Editorial

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The Efficacy and Safety of High-Dose Intravenous Immunoglobulin in the Treatment of Kawasaki Disease: How Can We Predict Resistance to Intravenous Immunoglobulin Treatment of Kawasaki Disease?

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Intravenous immunoglobulin

Furusho et al.[1] first administered high-dose intravenous immunoglobulin (IVIG) to patients with Kawasaki disease (KD) in the early 1980s. This trial was inspired by the report that high-dose IVIG therapy was very effective for idiopathic thrombocytopenic purpura[2] and that its potential mechanism of action was immunomodulation. At that time, Furusho et al.[1] suggested that high-dose IVIG had an anti-inflammatory effect in KD to prevent coronary aneurysm (CAA) formation. To date, there have been several hypotheses but little concrete data on the mechanism of action of IVIG in KD. IVIG could interact with many different parts of the immune and vascular systems to downregulate inflammation. Possible interactions of IVIG with elements of the immune system include those with macrophages/monocytes, dendritic cells (DCs), antibodies, T cells, neutrophils, and natural killer (NK) cells.[3-6] The changes following IVIG administration in patients with KD have largely been explained, although detailed mechanisms of action are lacking. These changes include a reduction in the levels of cytokines and chemokines; decreased numbers of circulating cluster of differentiation (CD) 14^+ monocyte/macrophages, neutrophils and activated T cells; increased numbers of circulating NK cells; and changes in lymphocyte subsets.[3]

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Mechanisms of action of intravenous immunoglobulin

Both the fragment, crystallizable (Fc) and fragment, antigen-binding (Fab') portions of the immunoglobulin G (IgG) molecule play important roles in this process. The finding that patients who develop CAA fail to expand the Fc-specific natural regulatory T cell (nTreg) population suggests an important role of nTreg in modulating tissue-level inflammation.[7] In contrast, a rapid reduction in clinical signs of inflammation is more likely due to the Fab'-mediated effects of anti-cytokine, anti-idiotype and possibly anti-toxin or anti-causative agent antibodies, but the exact mechanisms have not yet been determined. Clinical trials have revealed that an Fc-enriched IVIG preparation is as efficacious as intact IVIG, while a pepsin-treated IVIG enriched for Fab' fragments was not effective at preventing CAA.[8][9] Therefore, at least some of the beneficial effects of IVIG are likely mediated via Fc. The function of Fc following IVIG administration is related to the induction of immune regulation in KD via two mechanisms: stimulation of an immature myeloid population of DCs that secretes IL-10, which leads to the expansion of induced regulatory T cells (Tregs);[10] and stimulation of an antigen-specific-nTreg population that recognizes the Fc of IgG.[7] There is also an association between the development of CAA in patients with KD and failure to expand Fc-specific Tregs after IVIG.

Incomplete Kawasaki disease

The definition of incomplete Kawasaki disease (iKD) is the presence of two or three principal clinical features of KD in addition to fever when other possible causes of fever have been excluded. The reported worldwide prevalence of iKD has increased from 15% to 47% since the publication of the 2004 American Heart

Association guidelines.[11] Japanese scoring systems are quite useful for the early detection of IVIG-resistance in patients with complete Kawasaki disease (cKD), but they have limitations in predicting resistance to IVIG because of their low sensitivity.[12-14]

Resistance to intravenous immunoglobulin

Many putative factors affect IVIG-resistance as a treatment modality. Chang et al.[15] reported that FcγRIIA (Fc gamma receptor II A)/FcγRIIB expression is elevated in KD patients with IVIG resistance and coronary artery lesions, while FcγRIIA is a valuable marker for predicting the treatment outcome of KD. Since the early 2000s, N-terminal B type natriuretic peptide has been used for the early detection of patients with iKD and IVIG resistance.[16] Other factors involved in IVIG resistance are a high neutrophil count, high C-reactive protein, low hemoglobin, low albumin levels, high aspartate and alanine aminotransferase levels,[17] low sodium levels,[18] high total bilirubin levels,[19] and high gamma-glutamyl transferase[20] and Tenascin-C levels.[21]

The safety of high-dose intravenous immunoglobulin

High-dose IVIG infusion has several adverse effects that can be classified according to their severity.[22] Common and mild side effects[23-25] include hypertension, headache, malaise, nausea, low-grade fever and chills, urticaria, arthralgias, and myalgia. These symptoms typically resolve within several days after onset. Rare and serious side effects[23-25] include immunoglobulin A deficiency-related anaphylactic reactions, aseptic meningitis, acute renal failure, stroke, myocardial infarction, and thrombotic complications. A thorough medical evaluation must be performed for every KD patient being evaluated for high-dose IVIG therapy. Careful, constant and close monitoring by trained personnel during the infusion can also result in the early detection of adverse events. Finally, high-dose IVIG treatment is safe when administered at a slow infusion rate in well-hydrated KD patients.

