History and Future of Treatment for Acute Stage Kawasaki Disease

Masahiro Ishii, MD, FACC¹, Takasuke Ebato, MD², and Hirihisa Kato, MD, FACC³

¹Ishii Pediatrics and Pediatric Cardiology Office, Kanagawa, Japan
²Department of Pediatrics, Kitasato University, School of Medicine, Kanagawa, Japan
³Department of Pediatrics, Kurume University, School of Medicine, Kurume, Japan

ABSTRACT

Kawasaki disease is a form of vasculitis, mainly in small and medium arteries of unknown origin, occurring frequently in childhood. It is the leading form of childhood-onset acquired heart disease in developed countries and leads to complications of coronary artery aneurysms in approximately 25% of cases if left untreated. Although more than half a century has passed since Professor Tomisaku Kawasaki’s first report in 1957, the cause is not yet clear. Currently, intravenous immunoglobulin (IVIG) therapy has been established as the standard treatment for Kawasaki disease. Various treatment strategies are still being studied under the slogan, “Ending powerful inflammation in the acute phase as early as possible and minimizing the incidence of coronary artery lesions,” as the goal of acute phase treatments for Kawasaki disease. Currently, in addition to immunoglobulin therapy, steroid therapy, therapy using infliximab, biological products, suppression of elastase secretion inside and outside the neutrophils, inactivated ulinastatin therapy and cyclosporine therapy, plasma exchange, etc. are performed. This chapter outlines the history and transition of the acute phase treatment for Kawasaki disease.

Keywords: Kawasaki disease; Intravenous immunoglobulin; Infliximab; Intravenous methylprednisolone pulse; Prednisolone

INTRODUCTION

Kawasaki disease is a vasculitis syndrome mainly occurring in the medium and small arteries for unknown etiology, which occurs frequently in childhood. It ranks as one of the most common acquired cardiac diseases occurring in childhood in developed countries, with an occurrence rate of 25% of coronary artery aneurysm (CAA) as a complication in untreated patients. Since Dr. Tomisaku Kawasaki first reported it in 1957, despite more than half a century having passed, the causes have remained unclear. More recently, in 1984, Furusho et al. reported the effectiveness of intravenous immunoglobulin (IVIG) therapy as a treatment for acute stage Kawasaki disease. In 1991, Newburger et al. reported the effectiveness of single high-dose intravenous injection therapy (2 g/kg), which has currently been established...
as the standard therapy. Thereafter, although new additional treatments, combination therapies, etc. have been reported, cases are still seen which are refractory to first-line treatment or in which CAA still occurs as a complication (3%), with no radical treatment known. With the phrase “to bring an end to strong inflammation in the acute stage as soon as possible and minimize the incidence of coronary artery lesions (CALS)” as a goal in the treatment of acute stage Kawasaki disease, various therapeutic strategies have been examined to date. In this manuscript, we will outline the history and transition of treatment for acute stage Kawasaki disease.

THE HISTORY OF ASPIRIN

Aspirin (ASA) is the drug that was first established as a therapeutic agent for acute stage Kawasaki disease.\(^2\) When Kawasaki disease was discovered, prednisolone (PSL) was actively used as a treatment for vasculitis syndrome. In 1975, Kato et al.\(^2\) performed coronary angiography and reported that one complication of Kawasaki disease was asymptomatic CAA. At that time, PSL and ASA were the main options for treatment in the acute stage; however, Kato et al.\(^2\) reported that ASA resulted in lower incidence of CALs than PSL in 1979, with a higher complication rate in the group using PSL, as well as a large number of death cases in PSL groups. As a result, PSL became almost contraindicated as a treatment for acute stage Kawasaki disease, while the ASA treatment became main stream. Although the mortality rate decreased from approximately 2% to approximately 0.2% by ASA treatment, the complication rate of CALs remained approximately 25%, suggesting that ASA monotherapy is not an effective treatment for the prevention of CALs.

