

## Editorial

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# Factors Predicting Resistance to Intravenous Immunoglobulin and Coronary Complications in Kawasaki Disease: IVIG Resistance in Kawasaki Disease

### Ji Whan Han 回, MD

Department of Pediatrics, Yeouido St. Mary's Hospital, The Catholic University of Korea College of Medicine, Seoul, Korea

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#### Correspondence to

#### Ji Whan Han, MD

Department of Pediatrics, Yeouido St. Mary's Hospital, The Catholic University of Korea College of Medicine, 10, 63-ro, Yeongdeungpogu, Seoul 07345, Korea. E-mail: hanji59@gmail.com

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#### ORCID iDs

Ji Whan Han (D) https://orcid.org/0000-0002-3024-0609

#### **Conflict of Interest**

The author has no financial conflicts of interest.

The contents of the report are the author's own views and do not necessarily reflect the views of the *Korean Circulation Journal*.

▶ See the article "Factors Predicting Resistance to Intravenous Immunoglobulin Treatment and Coronary Artery Lesion in Patients with Kawasaki Disease: Analysis of the Korean Nationwide Multicenter Survey from 2012 to 2014" in volume 48 on page 71.

Downie et al.<sup>1)</sup> defined intravenous immunoglobulin (IVIG) resistance in patients with Kawasaki disease (KD) as any patient who receives a second dose of IVIG and had a fever (body temperature [BT] >38.0°C) since finishing the first IVIG dose (2 g/kg). In addition, patients who do not respond to IVIG (BT  $\geq$ 37.5°C more than 24 hours after the end of IVIG infusion) seem to develop coronary artery lesions (CALs).

Many factors that can affect IVIG resistance have recently been discovered and are outlined below.

Platelets, C-reactive protein (CRP), and aspartate aminotransferase (AST): Shin et al.<sup>2)</sup> reported the levels of platelets, CRP, and AST were independent predictors of IVIG resistance.

Levels of AST and lactate dehydrogenase and percent of neutrophils: patients with abnormal levels of liver markers (AST and lactic dehydrogenase [LDH]) and neutrophils have a high risk for IVIG resistance.<sup>3)</sup>

Neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR): Takeshita et al.<sup>4)</sup> reported that the combination of NLR and PLR is a novel and useful predictor of IVIG resistance. And high NLR and PLR ratios before receiving IVIG are useful predictors of IVIG resistance.

Fc gamma receptor II A (FcγRIIA)/FcγRIIB expression: Chang et al.<sup>5)</sup> reported that FcγRIIA/FcγRIIB expression is elevated in KD patients with IVIG resistance and CALs. FcγRIIA is also a valuable marker for predicting the effectiveness of treatment for KD. N-terminal-pro-brain natriuretic peptide (NT-proBNP) levels and percent of polymorphonuclear neutrophils (PMNs): patients resistant to IVIG have significantly higher serum levels of NT-proBNP and a percentage of PMNs compared to IVIG responders.<sup>6)</sup>

Other factors:

the other factors involved in IVIG resistance are high levels of alanine aminotransferase (ALT), total bilirubin, gamma-glutamyl transferase (GGT),<sup>7)</sup> and low levels of hemoglobin, albumin, sodium.<sup>8)</sup> In this study, authors<sup>9)</sup> found that PMN percentage and serum levels of NT-proBNP, CRP, AST, and ALT were significantly higher in KD patients with IVIG resistance.

The Japanese Ministry of Health classifies coronary arteries as abnormal if the internal lumen diameter is >3 mm in children <5 years old or >4 mm in children ≥5 years old, if the internal diameter of a segment measures ≥1.5 times that of an adjacent segment, or if the coronary lumen is clearly irregular.<sup>10</sup> Recent studies have investigated factors for predicting CALs in patients with KD, but the results are inconclusive. Cho and Kang<sup>8</sup> found that PMN percentage, CRP levels, and NT-proBNP levels were predictive factors for developing CALs. Other factors associated with CALs in KD patients include male sex and fever duration. In this study, authors<sup>9</sup> also found that serum levels of CRP were higher in KD patients with CAL.

This study is valuable due to the fact that the data were taken nationwide, the large number of cases, and the data were analyzed well by the Korean Society of Kawasaki Disease. However, there are several limitations, including its retrospective nature, partially incomplete data collection, different sampling times and reference ranges at each institution, and different cutoff values used between laboratories. Therefore, we will consider future studies with a prospective design, complete data collection, and standardized collection times, ranges, and cutoff values.

Early diagnosis and prompt IVIG infusion are the best ways to prevent CALs in KD. However, IVIG resistance can develop during or after the first IVIG treatment. Fast detection of IVIG resistance and subsequent administration of adjunctive therapies (IVIG, corticosteroids, tumor necrosis factor  $\alpha$  blockade) can prevent CALs. Therefore, pediatricians must recognize changes in laboratory findings as soon as possible to detect IVIG resistance and prevent CALs.

## REFERENCES

- Downie ML, Manlhiot C, Latino GA, et al. Variability in response to intravenous immunoglobulin in the treatment of Kawasaki disease. *J Pediatr* 2016;179:124-130.e1.
  PUBMED | CROSSREF
- Shin J, Lee H, Eun L. Verification of current risk scores for Kawasaki disease in Korean children. J Korean Med Sci 2017;32:1991-6.

PUBMED | CROSSREF

- Takeuchi M, Inuzuka R, Hayashi T, et al. Novel risk assessment tool for immunoglobulin resistance in Kawasaki disease: application using a random forest classifier. *Pediatr Infect Dis J* 2017;36:821-6.
  PUBMED | CROSSREF
- 4. Takeshita S, Kanai T, Kawamura Y, Yoshida Y, Nonoyama S. A comparison of the predictive validity of the combination of the neutrophil-to-lymphocyte ratio and platelet-to-lymphocyte ratio and other risk scoring systems for intravenous immunoglobulin (ivig)-resistance in Kawasaki disease. *PLoS One* 2017;12:e0176957.

PUBMED | CROSSREF

- Chang LS, Lo MH, Li SC, Yang MY, Hsieh KS, Kuo HC. The effect of FcyRIIA and FcyRIIB on coronary artery lesion formation and intravenous immunoglobulin treatment responses in children with Kawasaki disease. *Oncotarget* 2017;8:2044-52.
  PUBMED
- Lee HY, Song MS. Predictive factors of resistance to intravenous immunoglobulin and coronary artery lesions in Kawasaki disease. *Korean J Pediatr* 2016;59:477-82.
  PUBMED I CROSSREF
- Liu L, Yin W, Wang R, Sun D, He X, Ding Y. The prognostic role of abnormal liver function in IVIG unresponsiveness in Kawasaki disease: a meta-analysis. *Inflamm Res* 2016;65:161-8.
  PUBMED | CROSSREF
- Cho KH, Kang SJ. Clinically useful predictors of resistance to intravenous immunoglobulin and prognosis of coronary artery lesions in patients with incomplete Kawasaki disease. *Korean Circ J* 2014;44:328-35.
  PUBMED | CROSSREF
- Kim MK, Song MS, Kim GB. Factors predicting resistance to intravenous immunoglobulin treatment and coronary artery lesion in patients with Kawasaki disease: analysis of the Korean nationwide multicenter survey from 2012 to 2014. *Korean Circ J* 2018;48:71-79.
  PUBMED | CROSSREF
- 10. Research Committee on Kawasaki Disease (JP). *Report of Subcommittee on Standardization of Diagnostic Criteria* and Reporting of Coronary Artery Lesions in Kawasaki Disease. Tokyo: Ministry of Health and Welfare; 1984.