Combination Therapy of Cyclosporin A and Plasma Exchange for Infants with Immunoglobulin-resistant Kawasaki Disease

Saori YOKOTA, Noriko MOTOKI*, Shoko YAMAZAKI and Masafumi UTSUMI

Department of Pediatrics, Shinshu University School of Medicine

Kawasaki disease (KD) is an acute childhood febrile illness that is classified as a systemic vasculitis syndrome. Combination intravenous immunoglobulin (IVIG) and acetylsalicylic acid is the standard initial and second-line therapy for KD to resolve inflammation and reduce the occurrence of coronary artery lesions (CALs). The goal of treatment in the acute phase of KD is to decrease inflammation and arterial damage to prevent CALs. For IVIG-resistant KD, however, additional treatments should be administered promptly before CAL formation, such as steroids, infliximab, cyclosporin A (CsA), and plasma exchange (PE). Although the effectiveness of PE on refractory KD is well known, it is highly invasive, especially in infants. Therefore, safer treatments are needed to avoid or minimize the number of PE courses in severe infantile cases. We herein report the clinical outcomes of 2 infants with IVIG-resistant KD who were treated successfully with a combination therapy of CsA and PE as third-line treatment, thereby possibly reducing the number of PE sessions. *Shinshu Med J 70 : 225—231, 2022*

(Received for publication January 24, 2022 ; accepted in revised form April 25, 2022)

Key words : Kawasaki disease, infant, refractory, cyclosporin A, plasma exchange

I Introduction

Kawasaki disease (KD) is an acute childhood febrile illness that is classified as a systemic vasculitis syndrome. Histologically, the earliest changes in KD are seen in the tunica media of the vessel walls on day 6-8 of illness. Inflammation in the intima and adventitia emerges by day 10, and then coronary artery dilation occurs around day 12[1]. It has been reported that coronary artery lesions (CALs) develop in 20-25 % of untreated patients[2] versus only 1 % in promptly treated patients[3][4]. Thus, the therapeutic goal in acute-phase KD is to reduce inflammation and arterial damage as soon as possible to prevent CALs. Currently, combined intravenous immunoglobulin (IVIG) and acetylsalicylic acid (ASA) is the standard initial and second-line therapy for KD. Approximately 15-20 % of patients do not respond to initial KD therapy[5].

The Japanese Kawasaki Disease Treatment Guideline was recently revised in 2020[5]. However, additional treatments for the third line and beyond against IVIG-resistant KD remain unestablished. In the standard initial treatment of KD, patients receive a single dose of IVIG (2 g/kg infused over 12-24 hours) accompanied by high-dosage ASA (30-50 mg/kg/day orally). Prednisolone (PSL) and cyclosporin A (CsA) have been newly described as first-line intensive therapy in combination with the standard treatment for high-refractory risk cases identified by the IVIG refractory prediction score[6]. If the patient exhibits a persistent or recurrent fever within 48 hours of the initial therapy, second line treatment will be given next ; an additional dose of IVIG is currently the most recommended method. For third-line treatments and beyond, IVIG, steroids, infliximab (IFX ; a tumor necrosis factor-alpha inhibitor), CsA, and plasma exchange (PE) have all been suggested for monotherapy or in combination with other regimens. Ultimately, it is the decision of each clinician

* Corresponding author : Noriko Motoki
Department of Pediatrics, Shinshu University School of Medicine, 3-1-1 Asahi, Matsumoto, Nagano 390-8621, Japan
E-mail : nmotoki@shinshu-u.ac.jp

Table 1　Characteristics of the patients

Case	Sex	Age at onset (months)	Clinical symptoms as diagnostic criteria (at diagnosis/at initiation of PE)						Laboratory data immediately prior to IVIG		Laboratory data immediately prior to PE	
			Fever	Conjunctival injection	Cervical lymphadenopathy	Changes in the lips and oral cavity	Changes in the extremities	Polymorphous rash	WBC (/μL)	CRP (mg/dL)	WBC (/μL)	CRP (mg/dL)
1	M	8	(+/+)	(+/+)	(+/+)	(−/+)	(+/+)	(+/−)	7,450	19.47	26,200	24.74
2	M	8	(+/+)	(+/+)	(−/+)	(+/+)	(+/+)	(+/+)	18,610	10.03	28,900	18.05

+ : positive clinical symptom, − : negative clinical symptom
PE, plasma exchange ; IVIG, intravenous immunoglobulin ; WBC, white blood cell count ; CRP, C-reactive protein.

or institution to decide which treatment to select[5].

