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REVIEW ARTICLE

Intravenous immunoglobulin, pharmacogenomics, and Kawasaki disease

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Kawasaki disease (KD) is a systemic vasculitis of unknown etiology and it is therefore worth examining the multifactorial interaction of genes and environmental factors. Targeted genetic association and genome-wide association studies have helped to provide a better understanding of KD from infection to the immune-related response. Findings in the past decade have contributed to a major breakthrough in the genetics of KD, with the identification of several genomic regions linked to the pathogenesis of KD, including *ITPKC*, *CD40*, *BLK*, and *FCGR2A*. This review focuses on the factors associated with the genetic polymorphisms of KD and the pharmacogenomics of the response to treatment in patients with intravenous immunoglobulin resistance.

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Introduction

Kawasaki disease (KD) is a pediatric disease characterized as an acute systemic vasculitis syndrome. It was first reported in Japanese by Kawasaki et al[1] in 1967 and in English in 1974 and is currently thought to be the primary cause of acquired heart disease of children in industrialized countries. KD predominantly affects the coronary arteries and causes coronary artery lesions (CALs). The symptoms of KD are myocardial infarction, coronary artery fistulas, coronary artery aneurysms, and coronary artery dilatation, which can develop long-term sequelae, e.g., stenosis or obstruction.[2] Several genes, including *ITPKC*, *TGFBR2*, *CASP3*, *COL11A2*, and *SRC-1*, have been considered as being associated with the formation of CALs in KD.[3–7] However, to date, the etiology of KD remains unknown.[8–10] KD has a predilection for children younger than 5 years and epidemiology records have shown that Asian countries (especially Japan, Taiwan, and Korea) have a higher incidence rate than Western countries. In addition, the incidence rate is increasing worldwide, except in Taiwan.[11,12]

The etiology of KD may be attributed to the combined effects of infection, immune response, tropospheric winds, and genetic susceptibility.[13–22] The standard treatment with high doses of aspirin (80–100 mg/kg/day) and high doses of intravenous immunoglobulin (IVIG, 2 g/kg) has been shown to significantly decrease the rate of formation of coronary artery aneurysms from 20–25% to 3–5%.[23,24] Newburger et al[94] first reported that in the treatment of children with the acute stage of KD, the use of a single large dose of IVIG is more effective than the conventional four-dose or two-dose regimen. Burns et al[9] have also mentioned that a large and single dose of IVIG is now the gold standard treatment in KD. However, the effectiveness of IVIG in KD remains under investigation and *FCGR2A* may be worth considering based on genome-wide association studies.

The clinical characteristics of patients with KD include fever lasting for more than 5 days, diffuse mucosal inflammation with strawberry tongue and fissure lips, bilateral nonpurulent conjunctivitis, indurative angioedema over the hands and feet, dysmorphic skin rashes, and unilateral cervical lymphadenopathy. We have established the "Kuo mnemonic" for rapid memorization of the diagnostic criteria of KD (Table 1).

Table 1 "Kuo mnemonic" for the rapid memorization of the diagnostic criteria for Kawasaki disease

Number	Mnemonic	Clinical signs
1	"One" mouth	Diffuse mucosal inflammation with strawberry tongue and fissure lips
2	"Two" eyes	Bilateral nonpurulent conjunctivitis
3	"Three" fingers palpation of neck lymph nodes	Unilateral cervical lymphadenopathy
4	"Four" limbs − changes	Indurative angioedema over both hands and feet
5	"Five" = multiple skin rash	Dysmorphic skin rash

Treatment with IVIG

IVIG has been used for the treatment of KD since it was first reported by Furusho et al[25] in 1983, > 10 years after the first report of KD. A randomized controlled trial by Newburger et al[26] in 1986 showed that high doses of IVIG (400 mg/kg/d for 4 days) were safe and effective in reducing the prevalence of CALs from 20–25% to 3–5% when administered to patients with acute KD. In regard to the correct dose of IVIG, Newburger et al suggested in 1991 that a single high dose of IVIG (2 g/kg) is more effective than a 4-day regimen. Currently, a large and single dose of IVIG is considered to be the gold standard in the treatment of patients with KD in the acute phase.[94] Nevertheless, its mechanism for decreasing inflammation in KD remains unclear and requires investigation. It is suspected that the related mechanisms may include blockade of the Fc receptor,[16,27] neutralization of the pathogenic or toxic products of an unknown infectious agent, an immune-modulatory effect,[28] stimulation of suppressor activity, and modulation of cytokines and cytokine antagonists.[29]