HISTORY OF INTRAVENOUS IMMUNOGLOBULIN

In a nationwide survey in Japan for Japanese Kawasaki disease in 2015 and 2016, IVIG therapy was carried out as the first-line treatment for 92.6% of patients and was given mandatory status. The history of IVIG began from the report by Furusho et al.\(^3\) in 1983. Patients were randomized into 2 groups, a control group undergoing ASA therapy which had been the mainstream treatment until then, and a treatment group receiving ASA+IVIG (200 mg/kg/day: 5 days). The incidence of CAA was significantly lower in the IVIG combination group. In 1991, Newburger et al.\(^4\) conducted a randomized large-scale prospective controlled trial to compare ASA+IVIG (400 mg/kg/day: 5 days) and ASA+IVIG (2 g/kg/day: 1 day). It was reported that the group with a single high dose of ASA+IVIG (2 g/kg/day: 1 day) had a decreased incidence of CAA from 25% to less than 5%. Thereafter, a single administration of IVIG 2 g/kg/day became widespread, and in 2003, it was included under insurance coverage in Japan, having established its status as a standard treatment. In 2003, guidelines for the treatment of acute stage Kawasaki disease were prepared by the Japanese Society of Pediatric Cardiology and Cardiac Surgery, with a single ultra-dose regimen of IVIG at 2 g/kg/day replacing the position of a divided dosage of IVIG, which had played a leading role in the treatment for acute stage Kawasaki disease up until that point. On the other hand, ASA did not disappear upon the appearance of IVIG, but was thereafter used in combination in large-scale studies and became widely used as a standard treatment as with IVIG. In particular, low-dose ASA therapy (3–5 mg/kg) was widely used for protection of the vascular endothelium and inhibition of platelet aggregation ability for adults as well, which is considered to be effective against Kawasaki disease vasculitis as well.
LIMITATION OF INTRAVENOUS IMMUNOGLOBULIN TREATMENT

Despite the safety and high effectiveness of IVIG, it was revealed that patients refractory to first-line IVIG treatment account for 15–25% overall, indicating a high complication rate of CAA. Therefore, in order to determine patients refractory to first-line IVIG at an early stage, the development of scores in order to predict IVIG refractoriness began based on patient characteristics and blood test data prior to treatment, with reports made one after another from 2006 in Japan.\(^5\)\(^7\) With either method, the effect on IVIG can be predicted with high sensitivity and specificity at approximately 80%. For cases in which refractoriness is predicted using these scores, consolidation therapy combining another treatment with IVIG from first-line treatment has been used ever since.