Since IFX is restricted for infants under 1 year of age in Japan, the treatment options for infant cases of KD are limited. The effectiveness of PE for refractory KD is well known. However, PE in infants is highly invasive since it requires deep sedation and intensive care during vascular access and throughout the exchange[7]. CsA has been adopted as an immunosuppressant for various infant diseases. The use of CsA for IVIG-resistant KD is reportedly safe and well tolerated, even for infants[8][9].

We herein report the clinical outcomes of two 8-month-old male infants with IVIG-resistant KD who were treated successfully with a combination therapy of CsA and PE for third-line treatment.

Ⅱ　Cases

A　Case 1

An 8-month-old male infant exhibited a high-grade fever, followed 3 days later (day 4 of illness) by bilateral conjunctival infection, cervical lymphadenopathy, hardened edema and erythema of the finger and toe tips, and a polymorphous rash **(Table 1)**. There was no medical or family history of note, and he was fully immunized. The patient was first admitted to a municipal hospital with a diagnosis of KD. Laboratory investigation at the time revealed hemoglobin (Hb) 8.9 g/dL, white blood cell count (WBC) $7.45\times10^3/\mu$L, neutrophils (Neu) 86.8 % , platelets $36.3\times10^4/mm^3$, aminotransferase (AST) 69 U/L, alanine aminotransferase (ALT) 69 U/L, albumin 3.1 g/dL, sodium 132.5 mEq/L, and C-reactive protein (CRP) 19.4 mg/dL. No dilation of the coronary artery was present on echocardiography. Kobayashi risk score as a predictor of the response to IVIG therapy was 8 points, which indicated high IVIG refractory risk[6]. He was initially administered IVIG (2 g/kg) over 12 hours and oral flurbiprofen (5 mg/kg/day) instead of ASA due to high transaminase levels **(Fig. 1)**. 48 hours after the start of treatment, his fever persisted, and blood tests showed strong inflammatory findings (WBC $10.4\times10^3/\mu$L and CRP 18.6 mg/dL). Although a second dose of IVIG (2 g/kg) was given on day 6, he remained febrile with a further increase in CRP to 22.0 mg/dL. He was referred to our hospital for PE as an additional treatment on day 8.

After the first course of PE, his CRP level dropped temporarily from 24.7 mg/dL to 10.9 mg/dL, but by the next day increased to 26.2 mg/dL. Since his response to PE alone was insufficient, we added continuous infusion of CsA (4 mg/kg/day) from day 9. After 2 additional courses of PE combined with CsA, his CRP level had decreased to 6.9 mg/dL, which enabled a switch from intravenous to oral CsA medication (4 mg/kg/day divided into 2 doses). After completing the third course of PE, he became afebrile, and his CRP gradually decreased to 1.72 mg/dL. On day 15, however, in addition to a fever of 38.2 ℃ , echocardiography revealed mild coronary artery dilation, and so an additional course of IVIG was commenced. The coronary arteries were dilated up to the left main trunk (LMT) at 3.2 mm (Z-score 2.65), left anterior descending branch (LAD) at 2.5 mm (Z-score 2.76), and right coronary artery (RCA) at 2.7 mm (Z-score 2.50) but only transiently and without aneurysms. Since he remained afebrile with