Modern intravenous immunoglobulin

Recently, new trends in the production methods for better quality IVIG have been developed,[26] which could improve the purification and safety of IVIG for patients with KD. IVIG-SN[27] is a modern IVIG that has been subjected to multiple pathogen elimination steps. It is produced by Cohn-Oncley fractionization[28] and diethylaminoethyl cellulose-sepharose chromatography.[29] Nanofiltration and treatment with both cold ethanol and solvent detergent are used to remove and inactivate viruses. The product contains substantial levels of anti-HBsAg, anti-measles, anti-diphtheria, and anti-polio antibodies.

Comments

There are several limitations to the study by Yoon et al.[30] First, they did not enroll all cKD patients at their institution, so an unknown selection bias might have existed. Thus, they should include the entire cKD population in a larger future study. Second, the number of IVIG non-responders with iKD was too small to assess statistical significance. A larger sample population will be needed to obtain significant results. Third, the establishment of strict exclusion criteria for iKD is essential to produce valuable results. Accordingly, comprehensive laboratory tests should be ordered. Last, there was no description of "IVIG-SN;" they could have introduced this new IVIG product.

Despite these limitations, this is the first multicenter and clinically important study to compare predictors of IVIG resistance in both iKD and cKD groups in Korea. Other studies of the predictors of IVIG resistance have focused only on patients with cKD[11][31] or iKD,[32] respectively. Those studies also found that an elevated percentage of segmented neutrophils was of value for predicting IVIG resistance in patients with iKD, supporting leukocytosis as a characteristic finding during the acute phase of KD, especially the dominance of polymorphonuclear leukocytes.[33]

There are some arguments for using high-dose versus medium-dose IVIG for the treatment of patients with KD, especially when a second dose of IVIG is needed for patients with IVIG-resistant KD.

Conclusion

In conclusion, IVIG is the best treatment for KD along with aspirin. We still do not know the exact mechanism of action of IVIG. IVIG has a few side effects, although most of them are not serious because the immunological status of patients with KD is typically evaluated before they begin treatment. IVIG is initially infused very slowly, and then the infusion rate is gradually increased while carefully monitoring the patient's vital signs Finally, even though there are several biomarkers for detecting iKD, it is difficult for pediatricians to diagnose iKD. Therefore, close clinical observation and a supportive laboratory workup are the keys to early treatment of iKD and prevention of coronary artery complications.

References

1. Furusho K, Sato K, Soeda T, et al. High-dose intravenous gammaglobulin for Kawasaki disease. *Lancet* 1983;2:1359.
2. Imbach P, Barandun S, d'Apuzzo V, et al. High-dose intravenous gammaglobulin for idiopathic thrombocytopenic purpura in childhood. *Lancet* 1981;1:1228-31.
3. Burns JC, Franco A. The immunomodulatory effects of intravenous