STEROIDS

As mentioned earlier, although PSL was initially used as a treatment for the acute stage, from the mid-1980s, there was a period when PSL administration was contraindicated due to a potential increase in the incidence of CAL. However, with the report on intravenous methylprednisolone pulse (IVMP) therapy for refractory cases to immunoglobulin by Wright et al.\(^8\) in 1996 as a turning point, IVMP therapy once again garnered attention as a treatment for IVIG refractory cases. Hashino et al.\(^9\) reported on the efficacy and safety of IVMP therapy by conducting a prospective randomized trial on a group who underwent immunoglobulin therapy twice, but were refractory to treatment. Ogata et al.\(^10\) reported the effectiveness of IVMP as a second treatment technique for patients refractory to immunoglobulin therapy. As a result, it was revealed that steroid therapy had a rapid and powerful anti-inflammatory effect on patients refractory to immunoglobulin therapy and enabled a reduction in the occurrence of CALs, which had brought steroid therapy to the mainstream once again. Ogata et al.\(^11\) verified the molecular biological fluctuation of IVMP therapy using a microarray. As a result, it was demonstrated that a single dose of IVMP therapy in combination with immunoglobulin therapy as the first-line treatment of patients with intractable Kawasaki disease can more broadly inhibit mRNA expression compared to the single administration of immunoglobulin. For steroid usage, PSL is intravenously administered at 2 mg/kg/day, divided into 3 administrations a day, in the fever stage. This is changed to oral administration upon stabilization of the general condition, then tapered and discontinued after C-reactive protein (CRP) becomes negative. On the other hand, while IVMP is usually administered intravenously at 30 mg/kg once a day for 3 days, it is common to administer it for 1 to 3 days for Kawasaki disease. Treatment using steroids from the first-line treatment was initiated using prediction scores for the immunoglobulin refractory group which were developed in sequence. In 2009, Okada et al.\(^12\) used the Sano score\(^5\) to stratify patients predicted to be refractory and compared a group receiving IVIG+IVMP and a group receiving IVIG alone. The efficacy of the IVMP combination group was high, indicating a low complication rate of CALs. In 2012, Ogata et al.\(^13\) used the Egami score\(^6\) to stratify patients predicted to be refractory, conducting a prospective randomized controlled trial comparing a group receiving IVIG+IVMP treatment and a group receiving IVIG alone. They reported that the IVMP combination group had a shorter duration until their fever declined and significantly lower complication rate of CALs. In the same year, Kobayashi et al.\(^14\) conducted a large-scale multicenter prospective randomized controlled trial (RAISE study). In this study, the Kobayashi score\(^7\) was used to stratify patients predicted to be refractory, comparing a group receiving IVIG+PSL and a group receiving IVIG.
alone. The results indicated that the former group had a shorter time until their fever declined, decreased frequency of additional treatment required, and significantly reduced incidence of CALs. Based on the above reports, the usefulness of consolidation therapy using steroids was demonstrated. In 2013, steroid therapy for acute stage Kawasaki disease was included under insurance coverage in Japan. In 2017, Ebato et al. used a unified protocol including retreatment as follows to verify the treatment outcome and reported thereon: stratify patients with intractable Kawasaki disease using the Egami score, for whom a single dose of IVIG is administered in combination with immunoglobulin as the first-line treatment, followed by additional administration of immunoglobulin as the second-line therapy against refractory cases; for patients refractory to the second-line therapy, retreatment was carried out, such as plasma exchange for patients within 6 months of Bacillus Calmette-Guérin (BCG) inoculation and administration of infliximab for patients who received BCG inoculation 6 months or more prior. No cases were associated with CAA among 71 cases of intractable Kawasaki disease. Going forward, it is necessary to consider protocols including retreatment in order to improve the treatment outcome.

**INFLIXIMAB**

Infliximab (IFX) is a biological drug, an anti-tumor necrosis factor (TNF)-α drug developed as a remedy for rheumatoid arthritis. In 1989, Maury et al. and Lang et al. demonstrated that high TNF-α values are observed in the blood with Kawasaki disease. In Japan, Matsubara et al. reported similar results in 1990 and showed that there is a correlation between TNF and CAA complications. These results suggest an association between Kawasaki disease and TNF, leading to a discussion on the use of IFX.

In 2004, Weiss et al. carried out IFX administration on a 3-year-old boy who was not responsive to IVIG/IVMP therapy for the first time, and in 2005, Burns et al. reported on the outcomes of using IFX in 17 cases refractory to IVIG/IVMP therapy.