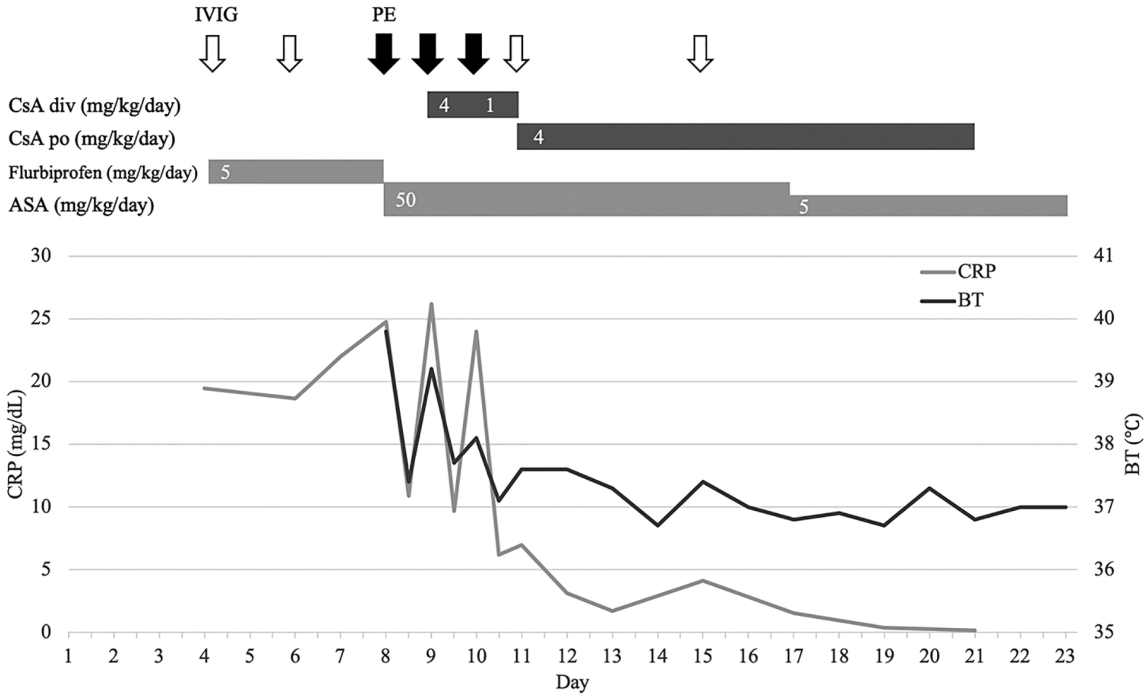

Fig. 1 Clinical course of case 1
IVIG, intravenous immunoglobulin ; PE, plasma exchange ; CsA, cyclosporin A ; div, drip intravenous ; po, per os ; ASA, acetylsalicylic acid ; CRP, C-reactive protein ; BT, body temperature.

normal CRP by day 21, we discontinued CsA. He was discharged on day 23 with low-dosage (5 mg/kg/day) ASA without any complications associated with PE or CsA. His CALs progressively regressed, and follow-up echocardiography 2 years after the onset of KD revealed normal findings of LMT 2.5 mm (Z-score 0.53), LAD 2.3 mm (Z-score 1.77), and RCA 2.5 mm (Z-score 1.76).

B Case 2

An 8-month-old male infant suffered a high-grade fever, followed 3 days later (day 4 of illness) by bilateral conjunctival infection, erythematous lips and strawberry tongue, hardened edema and erythema of the finger and toe tips, and a polymorphous rash **(Table 1)**. He was fully immunized and had no relevant medical history, although his cousin earlier had KD. He was first admitted to a municipal hospital with a diagnosis of KD. Laboratory investigation on admission revealed Hb 11.3 g/dL, WBC $18.6\times10^3/\mu$L, Neu 73.6 %, platelets $41.8\times10^4/mm^3$, AST 59 U/L, ALT 47 U/L, albumin 3.6 g/dL, sodium 132 mEq/L, and CRP 10.03 mg/dL. Coronary artery dilatation was absent on echocardiography. Kobayashi risk score was 6 points, indicating high risk of IVIG resistance. IVIG (2 g/kg) and high-dosage (30 mg/kg/day) ASA treatment was applied **(Fig. 2)**. After 2 courses of IVIG resulting in poor response (body temperature 39 ℃, WBC $26.6\times10^3/\mu$L, and CRP 20.8 mg/dL), he was transferred to our hospital for additional treatment on day 9.