IVIG appears to have a generalized anti-inflammatory effect. Possible mechanisms include the enhancement of regulatory T cell activity (transforming growth factor), neutralization of bacterial super-antigens or other unknown pathogenic agents, regulation of cytokine production, suppression of antibody synthesis and inflammatory markers (CD40–CD40L, nitric oxide, and inducible nitric oxide synthase expression),[17,18,30,31] the provision of anti-idiotypic antibodies, the Fc-gamma receptor and interleukin 1β, and balancing the T helper (Th) Th1/Th2 immune responses.[30–37]

For patients with KD, treatment with IVIG should be performed within 10 days of the onset of the illness. Existing data have shown that receiving treatment prior to Day 5 of the onset of illness appears to be no more likely to prevent cardiac sequelae than treatment on Days 5–9.[2,9,10] However, this phenomenon may, for unknown reasons, be associated with an increased need for retreatment with IVIG.

The efficacy of receiving IVIG treatment after 10 days of illness has not been well studied. Therefore we suggest that both early diagnosis and treatment are essential (within 10 days of the onset of illness). Patients with KD with incomplete treatment or delayed diagnosis should still be given IVIG. For example, children who develop symptoms such as persistent and systemic inflammation, continuous fever of unknown origin, the formation of aneurysms, and high concentrations of inflammatory markers as manifested by an increased erythrocyte sedimentation rate or C-reactive protein (with or without coronary artery abnormalities) should receive IVIG treatment even if the diagnosis is made after 10 days of the illness (i.e., delayed diagnosis). For IVIG-resistant patients who have a higher risk of developing CALs than IVIG-sensitive patients, earlier and highly effective anti-inflammatory treatment must be emphasized to reduce the risk of forming CALs. Infliximab has been shown to be effective in IVIG resistance; however, combining infliximab with the standard treatment in acute KD did not reduce resistance to treatment.[38,39]

The American Academy of Pediatrics and the American Heart Association have published treatment guidelines suggesting rapid treatment with a combination of high doses of immunoglobulins (2 g/kg) within 8–12 h and high doses of aspirin as the standard treatment for KD.[2] Immunoglobulins are obtained from human blood; however, although the World Health Organization has published production guidelines, there are some differences in the manufacturing processes that may affect the efficiency of treatment, such as purification, immunoglobulinA concentrations, and conditions related to preservation.[40] The association between preservation conditions and the effectiveness of treatment have also been studied. Tsai et al[41] reported that β-propiolactonation is related to the promotion of the rate of failure of the initial IVIG treatment. However, in a retrospective study of the existing Canadian data, Manlhiot et al[42] found a contradictory result, which noted that preserving immunoglobulins in acidic conditions led to a lower treatment failure rate, but increased the rate of coronary aneurysms. Lin et al[40] reached a similar conclusion, stating that β-propiolactonation in IVIG preparation resulted in an increased risk of treatment failure and prolonged use of antiplatelet or anticoagulant treatment. Acidification might have induced the formation of acute coronary aneurysms in the 3830 children enrolled in a population-based study in Taiwan.

IVIG resistance

Tremoulet et al[43] reported that the incidence of IVIG resistance ranged from 9.4% to 23% among hospitals and countries generally, but the highest percentage of IVIG-resistant patients reached 38%. As IVIG-resistant patients have a higher probability for CAL formation, it is important to treat them aggressively. There are several treatments available to combine with the second administration of IVIG for patients who do not respond to the initial IVIG treatment, such as tumor necrosis factor α (TNF-α) blockade,[39] methylprednisolone pulse treatment,[44] cytotoxic drugs (cyclophosphamide, cyclosporine A, and methotrexate[45]), plasmapheresis,[46] and plasma exchange.[47]

Tables 2 and 3 show that recent studies have identified a number of epidemiological and laboratory characteristics as predictors of IVIG resistance,[40,41,43,49–51,70–85] with biomarkers including age, illness day, platelet count, erythrocyte sedimentation rate, hemoglobin concentration, C-reactive protein, eosinophils, lactate dehydrogenase, albumin, alanine aminotransferase, clusterin, G-CSF, and sonographic gallbladder abnormalities.[48–53]

The plasma concentrations of TNF and soluble TNF receptors are increased in acute KD and are associated with the formation of CALs.[54] TNF-α is also reported to be necessary to incite the inflammation of coronary arteries and for the formation of aneurysms in an animal model of KD.[55] Some studies using infliximab or etanercept in patients resistant to an initial intravenous immunoglobulin treatment have been suggested as having some benefit.[38,56] TNF-α blockade has been shown to be beneficial in patients with KD with IVIG resistance, but this is not recommended as a primary treatment with IVIG. Although there is evidence to show that there are biomarkers associated with IVIG resistance, the accurate prediction of potentially IVIG-resistant patients and application of an aggressive treatment regimen remains a challenge for both clinicians and scientists. For patients with severe KD or for those in a high-risk group, Kobayashi et al[57] suggested that the addition of prednisolone to the standard regimen of IVIG could improve coronary artery outcomes.