Approximately 10 years later, Tremoulet et al. conducted a randomized controlled trial comparing an IFX+IVIG group and an IVIG alone group as first-line treatment. Although there was no difference in refractoriness between the 2 groups, shortened duration of fever and a decline in the incidence of CALs were observed in the IFX combination group, indicating its effectiveness. In Japan as well, the administration of IFX was initiated as off-label for Kawasaki disease patients refractory to IVIG from 2006. According to a survey on the actual situation of use conducted by the Japanese Society of Kawasaki Disease, IFX had been used in approximately 500 cases of Kawasaki disease by 2012, with antipyretic effect observed in approximately 80% of these cases, wherein, if used prior to the 9th disease day, it was possible to suppress the formation of CAA. In 2009, Hirono et al. reported on the blood cytokine dynamics before and after IFX administration for Kawasaki disease, demonstrating that interleukin (IL)-6 in serum was decreased by IFX administration, which suppressed inflammatory markers such as CRP and sTNF-αR1. In 2014, Ogihara et al. verified the molecular biological fluctuation of IFX using a microarray. It has been demonstrated that it controls major inflammatory cytokine pathways such as IL-1, IL-6, TNF-α in addition to controlling factors related to Kawasaki disease vasculitis and unresponsiveness to immunoglobulins (PI3, MMP8, CCR2, PTX3). IFX was included under insurance coverage for Kawasaki disease in October 2015. In the revised new guidelines, it is positioned as the third line; however, it may be upgraded to the second line for patients with intractable disease.

https://e-kcj.org https://doi.org/10.4070/kcj.2019.0290
refractory to first-line IVIG. It is anticipated that the use of IFX will increase, with major changes occurring upon shifting the treatment strategy from IVIG to IFX.

ULINASTATIN

Kanai et al.\textsuperscript{24} reported on the effectiveness of ulinastatin (UTI) against Kawasaki disease in 2011 in Japan. There have been numerous reports on IVIG refractory cases, increased neutrophil activity, and delayed high levels of elastase in cases refractory to IVIG and those associated with CALs. UTI, which suppresses and inactivates elastase secretion inside and outside the neutrophils, is believed to suppress vascular endothelial dysfunction and is considered to be one treatment option. However, its effects are closer to a supportive therapy, with no dramatic antipyretic effect. According to the guidelines, it shall be used in combination with IVIG, as a second line option or later.

CYCLOSPORIN

Cyclosporin (CyA) is an immunosuppressive agent that binds to and inhibits the activation of calcineurin (CN), which plays an important role in the signal transmission of T cell activation; however, it is unapproved for the treatment of acute stage Kawasaki disease. In 2001, Raman et al.\textsuperscript{25} reported that the use of CyA in immunosuppressive therapy might be effective against severe Kawasaki disease. Thereafter, Kawasaki disease-susceptible genes (\textit{ITPKC}, \textit{CASP3}) have been discovered as host factors mainly by Onouchi et al.\textsuperscript{26} after 2008. At first, these genes were believed to have a suppression function of cell activation in T cells and it was thought that excessive activation of T cells caused by abnormalities in these genes is involved in the pathology of Kawasaki disease. However, in recent years, it was revealed that these genes are expressed not only in T cells but also in vascular endothelial cells and cells involved in innate immunity. In 2011, Suzuki et al.\textsuperscript{27} thought that dephosphorylation of CN of CyA acts downstream of \textit{ITPKC} and could be an effective treatment against Kawasaki disease and so prepared a protocol involving the use of CyA against IVIG refractory cases and conducted a preceding study. CyA (4 mg/kg/day) was administered orally as the third line for patients refractory to the first-line IVIG, among which an antipyretic effect was observed in 78.6%. It was thought that this could be an effective treatment option based on the treatment results of this preceding study. Currently, Hamada et al.\textsuperscript{28} are conducting a randomized controlled investigator-initiated trial using a treatment protocol combining IVIG+CyA (5 mg/kg/day: 5 days) as the first-line treatment for stratified severe Kawasaki disease. The results for this study showed this combination treatment is effectiveness for refractory Kawasaki disease.