Initial continuous infusion of CsA (2.4 mg/kg/day) provided limited results, with further increases in fever and CRP. On day 10, we combined CsA with PE. After the second course of PE, he became afebrile, and his CRP level had decreased to 3.33 mg/dL. During CsA tapering and discontinuation, a mild fever and increases in inflammatory findings were detected. However, no CAL formation was observed, and so IVIG treatments were added accordingly. He was discharged on day 36 with low-dosage ASA, without any complications associated with CsA or PE. Repeated echocardiography showed no dilation of the coronary artery during the clinical course or at 2 years of follow-up.

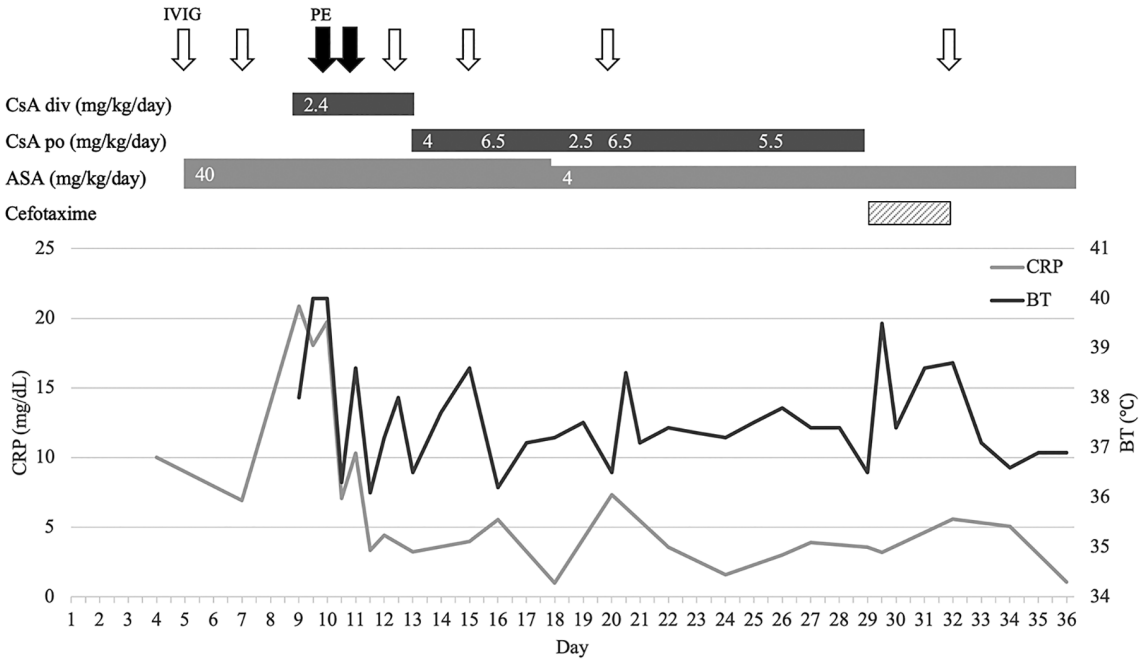

Fig. 2 Clinical course of case 2
IVIG, intravenous immunoglobulin ; PE, plasma exchange ; CsA, cyclosporin A ; div, drip intravenous ; po, per os ; ASA, acetylsalicylic acid ; CRP, C-reactive protein ; BT, body temperature.

Ⅲ Discussion

This study described the clinical outcomes of 2 infants with IVIG-resistant KD who were managed successfully with combination therapy of CsA and PE. Neither CsA nor PE alone was effective in both patients. By combining the therapies, however, we were able to minimize the number of PE sessions, a highly invasive treatment especially in infants under 1 year of age.