Table 2 Clinical characteristics in Kawasaki disease related to intravenous immunoglobulin resistance

Factor	High-risk group of IVIG resistance	Refs
Age	≤12 months	70,71
Sex	Male	51,72
Duration of fever	Long duration of fever	43,70,73–76
Gallbladder abnormalities	Sonographic gallbladder abnormalities	77
Treatment day	Day 4 or earlier; before the 5th day of illness	70–72,78,79
Recurrent Kawasaki disease	Onset of Kawasaki disease more than twice	72
Brand of IVIG	IVIG product prepared with beta-propiolactone	40,41

IVIG = intravenous immunoglobulin.

Aspirin

Aspirin has been prescribed as a treatment for KD for many years, even before IVIG was used. Although aspirin has

Table 3 Laboratory data related to intravenous immunoglobulin resistance in Kawasaki disease

Factor	High-risk group of IVIG resistance	Refs
Albumin	Albumin <2.9 g/dL	49,51,76,79–81
Sodium	≤133 mmol/L	71,79
Eosinophils	Increase in eosinophils indicates responsiveness	50
Platelet count	$\leq 30.0 \times 10^4/mm^3$	70,71,82
Hemoglobin	Anemia by age	43,81
Neutrophils	≥75%	70,74,76,81–84
Band form	Increased	43,80,81
CRP	≥10 mg/dL	43,70,71,73,74,76,84
Liver enzymes	ALT ≥ 84 IU/L, AST ≥ 100 IU/L, total bilirubin ≥ 0.9 mg/dL	43,51,70,71,76,82,83
ESR	Increased	75
PT/INR	Prolonged	85
NT-BNP	Increased	83

ALT = alanine aminotransferase; AST = aspartate aminotransferase; CRP = C-reactive protein; ESR = erythrocyte sedimentation rate; IVIG = intravenous immunoglobulin; NT-BNP = N-terminal fragment of B-type natriuretic peptide; PT/INR = prothrombin time international normalized ratio.

important anti-inflammatory (at high doses) and anti-platelet (at low doses, 3–5 mg/kg/day) effects, it does not appear to reduce the frequency of CAL formation and IVIG resistance in patients with KD. The integration of anti-inflammatory doses of aspirin with IVIG has been suggested, but the doses remain controversial. High doses of aspirin (80–100 mg/kg/d) are most widely applied in North America during the acute stage, whereas moderate doses (30–50 mg/kg/d) are recommended as a standard treatment in Japan.

However, a report has indicated that combining aspirin with the standard treatment in the acute stage of KD does not affect the IVIG response rate, continuing fever, nor CAL formation.[58] To date, the existing data show no benefit to patients in the acute phase of KD and thus treatment with high or medium doses of aspirin may not be necessary. Reye's syndrome is a potentially fatal syndrome; it is largely seen in children who are treated with salicylates while experiencing infection with a virus. Reye's syndrome has been reported in patients using high doses of aspirin for a long period of time after KD.[59] Although there is no proven causal link, some studies have shown an association between aspirin use and Reye's syndrome. Aspirin use in children should be limited to diseases with a clearly proven benefit, such as KD and juvenile idiopathic arthritis.[60] Hsieh et al[58] have reported that treatment without high doses of aspirin did not affect the response rate of IVIG treatment, fever duration, nor incidence of CAL for patients in the acute phase compared with children who were treated with high doses of IVIG as a single infusion. Chen et al[61] reported that patients with KD with glucose-6-phosphate dehydrogenase deficiency who did not receive aspirin during treatment had a good response without CAL complications. Whether high doses of aspirin should be given in the acute stage of KD or not warrants further multi-center randomized control trials before a definitive recommendation can be made.

