD-10 code I25.2); and (iii) had a valvular disease (ICD-10 codes I05.x, I06.x, I07.x, I08.x, I34.x, I36.x, I37.x, and I39.x). We also excluded patients who received IVIG before receiving mechanical circulatory support. The eligible patients were divided into 2 groups: patients who received IVIG (IVIG group) and patients who did not receive IVIG (control group).

For covariates, we extracted the following information from the database: age, sex, initial cardiopulmonary resuscitation performed within 7 days after admission, type of mechanical circulatory support (IABP alone or IABP plus ECMO or VAD), time when mechanical circulatory support was initiated (on the day of admission or on day 2 or later), temporary pacing therapy, mechanical ventilation, hypothermia therapy, renal replacement therapy, plasma exchange, drugs (catecholamines, phosphodiesterase III inhibitors, carperitide [alpha−human A-type natriuretic peptide], and methyl-prednisolone), endomyocardial biopsy (EMB) performed within 7 days after admission, and type of hospital (academic or nonacademic).

Outcomes

The primary outcome was in-hospital mortality. The secondary outcome was total cost.

Statistical Analysis

Categoric variables were presented as number and percentage and compared with the use of the chi-square test. The total costs were presented as median and interquartile range and compared with the use of the Mann-Whitney *U* test.

An unadjusted comparison in an analysis using observational data is often subject to selection bias. To overcome this bias, we performed propensity score analyses.[28] To calculate the propensity scores, we fitted a logistic regression model with all measured covariates. The C-statistic was calculated to evaluate the goodness of fit. We performed 1-to-1 matching of patients between the IVIG and control groups with the closest estimated propensity score within a caliper (≤0.25 of the pooled SD of estimated logits) with the use of the nearest-neighbor method without replacement. We also performed a multivariable logistic regression analysis to determine odds ratios and 95% confidence intervals in the propensity score−matched patients. Additionally, we performed a survival analysis with the use of the log rank test and compared the 30-day readmission rate between the IVIG and control groups among propensity score−matched patients with the use of the chi-square test.

Because propensity score matching generally results in a reduction in sample size, we also used the propensity score method of inverse probability of treatment weighting as a sensitivity analysis.[29] Each patient was weighted by the inverse probability of their being in their observed group.

For subgroup analysis of propensity score−matched patients, we extracted data on the total dose of IVIG recorded for each patient in the database and subdivided the patients treated with IVIG into quartiles (low, medium-low, medium-high, and high dose) groups, with approximately equal numbers of patients in each group. We then compared the in-hospital mortalities and total costs among the 4 IVIG dose groups, with the use of the chi-square test and the Kruskal-Wallis test, respectively. We similarly subdivided the propensity score−matched patients treated with methyl-prednisolone into high dose (total dose ≥3 g) and low dose (<3 g) categories and compared the proportions of patients in each dose category with the use of the chi-square test.