The therapeutic aim in acute-phase KD is the reduction of inflammation and arterial damage to prevent CALs. Even in IVIG-refractory cases, additional treatments aim for successful symptom resolution by day 9, before the onset of coronary artery dilation[5]. At our institution, the first- and second-line treatments for KD are IVIG with high-dosage ASA, followed by IFX. The advantage of IFX is that it takes only 2 hours for administration and that the efficacy can be determined after a single dose. The average time for fever alleviation is as short as 16.6 hours, and the antipyretic rate at 48 hours after administration is 77.4-83.6 %[10)11)]. However, there are several contra-indications to IFX, including patients under 1 year old, those vaccinated against BCG within 6 months prior or given a live vaccine within 1 month prior, and those already with CALs[5]. Accordingly, CsA or PE is likely to be chosen as the third-line therapy and beyond in infants less than 1 year of age. In 2013, Kobayashi et al. demonstrated that the incidence of CALs and the need for additional treatment were significantly lower for PSL + IVIG than for IVIG alone[12]. However, PSL can mask fever and CRP elevation, making it difficult to predict CAL progression. Long-term steroid administration may also weaken arterial walls[5] ; we have encountered several cases of giant aneurisms and coronary artery rupture during and after steroid use. Thus, from the viewpoint of safety and effectiveness that can be judged in a short time, we have adopted a protocol using IFX from the third line of treatment onward.

In Europe and the U.S., the first line of treatment for KD is IVIG (2 g/kg) and ASA, whose efficacy is determined at 48 hours. For the second line, additional IVIG or combination with methylprednisolone (MP) or PSL is considered, with CsA, PE, and IFX as

options for third line and beyond. MP or PSL is also considered for high-risk patients. However, since evidence on additional treatments are lacking and risk scores are less accurate, steroids are not highly recommended in such cases[13)14)]. Our therapeutic strategy is comparable to that of general treatment in Europe and the U.S.

In the post-RAISE study, younger age (<6 months of age) was associated with a higher risk of CALs at 1 month after onset[15)]. Another report also indicated that even in a low-risk group, younger age (<12 months of age) was a risk factor for CALs[16)]. Considering that "age under 12 months" is included in the Kobayashi risk score as well, aggressive treatment should be pursued to promptly resolve vasculitis, especially in infants.

PE has been a treatment option for KD long before IVIG and has a history of nearly 40 years[7)]. Since it can remove excessive inflammatory cytokines in the circulation, PE has become the last resort for IVIG-resistant KD[17)]. PE has a wider range of therapeutic indications than other treatment options and can be adapted to various pathological conditions, including infection and heart failure, even in infants. Despite its effectiveness, however, PE can only be performed at specialized facilities in which intensive pediatric care is possible because invasive procedures, such as catheter placement in the inguinal or external jugular vein, deep sedation, and artificial respiration, are required in infants. The complications of PE have been discussed in various studies[18)-21)]. When the technique is performed in children with a small body size and low circulating blood volume, it is necessary to ensure reliable vascular access, reduce priming volume, prevent hypothermia, use anticoagulants, and provide safe sedation[7)]. PE requires 2 hours per procedure and can be performed up to 5 consecutive days, although shorter periods lead to fewer complications.

CsA is used relatively frequently in children since it has long been indicated for nephrotic syndrome and post-organ transplantation. No serious side effects have been reported to date, with minor complications including pseudohyperkalemia, hypomagnesemia without arrhythmia, elevated blood pressure, nausea, vomiting, tremor, and in long-term use cases, temporary hirsutism[5)8)9)].

Additional indications for CsA were added for KD in 2020 after the publication of the KAICA trial[22)], which proved the significant effect of the drug on preventing CALs, namely: 1) for predicted IVIG-resistant KD as first-line intensive treatment in combination with IVIG, and 2) for IVIG-resistant KD as an additional treatment. Unlike IFX, CsA can be used in infants 4 months and older. As supplemental treatment, CsA (5 mg/kg/day) is orally administered in equally divided doses before morning and evening meals. If oral intake is difficult, intravenous CsA can be administered at 3-4 mg/kg/day divided into 2 doses, and then switched to oral CsA whenever possible[5)8)]. Since intravenous CsA often results in higher blood concentrations, we started with a lower dose (2.4 mg/kg/day) in Case 2. Trough value is measured before administration on the third day for adjusting the dose to reach the target concentration of 60-200 ng/mL. Five days are needed to determine the effect of CsA and decide whether to continue it for 10-14 days until CRP decreases sufficiently[9)]. In studies whereby CsA was given as additional treatment beyond the third line, the fever resolved within 5 days and CRP decreased in many cases. CsA is also recommended as initial treatment in combination with IVIG for high-risk patients[5)]. However, it should be noted that CsA requires a longer time to determine efficacy than other treatments, which may delay the start of second-line treatment. Nevertheless, CsA may be considered in high-risk infants for whom IFX is unavailable.