PLASMA EXCHANGE THERAPY

In the guidelines for the treatment of acute stage Kawasaki disease, plasma exchange therapy (PE) is class III, grade C as a treatment for IVIG refractory cases. Although IFX has been included under insurance coverage in recent years, there are some serious cases refractory to any treatment and receiving PE. In 2004, Mori et al.\textsuperscript{29} and Imagawa et al.,\textsuperscript{30} reported on the effectiveness of PE in sequence. According to the report by Hokosaki et al.\textsuperscript{31} in 2012, CALs can be said to be suppressed by initiating PE prior to the occurrence of CALs on the 9th disease day from onset. While the mechanism of action is thought to be the removal
of inflammatory cytokines and the blockade of the cytokine network, the details remain unclear. In recent years, IFX has come to be included under insurance coverage and the frequency of PE is expected to decrease. It needs to be performed at an advanced medical institution and has higher invasiveness than other treatments. It is necessary to sufficiently discuss the indication, which is thought to be the treatment for acute stage as the last resort.

**FUTURE**

Guidelines have been newly revised in the United States and Japan over the past 10 years, with new treatment methods emerging. However, it is also a major problem that various treatment methods have been established, with selection of the treatment method and timing of therapeutic intervention mainly left to the judgment of the attending physician. First, clarifying the unknown causes of Kawasaki disease will lead to the selection of the best treatment method, which is believed will save the future of children affected by Kawasaki disease. In addition, from another viewpoint, while various treatment methods exist, there are refractory cases to each treatment. This may be due to the fact that the cause and pathology of Kawasaki disease are not uniform. In the future, we believe that a treatment method suitable to the genetic polymorphism and pathology of each case, a custom-made treatment strategy, will become available, as well as a treatment method which does not cause subsequent complications of coronary artery diseases.

**REFERENCES**

1. Kawasaki T. Acute febrile mucocutaneous lymph node syndrome in children with specific desquamation of the digits (clinical observation of 50 self-reported cases). *Arerugi* 1967;16:178-222. [PUBMED](https://doi.org/10.4070/kcj.2019.0290)

2. Kato H, Koike S, Yokoyama T. Kawasaki disease: effect of treatment on coronary artery involvement. *Pediatrics* 1979;63:175-9. [PUBMED](https://doi.org/10.4070/kcj.2019.0290)

3. Furusho K, Sato K, Soeda T, et al. High-dose intravenous gammaglobulin for Kawasaki disease. *Lancet* 1983;322:1399. [PUBMED](https://doi.org/10.4070/kcj.2019.0290)

4. Newburger JW, Takahashi M, Beiser AS, et al. A single intravenous infusion of gamma globulin as compared with four infusions in the treatment of acute Kawasaki syndrome. *N Engl J Med* 1991;324:1633-9. [PUBMED](https://doi.org/10.4070/kcj.2019.0290)

5. Sano T, Kurotobi S, Matsuzaki K, et al. Prediction of non-responsiveness to standard high-dose gammaglobulin therapy in patients with acute Kawasaki disease before starting initial treatment. *Eur J Pediatr* 2007;166:1317. [PUBMED](https://doi.org/10.4070/kcj.2019.0290)

6. 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. [PUBMED](https://doi.org/10.4070/kcj.2019.0290)

7. Kobayashi T, Inoue Y, Takeshi K, et al. Prediction of intravenous immunoglobulin unresponsiveness in patients with Kawasaki disease. *Circulation* 2006;113:2606-12. [PUBMED](https://doi.org/10.4070/kcj.2019.0290)

8. Wright DA, Newburger JW, Baker A, Sundel RP. Treatment of immune globulin-resistant Kawasaki disease with pulsed doses of corticosteroids. *J Pediatr* 1996;128:146-9. [PUBMED](https://doi.org/10.4070/kcj.2019.0290)

