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KAWASAKI'S DISEASE

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ABSTRACT

Effective therapies to reduce the acute symptoms of the pediatric syndrome Kawasaki's disease can prevent the development of future cardiovascular complications, particularly fatal coronary artery aneurysms. The first line of therapy for Kawasaki's disease is generally intravenous immunoglobulin (IVIG); however, issues involving the cost of this treatment and the fact that an increasing proportion of the Kawasaki's disease population demonstrates resistance to IVIG have challenged standard-of-care practices. This review highlights emerging therapeutic strategies for Kawasaki's disease, including IVIG combination therapies, blockers of TNF-α, statins and steroids.

INTRODUCTION

Kawasaki's disease (also known as Kawasaki's syndrome or mucocutaneous lymph node syndrome) is a potentially life-threatening acute vasculitis (inflammation of the walls of small- and medium-sized arteries throughout the body, including the coronary arteries) that can occur in children (as a result, it is also known as infantile polyarteritis). Eighty percent of Kawasaki's disease cases are diagnosed in children under five years of age; the disorder is uncommonly diagnosed in older children and teenagers (1). Its effects on the heart can cause significant long-term cardiac sequelae (2). Other organs affected in Kawasaki's disease include the skin, mucous membranes of the mouth, nose and throat, and the lymph nodes. Kawasaki's disease is named after the Japanese pediatrician Tomisaku Kawasaki, who first identified the syndrome in 1967 (3). The cause of Kawasaki's disease is currently unconfirmed, with several links to bacteria, viruses, environmental factors and genetic susceptibility (4-6).

Kawasaki's disease is described as appearing in phases: characterized by fever, conjunctivitis, trunk/genital rash, cracked lips, swollen tongue, inflamed skin on the palms of the hands and the soles of the feet, and swollen lymph nodes during the first phase; peeling of the skin on the hands and feet, joint pain, diarrhea, vomiting and abdominal pain during the second phase; and abatement or complication of symptoms depending on the effectiveness of therapeutic intervention during the third phase. Long duration of fever during the acute stages of Kawasaki's disease has been shown to increase cardiac risk, with most deaths as a result of cardiac complications occurring unpredictably. It has been reported that over 50% of deaths occur within 1 month of onset, 75% within 2 months and 95% within 6 months, but mortalities have also been reported up to 10 years after diagnosis (7). Kawasaki's disease occurs in 19 of every 100,000 children in the United States, but it is predominant in children of Japanese and Korean descent (8).

Without therapy, mortality associated with Kawasaki's disease has been reported to be 1%, usually occurring within 6 weeks of onset. However, with adequate therapy, the mortality rate in the U.S. is 0.17%. Effective therapy can reduce acute symptoms and, more importantly, the incidence of coronary artery aneurysms from 20% to < 5% (7). An update of clinical trials to assess the impact of novel and long-standing pharmaceuticals for the treatment of Kawasaki's disease is outlined in Table I. This review will highlight the recent advances emerging from publications and congresses in the Kawasaki's disease research field.

UPDATE OF THERAPEUTICS

Activation of the immune system is a key feature of Kawasaki's disease (13, 14); therefore, agents targeting this pathway have facilitated progress in the treatment of the disease.

Intravenous immunoglobulin (IVIG)

The first line of therapy for Kawasaki's disease in the U.S., the U.K., Europe, Australia and parts of Asia is intravenous immunoglobulin (IVIG). Giving IVIG (2 g/kg over 10-12 h) during the first 10 days of illness has been proven to shorten the duration of fever and decrease the risk of aneurysm formation (14). Furthermore, treatment with IVIG plus aspirin has been shown to reduce the incidence of coronary artery lesions from approximately 20-40% to < 5% (15, 16). However, there are concerns over the cost of this treatment (as it is obtained from human blood specimens).

A Japanese research group recently assessed the efficacy of a lower dose of IVIG (1 g/kg). In a randomized, prospective clinical trial in 119 patients, they showed that the incidence of aneurysm is not significantly different for those treated with 1 or 2 g/kg of IVIG (17). Studies are also emerging regarding the current effectiveness of IVIG (18).

Table I. *Active and recently completed Kawasaki's disease clinical trials.*

Agent	Phase	Collaborators	Status	Location	Ref.
Infliximab plus intravenous immunoglobulin (IVIG)	0	University of California, San Diego University of Texas Southwestern Medical Center	Recruiting	U.S.	9
Infliximab	I/II	University of California, San Diego Centocor	Recruiting	U.S.	10
Etanercept	II	Seattle Children's Hospital FDA Office of Orphan Products Developmen Amgen	Recruiting	U.S. and Canada	11
Steroids	III	National Heart, Lung, and Blood Institute (NHLBI) Pediatric Heart Network	Completed	U.S.	12

A recent study by U.S. collaborators highlighted the significance of IVIG resistance in children with Kawasaki's disease. Their 2006 depiction of Kawasaki's disease patients in San Diego County in the U.S. indicated that, of 362 children treated between 1998 and 2005, 9.8-20% were IVIG-resistant. Alarmingly, this rose to 38.3% in 2006, despite confirmation that the IVIG therapy given to these patients had not changed. This study also helped to identify biomarkers associated with IVIG resistance, and these included higher levels of C-reactive protein (CRP), alanine aminotransferase and γ-glutamyltransferase (19).

Recent studies have also identified novel mechanisms of action for IVIG, indicating that its effects in Kawasaki's disease may be mediated by suppression of genes involved in immune activation that reside in monocytes (those activating Fcγ receptors and the S100A8/A9 heterocomplex) (20). Furthermore, studies in human coronary endothelial cells have suggested that IVIG elicits its anti-inflammatory effect by attenuating monocyte chemotactic protein 1 (MCP-1) and intracellular adhesion molecule 1 (ICAM-1) (21).