The combination therapy of CsA and PE is also used for other immunosuppressive-resistant diseases, such as autoimmune diseases[23)-25)] and after kidney transplantation[26)], by exerting complimentary actions. Shimada et al.[27)] reported that IFX prior to PE could decrease the total duration of PE (median number of PE sessions of the IFX + PE group vs. the PE group: 2.0 vs. 4.5) and reduce the physical and mental burden of patients related to vascular access, physical restraint, and deep sedation. Even if IFX therapy be-

fore PE alone seems clinically ineffective, it helps to lower the levels of granulocyte colony-stimulating factor, monocyte chemotactic protein-1, human tumor necrosis factor alpha, and other cytokines, thus indicating an ability to rapidly suppress inflammation[27]. In the 2 presented cases, the lack of a response to PE alone (Case 1) or CsA alone (Case 2) coincidentally led to combination therapy. According to the study by Shimada et al.[27], we would like to prospectively investigate the effectiveness of combination treatment by pre-administering CsA and adding PE based on cytokine profiles.

The therapeutic goal of acute-phase KD is rapid fever elimination without CAL formation. In cases where CsA or PE alone is insufficient, combining the therapies may shorten the febrile period and minimize the number of invasive PE procedures as well as IFX prior to PE. Further studies are needed to evaluate the effect and mechanism of CsA on PE.

Ⅳ Conclusion

We successfully treated 2 infants with IVIG-resistant KD using a combination therapy of CsA and PE, which may have reduced the number of invasive PE sessions. Combined CsA and PE may be a new treatment strategy for infants with IVIG-resistant KD, which currently has few treatment options.

References

1) Masuda H NS, Tanaka N : The pathology of coronary arteries in Kawasaki disease (MCLS) : A consideration of the relationship between coronary arteritis and the development of aneurysms. Jpn Coll Angiol 21 : 899-912, 1981
2) Kato H, Sugimura T, Akagi T, et al : Long-term consequences of Kawasaki disease. A 10- to 21-year follow-up study of 594 patients. Circulation 94 : 1379-1385, 1996
3) Makino N, Nakamura Y, Yashiro M, et al : Descriptive epidemiology of Kawasaki disease in Japan, 2011-2012 : from the results of the 22nd nationwide survey. J Epidemiol 25 : 239-245, 2015
4) Tremoulet AH, Best BM, Song S, et al : Resistance to intravenous immunoglobulin in children with Kawasaki disease. J Pediatr 153 : 117-121, 2008
5) Miura M, Ayusawa M, Fukazawa R, et al : Guidelines for Medical Treatment of Acute Kawasaki Disease (2020 Revised Version). J Pediatr Cardiol Card Surg : 41-73, 2021
6) Kobayashi T, Inoue Y, Takeuchi K, et al : Prediction of intravenous immunoglobulin unresponsiveness in patients with Kawasaki disease. Circulation 113 : 2606-2612, 2006
7) Mori M, Yamazaki S, Naruto T : The Benefits and Respective Side-Effects of PE Therapy for Intractable Kawasaki Disease. J Clin Med 10 : 1062, 2021
8) Tremoulet AH, Pancoast P, Franco A, et al : Calcineurin inhibitor treatment of intravenous immunoglobulin-resistant Kawasaki disease. J Pediatr 161 : 506-512, 2012
9) 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 30 : 871-876, 2011
10) Miura M, Kobayashi T, Igarashi T, et al : Real-world Safety and Effectiveness of Infliximab in Pediatric Patients With Acute Kawasaki Disease : A Postmarketing Surveillance in Japan (SAKURA Study). Pediatr Infect Dis J 39 : 41-47, 2020
11) Masuda H, Kobayashi T, Hachiya A, et al : Infliximab for the Treatment of Refractory Kawasaki Disease : A Nationwide Survey in Japan. J Pediatr 195 : 115-120, 2018
12) Kobayashi T, Morikawa A, Ikeda K, et al : Efficacy of intravenous immunoglobulin combined with prednisolone following resistance to initial intravenous immunoglobulin treatment of acute Kawasaki disease. J Pediatr 163 : 521-526, 2013
13) McCrindle BW, Rowley AH, Newburger JW, et al : Diagnosis, Treatment, and Long-Term Management of Kawasaki Disease : A Scientific Statement for Health Professionals From the American Heart Association. Circulation 135 :