9. Hashino K, Ishii M, Iemura M, Akagi T, Kato H. Re-treatment for immune globulin-resistant Kawasaki disease: a comparative study of additional immune globulin and steroid pulse therapy. *Pediatr Int* 2001;43:213-7. [PUBMED](https://doi.org/10.4070/kcj.2019.0290)
10. Ogata S, Bando Y, Kimura S, et al. The strategy of immune globulin resistant Kawasaki disease: a comparative study of additional immune globulin and steroid pulse therapy. *J Cardiol* 2009;53:15-9. [PUBMED](https://www.ncbi.nlm.nih.gov/pubmed) | [CROSSREF](https://doi.org/10.1016/j.jjcc.2008.11.009)  
11. Ogata S, Ogihara Y, Nomoto K, et al. Clinical score and transcript abundance patterns identify Kawasaki disease patients who may benefit from addition of methylprednisolone. *Pediatr Res* 2009;66:577-84. [PUBMED](https://www.ncbi.nlm.nih.gov/pubmed) | [CROSSREF](https://doi.org/10.1203/01.pdr.0000361516.27599.36)  
12. Okada K, Hara J, Maki I, et al. Pulse methylprednisolone with gammaglobulin as an initial treatment for acute Kawasaki disease. *Eur J Pediatr* 2009;168:181-5. [PUBMED](https://www.ncbi.nlm.nih.gov/pubmed) | [CROSSREF](https://doi.org/10.1007/s00431-009-1180-9)  
13. Ogata S, Ogihara Y, Honda T, Kon S, Akiyama K, Ishii M. Corticosteroid pulse combination therapy for refractory Kawasaki disease: a randomized trial. *Pediatrics* 2012;129:e17-23. [PUBMED](https://www.ncbi.nlm.nih.gov/pubmed) | [CROSSREF](https://doi.org/10.1542/peds.2011-0521)  
14. Kobayashi T, Saji T, Otani T, et al. Efficacy of immunoglobulin plus prednisolone for prevention of coronary artery abnormalities in severe Kawasaki disease (RAISE study): a randomised, open-label, blinded-endpoints trial. *Lancet* 2012;379:1613-20. [PUBMED](https://www.ncbi.nlm.nih.gov/pubmed) | [CROSSREF](https://doi.org/10.1016/S0140-6736(12)60097-4)  
15. Ebato T, Ogata S, Ogihara Y, et al. The clinical utility and safety for treatment of refractory Kawasaki disease: a single institution experience. *J Pediatr* 2017;191:140-4. [PUBMED](https://www.ncbi.nlm.nih.gov/pubmed) | [CROSSREF](https://doi.org/10.1016/j.jspedr.2017.06.021)  
16. Maury CP, Salo E, Pelkonen P. Elevated circulating tumor necrosis factor-alpha in patients with Kawasaki disease. *J Lab Clin Med* 1989;113:651-4. [PUBMED](https://www.ncbi.nlm.nih.gov/pubmed) | [CROSSREF](https://doi.org/10.1016/0022-2143(89)90079-5)  
17. Lang BA, Silverman ED, Laxer RM, Lau AS. Spontaneous tumor necrosis factor production in Kawasaki disease. *J Pediatr* 1989;115:939-43. [PUBMED](https://www.ncbi.nlm.nih.gov/pubmed) | [CROSSREF](https://doi.org/10.1016/0022-3476(89)90657-9)  
18. Matsubara T, Furukawa S, Yabuta K. Serum levels of tumor necrosis factor, interleukin 2 receptor, and interferon-gamma in Kawasaki disease involved coronary-artery lesions. *Clin Immunol Immunopathol* 1990;56:29-36. [PUBMED](https://www.ncbi.nlm.nih.gov/pubmed) | [CROSSREF](https://doi.org/10.1016/0197-212X(90)90110-3)  
19. Weiss JE, Eberhard BA, Chowdhury D, Gottlieb BS. Infliximab as a novel therapy for refractory Kawasaki disease. *J Rheumatol* 2004;31:808-10. [PUBMED](https://www.ncbi.nlm.nih.gov/pubmed) | [CROSSREF](https://doi.org/10.3899/jrheum.030862)  
