Received: 11 May 2017 | Accepted: 20 May 2017

DOI: 10.1111/chd.12502

SPECIAL SECTION ON CORONARY ANOMALIES

WILEY Congenital Heart Disease

Kawasaki disease: Medical therapies

Jane W. Newburger, MD, MPH

Department of Cardiology, Boston Children's Hospital, Department of Pediatrics, Harvard Medical School, Boston, Massachusetts

Correspondence
Jane W. Newburger, MD, MPH, Department of Cardiology, Boston Children's Hospital, 300 Longwood Avenue, Boston, MA 02115.
Email: jane.newburger@cardio.chboston.org

Abstract

Medical therapies in patients with Kawasaki disease (KD) are administered to reduce the prevalence of coronary aneurysms, reduce systemic inflammation, and prevent coronary thrombosis. All patients with acute KD should be treated with intravenous immunoglobulin (IVIG) 2 g/kg, generally administered over 10–12 hours. Aspirin has never been shown to prevent aneurysms, but is given for its anti-inflammatory and antipyretic effects until the patient has been afebrile for ~2 days, then lowered to an antiplatelet dose. Adjunctive therapy with a longer course of corticosteroids, together with IVIG and aspirin, may be considered for primary treatment in patients at high risk for development of aneurysms. For patients who have persistent or recrudescent fever after IVIG treatment without other explanation, adjunctive therapies include retreatment with IVIG, a tapering course of corticosteroids, infliximab, cyclosporine, cyclophosphamide, and other immunomodulatory therapies. Antithrombotic therapies are tailored to the risk of thrombosis, and range from aspirin alone for 4–6 weeks in children without aneurysms to a combination of anticoagulation and antiplatelet therapy for those with giant aneurysms.

KEYWORDS

anticoagulation, coronary thrombosis, immune therapy, IVIG, Kawasaki disease

This brief report focuses on medical therapy for patients with Kawasaki disease (KD) in the acute phase of disease, antithrombotic prophylaxis, treatment of coronary thrombosis, and management of ischemic heart disease in children. Percutaneous and surgical coronary intervention will not be addressed here.

The goal of medical therapy in the acute phase is to reduce the systemic inflammatory response, prevent coronary aneurysms, and if aneurysms are already present, to minimize the peak dimensions reached and to prevent coronary thrombosis. Recommended therapy for all KD patients in the acute phase includes intravenous immunoglobulin (IVIG), 2 g/kg over 8–12 hours, together with aspirin in first antipyretic and then antiplatelet dosages.[1] Meta-analyses have demonstrated a dose-response effect of IVIG on incidence of coronary aneurysms[2]; this forms the basis for current practice of IVIG retreatment (2 g/kg) at least 36 hours after completion of the initial IVIG infusion for children with recrudescent or persistent fever without other cause. Other "rescue" therapies for IVIG resistance include corticosteroids, for which the most compelling data include the so-called RAISE regimen of a tapering dose of prednisolone over several weeks.[3] Rescue therapy with TNFα blocker infliximab has been shown to reduce fever and the inflammatory response in IVIG-resistant patients.[4]

Another approach to treatment of acute KD is to provide more aggressive primary treatment. With this strategy, one can either target patients at high risk for IVIG resistance and coronary lesions, or treat all patients regardless of risk. The former strategy was used in the RAISE study, a randomized controlled trial of IVIG plus prednisolone conducted at 74 institutions in Japan, in which subjects were at high risk for IVIG resistance by the Kobayashi score.[5] Remarkably, the IVIG plus prednisolone group, compared to those treated with IVIG alone, had significantly fewer coronary artery aneurysms at any time during the study period and also specifically at week 4, as well as less need for additional rescue therapy. Studies treating unselected KD patients with more aggressive primary therapies, such as pulsed-dose corticosteroids[6] and infliximab,[7] showed improvement in the inflammatory response, but no important differences in coronary artery outcomes.

Once coronary artery disease occurs, it is treated with all the usual tools of the adult cardiologist. However, prevention is much better than treatment. Approximately one third of KD patients with aneurysms never meet the classic criteria of KD, emphasizing the importance of use of the American Heart Association (AHA) treatment algorithm for the patient with suspected incomplete KD.[8] In addition, infants ≤6 months of age have the highest incidence of coronary aneurysms and also of incomplete disease. For this reason, AHA guidelines recommend

that echocardiography be performed in any infant ≤6 months old who has fever for at least 7 days, without other explanation, and with laboratory measures of inflammation, even in the absence of any principal clinical criteria.

Fatalities from Kawasaki disease virtually always result from coronary thrombosis. For this reason, antithrombotic therapy is of paramount importance in the patient with KD and coronary aneurysms. The choice of antithrombotic therapy in KD patients depends upon the severity and extent of coronary involvement.[1,8] No prospective trials of antithrombotic therapy have been performed in patients with Kawasaki disease. Therefore, recommendations are based upon known pathophysiology, retrospective case series, and extrapolation from experience in adults with coronary artery disease.