More recent clinical investigations have explored the possibilities of new combination strategies. A retrospective study carried out in Japan (N = 2,350) has shown that IVIG combination therapy with aspirin (5-100 mg/kg) and warfarin (0.1 mg/kg; international normalized ratio [INR] of 1.5-2.5) is superior to aspirin without warfarin for preventing myocardial infarction in Kawasaki's disease patients with giant coronary aneurysms (22).

Corticosteroids

There is a great deal of evidence to suggest that combining IVIG therapy with corticosteroids can enhance therapeutic efficacy in Kawasaki's disease. A study by Japanese clinicians in 92 Kawasaki's disease patients indicated that 0.3 mg/kg/day dexamethasone plus heparin given i.v. for 3 consecutive days plus 2 g/kg IVIG over 4-5 days can accelerate the resolution of systemic inflammation versus treatment with IVIG plus aspirin (23). In addition, a prospective, multicenter, randomized trial in 178 Japanese patients showed that IVIG (1 g/kg/day for 2 consecutive days) plus corticosteroids (prednisolone sodium succinate 2 mg/kg/day t.i.d. i.v. given until fever resolution) as an initial therapy for Kawasaki's disease significantly prevents coronary artery abnormalities (coronary artery dilatation) versus IVIG given alone (24, 25).

I.v. methylprednisolone pulse (IVMP) therapy has also shown efficacy in IVIG-resistant patients (N = 42). A single dose of IVMP (15 mg/kg) could successfully reduce fever and CRP levels, with an associated reduction in the incidence of coronary artery dilatation (26). An additional study in 15 Kawasaki's disease patients demonstrating IVIG resistance also showed that IVMP-mediated fever attenuation (achieved at a dose of 30 mg/kg/day over 3 days) is associated with significantly lower plasma levels of TNF-α and MCP-1 compared to patients on IVIG (2 g/kg) (27).

TNF-α blockers

Multiple case studies have demonstrated the efficacy in refractory Kawasaki's disease of the TNF-α-blocking agent infliximab (28-34), an agent which has already received approval by the U.S. Food and Drug Administration (FDA) for the treatment of psoriasis, Crohn's disease, ankylosing spondylitis, psoriatic arthritis, rheumatoid arthritis and ulcerative colitis. As a result of these preliminary findings, larger trials have been carried out.

A multicenter study conducted in Korea in 13 Kawasaki's disease patients resistant to previous IVIG or IVMP therapy provided evidence to suggest that infliximab may prevent rapid progressive dilatation of coronary artery aneurysms (35). A further study in Japan of infliximab treatment (5 mg/kg) in 7 refractory Kawasaki's disease patients showed that efficacy is associated with decreased serum levels of the proinflammatory cytokine interleukin-6 (IL-6) (36).

A multicenter, randomized, prospective trial in the U.S. assessed the efficacy of a second IVIG (2 g/kg) infusion versus infliximab infusion (5 mg/kg). In 24 children with acute Kawasaki's disease, it was shown that the pharmacokinetics of the TNF-α blocker do not differ with age, with evidence for tolerability and safety in the pediatric population studied; however, infliximab did not provide any further benefits with regard to laboratory variables, fever or cardiac assessment (37).

A U.S. study investigated the effects of another TNF-α antagonist, etanercept, which is approved by the FDA for rheumatoid arthritis, juvenile idiopathic arthritis, psoriatic arthritis, ankylosing spondylitis and plaque psoriasis. Preliminary data from a prospective, open-label, single-center trial in 5 patients showed that etanercept (0.4-0.8 mg/kg s.c.) was safe, demonstrating pharmacokinetics suitable

for pediatric treatment, without evidence for expansion of the coronary artery diameter (38).

Statins

Recent in vivo studies have assessed the effects of atorvastatin in a superantigenic mouse model of Kawasaki's disease. This agent provided a dose-dependent reduction in T-cell proliferation (1.72-13.78 μM) and was associated with inhibition of IL-2 production and elevated MMP-9 expression (39). Further studies in a rabbit model of Kawasaki's disease demonstrated that fluvastatin and pravastatin reduce mononuclear cell infiltration and improve vascular thickening (40).

A study from Taiwan reported on the effects of statin therapy in Kawasaki's disease. Oral simvastatin (10 mg/day for 3 months) was evaluated in 11 children experiencing coronary arterial abnormalities as a result of their disease despite acute IVIG therapy and low-dose aspirin. After a mean follow-up interval from first episode of 10.77 ± 3 years, simvastatin appeared to significantly improve chronic vascular inflammation (assessed via high-sensitivity CRP) and endothelial dysfunction, without adverse events (41).

Methotrexate

A study from a research group in Korea indicated the potential for methotrexate, an inhibitor of folic acid metabolism, in Kawasaki's disease. In 17 patients resistant to IVIG, low-dose methotrexate (10 mg/kg once weekly) was shown to quickly resolve fever and provided rapid improvement in markers of inflammation, without causing adverse events (42).

Doxycycline

Canadian researchers have identified the potential for targeting matrix metalloproteinase (MMP) activity in Kawasaki's disease. Investigations in a murine coronary arteritis model of Kawasaki's disease have shown that the MMP-9 inhibitor doxycycline inhibits lymphocyte proliferation in a dose-dependent manner, ameliorating MMP-9 and TNF-alpha production in vascular smooth muscle cells and significantly reducing the incidence of coronary artery aneurysms (43).

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