20. Burns JC, Mason WH, Hauger SB, et al. Infliximab treatment for refractory Kawasaki syndrome. *J Pediatr* 2005;146:662-7. [PUBMED](https://www.ncbi.nlm.nih.gov/pubmed) | [CROSSREF](https://doi.org/10.1016/j.jspedr.2004.12.018)  
21. Tremoulet AH, Jain S, Jaggi P, et al. Infliximab for intensification of primary therapy for Kawasaki disease: a phase 3 randomised, double-blind, placebo-controlled trial. *Lancet* 2014;383:1731-8. [PUBMED](https://www.ncbi.nlm.nih.gov/pubmed) | [CROSSREF](https://doi.org/10.1016/S0140-6736(13)62693-6)  
22. Hirono K, Kemmotsu Y, Wittkowski H, et al. Infliximab reduces the cytokine-mediated inflammation but does not suppress cellular infiltration of the vessel wall in refractory Kawasaki disease. *Pediatr Res* 2009;65:696-701. [PUBMED](https://www.ncbi.nlm.nih.gov/pubmed) | [CROSSREF](https://doi.org/10.1203/01.PDR.0000351509.89700.8b)  
23. Ogihara Y, Ogata S, Nomoto K, et al. Transcriptional regulation by infliximab therapy in Kawasaki disease patients with immunoglobulin resistance. *Pediatr Res* 2014;76:287-93. [PUBMED](https://www.ncbi.nlm.nih.gov/pubmed) | [CROSSREF](https://doi.org/10.1203/PDR.0000000000000786)  
24. Kanai T, Ishiwata T, Kobayashi T, et al. Ulinastatin, a urinary trypsin inhibitor, for the initial treatment of patients with Kawasaki disease: a retrospective study. *Circulation* 2011;124:2822-8. [PUBMED](https://www.ncbi.nlm.nih.gov/pubmed) | [CROSSREF](https://doi.org/10.1161/CIRCULATIONAHA.111.029474)  
25. Raman V, Kim J, Sharkey A, Chatila T. Response of refractory Kawasaki disease to pulse steroid and cyclosporin A therapy. *Pediatr Infect Dis J* 2001;20:635-7. [PUBMED](https://www.ncbi.nlm.nih.gov/pubmed) | [CROSSREF](https://doi.org/10.1097/00002271-200109000-00014)  
26. Onouchi Y, Suzuki Y, Suzuki H, et al. *ITPKC* and *CASP3* polymorphisms and risks for IVIG unresponsiveness and coronary artery lesion formation in Kawasaki disease. *Pharmacogenomics* 2013;13:52-9. [PUBMED](https://www.ncbi.nlm.nih.gov/pubmed) | [CROSSREF](https://doi.org/10.2217/pgs.12.135)  
27. Suzuki H, Terai M, Hamada H, et al. Cyclosporin A treatment for Kawasaki disease refractory to initial and additional intravenous immunoglobulin. *Pediatr Infect Dis J* 2011;30:871-6. [PUBMED](https://www.ncbi.nlm.nih.gov/pubmed) | [CROSSREF](https://doi.org/10.1097/INF.0b013e31820a376c)  
28. Hamada H, Suzuki H, Onouchi Y, et al. Efficacy of primary treatment with immunoglobulin plus cyclosporin for prevention of coronary artery abnormalities in patients with Kawasaki disease predicted to
be at increased risk of non-response to intravenous immunoglobulin (KAICA): a randomised controlled, open-label, blinded-endpoints, phase 3 trial. *Lancet* 2019;393:1128-37.

29. Mori M, Imagawa T, Katakura S, et al. Efficacy of plasma exchange therapy for Kawasaki disease intractable to intravenous gamma-globulin. *Mod Rheumatol* 2004;14:43-7.

30. Imagawa T, Mori M, Miyamae T, et al. Plasma exchange for refractory Kawasaki disease. *Eur J Pediatr* 2004;163:263-4.

31. Hokosaki T, Mori M, Nishizawa T, et al. Long-term efficacy of plasma exchange treatment for refractory Kawasaki disease. *Pediatr Int* 2012;54:99-103.