Biomarkers, pharmacogenomics, and IVIG treatment

Several biomarkers and genetic polymorphisms have been reported to predict IVIG resistance (Table 4).[28,53,84,86–88] Based on their work on T cell markers, Hirabayashi et al[62] have indicated that a lower percentage of CD4(+)CD25(+) FOXP3(+) regulatory T cells was observed in the peripheral blood of patients with KD. Furthermore, the study showed that IVIG resistance was related to a lack of CD4(+)CD25(+) FOXP3(+) regulatory T cells. FOXP3 was also reported to play an important part in the development of breast cancer and had implications for treatment and diagnosis.[63]

Brain natriuretic peptide (BNP), a cardiac hormone secreted by the ventricle, has been proposed as a marker of the acute phase of KD. The concentrations of BNP have been found to increase in plasma during the acute stage and then decrease to within the normal range in the convalescent stage of KD.[64] NT-proBNP, the N-terminal fragment of BNP, increases in the acute phase, but decreases in the convalescent phase of KD. Kim et al[65] indicated that a higher level of serum NT-proBNP was associated with IVIG resistance in patients with KD. An NT-proBNP level ≥1093 pg/dL might be a potential predictor of the failure of IVIG treatment. In addition, genetic variations were associated with IVIG resistance in patients with KD. In 2011, Shrestha et al[66] showed that the TT genotype of the *FcγRIIB* (−120T/a) gene showed a significant association with unresponsiveness to IVIG in patients with KD. Gene copy number and polymorphism of *FcγR* influences of the IVIG treatment response and in the susceptibility of KD were reported, providing potential insights into understanding the mechanism of the *FcγR* gene family in the IVIG pathway.[27,67] The fragment crystallizable (Fc) region links the key pathogen identification and destruction properties of immunoglobulin G. Pathogen opsonization positions Fcs to activate proinflammatory Fcγ receptors on immune

Table 4 IVIG resistance-related cytokines in Kawasaki disease

Factor	High-risk group of IVIG resistance	Refs
Clusterin	Post-IVIG − pre-IVIG >8.52 mg/L	53
IL-6	Pre-IVIG, 70 pg/mL ≤IL-6 level <140 pg/mL	84
IL-10	Post-IVIG, >10 pg/mL	28
TNF-α	Post-IVIG, <2 pg/ mL	28
IL-17	Higher expression	86
CD4 + CD25 + FoxP3 T_{reg}	Higher expression frequency	86
NT-proBNP	>800 pg/mL	87
G-CSF	Higher expression	88

G-CSF = granulocyte colony-stimulating factor; IVIG = intravenous immunoglobulin; IL = interleukin; NT-proBNP = N-terminal fragment of pro-B-type natriuretic peptide; TNF = tumor necrosis factor.

Table 5 Genetic variants in Kawasaki disease related to intravenous immunoglobulin resistance

Factor	High-risk group of IVIG resistance	Refs
ITPKC	rs28493229 C allele	68,69,89
CASP3	rs113420705 A allele	68,69,89
FCGR2A	rs1801274 A allele	89
DC-SIGN (CD209)	rs4804803 G allele, rs2287886 A allele	90,91
CCR2-CCR5	HHF*2 haplotype	92
CCL3L1	<4 copies	92
IL-1B	−511 TT genotype, −31 CC genotype	93
PAF-AH	V279F GG genotype	73

CASP3 = caspase 3; CCL3L1 = chemokine (C-C motif) ligand 3-like 1; CCR2 = CC chemokine receptor 2; CCR5 = CC chemokine receptor 5; DC-SIGN = dendritic cell-specific intercellular adhesion molecule-3-grabbing nonintegrin; FCGR2A = Fc fragment of immunoglobulin G, low affinity IIa, receptor; IVIG = intravenous immunoglobulin; ITPKC = inositol 1,4,5-trisphosphate 3-kinase C; PAF-AH = platelet-activating factor acetylhydrolase.

cells. The expression of Fcγ receptors and the association between receptors and genetic polymorphism and epigenetic effects are needed to clarify the role of Fcγ receptors in KD and the IVIG treatment response. The Fc domain or other Fc fragment may be more effective in the treatment of KD than IVIG; further studies are needed.

The C allele of *ITPKC* (rs28493229) and the A allele of *CASP3* (rs113420705) were associated with susceptibility to KD and CAL formation, but not to the IVIG treatment response.[5,14,15,33] A combination of *ITPKC* (rs28493229) and *CASP3* (rs113420705) polymorphisms affected the IVIG treatment response and the risk of CAL formation.[68,69] Table 5 shows the IVIG resistance-related genetic variants in KD.[68,69,73,89–93]

As high-throughput genomic technology and genomic information become more readily available, further insightful research is expected to better elucidate the markers responsible for the response to IVIG treatment in patients with KD.

Conflicts of interest

All contributing authors declare no conflicts of interest.

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