e927–e999, 2017

14) de Graeff N, Groot N, Ozen S, et al : European consensus-based recommendations for the diagnosis and treatment of Kawasaki disease-the SHARE initiative. Rheumatology (Oxford) 58 : 672–682, 2019

15) Iio K, Morikawa Y, Miyata K, et al : Risk Factors of Coronary Artery Aneurysms in Kawasaki Disease with a Low Risk of Intravenous Immunoglobulin Resistance : An Analysis of Post RAISE. J Pediatr 240 : 158–163, 2022

16) Miyata K, Miura M, Kaneko T, et al : Evaluation of a Kawasaki Disease Risk Model for Predicting Coronary Artery Aneurysms in a Japanese Population : An Analysis of Post RAISE. J Pediatr 237 : 96–101, 2021

17) Fujimaru T, Ito S, Masuda H, et al : Decreased levels of inflammatory cytokines in immunoglobulin-resistant Kawasaki disease after plasma exchange. Cytokine 70 : 156–160, 2014

18) Brunetta Gavranić B, Bašić-Jukić N, Kes P : Therapeutic Plasma Exchange-Does Age Matter ? A Single-Center Study. Artif Organs 8 : 782–792, 2016

19) Lu J, Zhang L, Xia C, Tao Y : Complications of therapeutic plasma exchange : A retrospective study of 1201 procedures in 435 children. Medicine (Baltimore) 98 : e18308, 2019

20) Michon B, Moghrabi A, Winikoff R, et al : Complications of apheresis in children. Transfusion 47 : 1837–1842, 2007

21) Mokrzycki MH, Balogun RA : Therapeutic apheresis : a review of complications and recommendations for prevention and management. J Clin Apher 26 : 243–248, 2011

22) Hamada H, Suzuki H, Onouchi Y, et al : Efficacy of primary treatment with immunoglobulin plus ciclosporin 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 393 : 1128–1137, 2019

23) Bambauer R, Schwarze U, Schiel R : Cyclosporin A and therapeutic plasma exchange in the treatment of severe systemic lupus erythematosus. Artif Organs 24 : 852–856, 2000

24) Schiel R, Bambauer R, Latza R, Klinkmann J : Cyclosporin and therapeutic plasma exchange in treatment of progressive autoimmune diseases. Artif Organs 21 : 983–988, 1997

25) Bonifati DM, Angelini C : Long-term cyclosporine treatment in a group of severe myasthenia gravis patients. J Neurol 244 : 542–547, 1997

26) Demir ME, Uyar M, Merhametsiz O : Combination of High-Dose Intravenous Cyclosporine and Plasma Exchange Treatment Is Effective in Post-Transplant Recurrent Focal Segmental Glomerulosclerosis : Results of Case Series. Transplant Proc 52 : 843–849, 2020

27) Shimada S, Matsuoka D, Murase T, et al : Impact of infliximab administration before plasma exchange therapy on patients with Kawasaki disease. Ther Apher Dial 24 : 718–724, 2020

（2022. 1. 24 received ; 2022. 4. 25 accepted）