immunoglobulin therapy in Kawasaki disease. *Expert Rev Clin Immunol* 2015;11:819-25.
4. Negi VS, Elluru S, Sibéril S, et al. Intravenous immunoglobulin: an update on the clinical use and mechanisms of action. *J Clin Immunol* 2007;27:233-45.
5. Bayry J, Negi VS, Kaveri SV. Intravenous immunoglobulin therapy in rheumatic diseases. *Nat Rev Rheumatol* 2011;7:349-59.
6. Schwab I, Nimmerjahn F. Intravenous immunoglobulin therapy: how does IgG modulate the immune system? *Nat Rev Immunol* 2013;13:176–89.
7. Franco A, Touma R, Song Y, et al. Specificity of regulatory T cells that modulate vascular inflammation. *Autoimmunity* 2014;47:95-104.
8. Hsu CH, Chen MR, Hwang FY, et al. Efficacy of plasmin-treated intravenous gamma-globulin for therapy of Kawasaki syndrome. *Pediatr Infect Dis J* 1993;12:509-12.
9. Harada K. Intravenous gamma-globulin treatment in Kawasaki disease. *Acta paediatrica Japonica* 1991;33:805-10.
10. Newburger JW, Takahashi M, Burns JC, et al. The treatment of Kawasaki syndrome with intravenous gamma globulin. *N Engl J Med* 1986;315:341-7.
11. Newburger JW, Takahashi M, Gerber MA, et al. Diagnosis, treatment, and long-term management of Kawasaki disease: a statement for health professionals from the committee on rheumatic fever, endocarditis and Kawasaki disease, council on cardiovascular disease in the young, American heart association. *Circulation* 2004;110:2747-71.
12. Egami K, Muta H, Ishii M, et al. Prediction of resistance to intravenous immunoglobulin treatment in patients with Kawasaki disease. *J Pediatr* 2006;149:237-40.
13. Sano T, Kurotobi S, Matsuzaki K, et al. Prediction of non-responsiveness to standard high-dose gamma-globulin therapy in patients with acute Kawasaki disease before starting initial treatment. *Eur J Pediatr* 2007;166:131-7.
14. Kobayashi T, Inoue Y, Takeuchi K, et al. Prediction of intravenous immunoglobulin unresponsiveness in patients with Kawasaki disease. *Circulation* 2006;113:2606-12.
15. Chang LS, Lo MH, Li SC, Yang MY, Hsieh KS, Kuo HC. The effect of FcγRIIA and FcγRIIB on coronary artery lesion formation and intravenous immunoglobulin treatment responses in children with Kawasaki disease. *Oncotarget* 2017;8:2044-52.
16. Nagib D, Ana S, Anne F, et al. Natriuretic peptide as an adjunctive diagnostic test in the acute phase of Kawasaki disease. *Pediatr Cardiol* 2009;30:810–17
17. Eladawy M, Dominguez SR, Anderson MS, Glode MP. Abnormal liver panel in acute Kawasaki disease. *Pediatr Infect Dis J* 2011;30:141-4.
18. Lim GW, Lee M, Kim HS, Hong YM, Sohn S. Hyponatremia and syndrome of inappropriate antidiuretic hormone secretion in kawasaki disease. *Korean Circ J* 2010;40:507-13.
19. Kim BY, Kim D, Kim YH, et al. Non-responders to intravenous immunoglobulin and coronary artery dilatation in Kawasaki disease: predictive parameters in Korean children. *Korean Circ J* 2016;46:542-9.
20. Wang Y, Li Z, Hu G, et al. Unique molecular patterns uncovered in Kawasaki disease patients with elevated serum gamma glutamyl transferase levels: implications for intravenous immunoglobulin responsiveness. *PLoS One* 2016;11:e0167434.
21. Okuma Y, Suda K, Nakaoka H, et al. Serum tenascin-C as a novel predictor for risk of coronary artery lesion and resistance to intravenous immunoglobulin in Kawasaki disease- a multicenter retrospective study. *Circ J* 2016;80:2376-81.
22. Bonilla FA. Intravenous and subcutaneous immunoglobulin G replacement therapy. *Allergy Asthma Proc* 2016;37:426-31.
23. Marie I, Chérin P, Michallet M, et al. Management of adverse effects related to human immunoglobulin therapy: Recommendations for clinical practice. *Rev Med Interne* 2016. [Epub ahead of print] doi: 10.1016/j.revmed.2016.10.390.
24. Katz U, Achiron A, Sherer Y, Shoenfeld Y. Safety of intravenous immunoglobulin (IVIG) therapy. *Autoimmun Rev* 2007;6:257-9.
25. Hamrock DJ. Adverse events associated with intravenous immunoglobulin therapy. *Int Immunopharmacol* 2006;6:535-42.
26. Radosevich M, Burnouf T. Intravenous immunoglobulin G: trends in production methods, quality control and quality assurance. *Vox Sang* 2010;98:12-28.
27. Stein MR, Wasserman RL, Moy J, et al. Efficacy, safety, and tolerability of IVIG-SN in patients with primary immunodeficiency. *Lymphosign J* 2015;2:21-9.
28. Cohn EJ, Strong LE, Hughes WL, et al. Preparation and properties of serum and plasma proteins: a system for the separation into fractions of the protein and lipoprotein components of biological tissues and fluids. *J Am Chem Soc* 1946;68:459–75.
29. Melin JL, Oncley M, Richert DA. The separation of the antibodies, isoagglutinins, prothrombin, plasminogen and beta-lipoprotein into subfractions of human plasma. *J Am Chem Soc* 1949;71:541–50.
30. Yoon KL, Lee HY, Yu JJ, et al. Multicenter, single-arm, phase IV study to evaluate the efficacy and safety of the combined therapy of aspirin and high-dose "IVIG-SN" for pediatric patients with Kawasaki disease. *Korean Circ J* 2017;47:209-14.
31. Durongpisitkul K, Soongswang J, Laohaprasitiporn D, et al. Immunoglobulin failure and retreatment in Kawasaki disease. *Pediatr Cardiol* 2003;24:145-8.
32. 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.
33. Yeo Y, Kim T, Ha K, et al. Incomplete Kawasaki disease in patients younger than 1 year of age: a possible inherent risk factor. *Eur J Pediatr* 2009;168:157-62.

 https://doi.org/10.4070/kcj.2017.0011