All patients are administered antiplatelet dose aspirin until it is clear that they will not be developing coronary lesions, or unless they have a specific contraindication; clopidogrel is used in place of aspirin for children with G5PD deficiency or exposure to chicken pox.[1,8]

Among patients with coronary aneurysms, an optimal milieu for thrombosis is created by low blood flow velocity and stasis of flow, stenosis at the proximal and or distal ends of aneurysms, activation of platelets by high sheer stress at coronary stenosis, and endothelial activation. For children with small aneurysms (ie, ≤4 mm), treatment with aspirin alone is standard. For those with large but not giant aneurysms, aspirin is sometimes combined with clopidogrel. The risk of coronary thrombosis is highest among patients with giant coronary aneurysms, classically defined as having a maximal coronary artery diameter of at least 8 mm. For small infants, similar physiology may occur at smaller dimensions, prompting some to consider a z score criterion of ≥10 for treatment with anticoagulants. A recent meta-analysis of 6 retrospective studies included 159 patients treated with warfarin and aspirin, and 158 treated with aspirin alone.[9] Compared to patients treated with aspirin alone, those receiving warfarin and aspirin together had a significantly lower odds of mortality (OR 0.18 ($P = .03$), coronary artery occlusion (OR 0.08 ($P = .001$), and myocardial infarction (OR 0.27, $P = .003$). The groups did not differ in the prevalence of coronary artery stenosis or regression.

For treatment of coronary thrombosis, there are once again no randomized trials in children. Of note, the mechanism of coronary thrombosis in different in children with Kawasaki disease than in older patients with atherosclerotic coronary artery disease, in whom acute plaque rupture precipitates myocardial infarction. The goals of therapy, however, are similar in children and adults with coronary thrombosis, namely to reestablish coronary patency, salvage myocardium, and improve survival.[8,9]

Coronary thrombosis may be treated with percutaneous coronary intervention for mechanical restoration of coronary blood flow, particularly in the older child or adult.[8] In younger children, thrombolytic therapy with tissue plasminogen activator is standard, with concomitant administration of aspirin, low-dose heparin, and gastrointestinal prophylaxis.[1,8] For patients with nonocclusive thrombus, some experts administer abciximab, a platelet glycoprotein IIb/IIIa receptor inhibitor, with concomitant low-dose heparin, to prevent thrombus extension.[1,8]

Other medical therapies in children with Kawasaki disease and coronary artery aneurysms derive from the recommendations in the adult cardiology literature. Beta blockers are administered prophylactically when coronary thrombosis is felt to be likely, as well as in patients with stable ischemic heart disease or who have had myocardial infarction. Angiotensin converting enzyme inhibitors, are administered to those who have had a myocardial infarction. The role of statin therapy to provide pleotropic anti-inflammatory effects in children with aneurysms is under investigation.

Finally, the use of implantable cardioverter defibrillators in KD patients after myocardial infarction must be considered on an individual basis, depending upon the risks of the device itself in young children and the risks of sudden death. Of note is the high prevalence of ventricular tachycardia after myocardial infarction in KD, as well as the low 30-year survival (<50%) among patients with myocardial infarction and ejection fraction <45%.[10] Cardiac transplantation continues to be reserved for patients with end-stage ischemic cardiomyopathy.

CONFLICT OF INTEREST

Consultant to Bristol-Myers Squibb, Merck, and Daichii Sankyo; grants from Bristol-Myers Squibb, Pfizer, and Novartis; expert reviewer for two legal cases.

DISCLOSURES

None.

AUTHOR CONTRIBUTIONS

The author contributed in the concept/design, drafting, critical revision and approval of the article.

REFERENCES

[1] Newburger JW, Takahashi M, Gerber MA, et al. Diagnosis, treatment, and long-term management of Kawasaki disease: a statement for health professionals from the Committee on Rheumatic Fever, Endocarditis and Kawasaki Disease, Council on Cardiovascular Disease in the Young, American Heart Association. *Circulation*. 2004; 110(17):2747–2771.

[2] Terai M, Shulman ST. Prevalence of coronary artery abnormalities in Kawasaki disease is highly dependent on gamma globulin dose but independent of salicylate dose. *J Pediatr*. 1997;131:888–893.

[3] Kobayashi T, Kobayashi T, Morikawa A, et al. Efficacy of intravenous immunoglobulin combined with prednisolone following resistance to initial intravenous immunoglobulin treatment of acute Kawasaki disease. *J Pediatr*. 2013;163:521–526.

[4] Son MB, Gauvreau K, Burns JC, et al. Infliximab for intravenous immunoglobulin resistance in Kawasaki disease: a retrospective study. *J Pediatr*. 2011;158:644–649.

[5] Choueiter NF, Olson AK, Shen DD, Portman MA. Prospective open-label trial of etanercept as adjunctive therapy for Kawasaki disease. *J Pediatr*. 2010;157:960–966.

[6] Newburger JW, Sleeper LA, McCrindle BW, et al. Randomized trial of pulsed corticosteroid therapy for primary treatment of Kawasaki disease. *N Engl J Med*. 2007;356:663–675.

[7] 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;383:1731–1738.

[8] Giglia TM, Massicotte MP, Tweddell JS, et al. Prevention and treatment of thrombosis in pediatric and congenital heart disease: a scientific statement from the American Heart Association. *Circulation*. 2013;128:2622–2703.

[9] Su D, Wang K, Qin S, Pang Y. Safety and efficacy of warfarin plus aspirin combination therapy for giant coronary artery aneurysm secondary to Kawasaki disease: a meta-analysis. *Cardiology*. 2014;129:55–64.

[10] Tsuda E, Hirata T, Matsuo O, Abe T, Sugiyama H, Yamada O. The 30-year outcome for patients after myocardial infarction due to coronary artery lesions caused by Kawasaki disease. *Pediatr Cardiol*. 2011;32:176–182.

How to cite this article: Newburger JW. Kawasaki disease: Medical therapies. *Congenital Heart Disease*. 2017;12:641–643. https://doi.org/10.1111/chd.12502