Journal of Microbiology, Immunology and Infection (2016) 49, 1–7

Available online at www.sciencedirect.com

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journal homepage: www.e-jmii.com

REVIEW ARTICLE

Intravenous immunoglobulin, pharmacogenomics, and Kawasaki disease

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Received 17 April 2014; received in revised form 14 July 2014; accepted 4 November 2014
Available online 11 November 2014

KEYWORDS
genetic polymorphisms;
genome-wide association studies;
intravenous immunoglobulin resistance;
Kawasaki disease;
pharmacogenomics

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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http://dx.doi.org/10.1016/j.jmii.2014.11.001

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]