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Review Article

Recent advances in the treatment of Kawasaki disease

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Abstract

Kawasaki disease (KD) is acute systemic vasculitis that occurs mainly in infants and children under 5 years of age. The etiology of KD remains unknown. KD is liable to be complicated by coronary artery lesions (CALs), which develop in approximately 15–25% of untreated KD children and in approximately 5% of KD children after intravenous immunoglobulin (IVIG) therapy. A single high dose of IVIG (2 g/kg) is the gold standard therapy in the acute stage of KD. However, approximately 8–38% of children are unresponsive to initial IVIG treatment and at increased risk for CAL development. Anti-inflammatory high doses of aspirin are recommended in conjunction with IVIG, but our study demonstrated that there is no evidence of efficacy in preventing CAL development. The usefulness of steroids in initial therapy for KD or treatment of IVIG-resistant patients is not well established. Other immunosuppressive therapies, including infliximab, have been used in the treatment of refractory KD, but merit additional investigation. Subclinical atherosclerosis may develop early in KD patients, which makes early initiation of therapy to improve chronic inflammation an important issue. Future multicenter studies may help to define the optimal management of KD patients.

Keywords: coronary artery lesions; intravenous immunoglobulin; Kawasaki disease

1. Introduction

Kawasaki disease (KD), an acute systemic vasculitis more prevalent in Asian races, occurs mainly in infants and children under 5 years of age.[1] This multisystem vasculitis is characterized by prolonged fever, polymorphous skin rash, nonpurulent conjunctival injection, extremity changes, oral mucosal changes, and cervical lymphadenopathy. KD is liable to be complicated by coronary artery lesions (CALs), which develop in approximately 15–25% of untreated KD children[2–4] and in approximately 5% of KD children after intravenous immunoglobulin (IVIG) therapy.[5,6] The etiology of KD remains unknown and may be attributed to combined effects of infection, immune response, and genetic susceptibility.[1] The annual incidence of KD in Taiwan is estimated to be 69/100,000 children, the third highest in the world after Japan and Korea.[7–9] Many researchers have made great efforts to unravel the mystery of the disease. Evidence on the treatment of KD from randomized clinical trials is well established.[5] The present review article covers previous important publications with a special focus on the treatment of KD.

2. IVIG

Treatment with a single high dose (2 g/kg) of IVIG is effective in reducing the incidence of CALs.[6,10,11] A study by Newburger et al[11] contributed greatly in this regard, and a single high dose of IVIG is the gold standard therapy in the acute stage of KD. The mechanism of IVIG in reducing inflammation in KD is not clearly understood. Five possible mechanisms include Fc receptor blockade, neutralization of the causative agents or a toxin produced by an infectious agent, an immunomodulating effect, induction of suppressor

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activity, and modulation of the production of cytokines and cytokine antagonists.[12] Takatsuki et al showed that IVIG reduced the activity of oxidative stress,[13] which provokes vasculitis in KD. Using a murine model of KD, Lau et al demonstrated that at therapeutic concentrations, IVIG effectively reduced the immune response leading to tumor necrosis factor (TNF) expression (a prerequisite for coronary arteritis).[14] However, 7.8−38.3% of children are unresponsive to initial IVIG treatment and at increased risk for CAL development.[15−20] Additional IVIG,[15] steroid,[21] infliximab,[22] or other treatments have been used for IVIG-resistant patients, but controversy remains as regards alternative treatments. Additional treatments after initial IVIG treatment failure may not be effective for reducing fever or preventing coronary artery injury.[15,23] For IVIG-resistant patients, earlier and more effective primary therapy might not be emphasized enough for reducing the risk of CALs. Potentially effective initial treatments for high-risk patients might be IVIG plus corticosteroids or another new agent, such as infliximab.[24,25] Additional studies of KD pathogenesis are warranted to determine the role of these therapies for IVIG nonresponders.

3. Aspirin

Anti-inflammatory doses of aspirin are recommended in conjunction with IVIG, but controversy remains regarding anti-inflammatory doses of aspirin.[1] In North America, high-dose (80−100 mg/kg per day) aspirin is most widely used during the acute phase.[26] In Japan, concern about hepatic toxicity has led to the use of moderate-dose (30−50 mg/kg per day) aspirin as a recommended standard therapy in the acute phase.[27] In Taiwan, IVIG with concomitant aspirin is used during acute-stage KD in most hospitals except Kaohsiung Veterans General Hospital. The results of our previous study indicate that treatment without aspirin in acute-stage KD had no effect on the response rate of IVIG therapy, duration of fever, or CAL incidence.[6] Using a murine model of KD, Lau et al showed that at therapeutic concentrations, IVIG effectively reduced the immune response leading to TNF-α, but pharmacologic doses of salicylate enhanced its production.[14] This finding may partly support our treatment without aspirin in acute-stage KD. We suggest that it is unnecessary to expose children to high- or medium-dose aspirin therapy in acute KD when the available data show no appreciable benefit in preventing the failure of IVIG therapy or CAL formation or in shortening fever duration.

4. Steroids

Although corticosteroids are the treatment of choice in other forms of vasculitis, the usefulness of steroids in treatment of KD is not well established. Corticosteroids were used as the initial therapy for KD long before the first report of IVIG efficacy by Furusho et al.[28] An early study by Kato et al[29] suggested that steroids exerted a negative effect when used as the initial therapy for KD, but some recent studies have shown possible benefit. Okada et al reported that corticosteroid therapy combined with IVIG as the initial treatment rapidly ameliorated symptoms by reducing cytokine levels in children with KD.[30] Okada et al also showed that methylprednisolone and IVIG was effective and safe as a primary treatment for high-risk KD patients.[24] However, Newburger et al demonstrated that their data do not provide support for the addition of a single pulsed dose of intravenous methylprednisolone to IVIG for routine primary treatment of children with KD.[31] Further multicenter controlled trials are required to elucidate the role of methylprednisolone in initial therapy for KD or treatment of IVIG-resistant patients.

5. Other treatments

A new class of therapies directed against specific cytokines has expanded treatment for KD. Infliximab is a monoclonal antibody to TNF-α and has been effective in the treatment of patients with refractory KD.[32,33] Treatment with infliximab might also be an initial therapy for high-risk KD patients.[25] Our previous study showed an effect of IL-1B polymorphism on the association with IVIG resistance in Taiwanese children with KD,[34] which suggests the potential usefulness of monoclonal antibodies to IL-1, such as anakinra, for IVIG-resistant patients.[35] Other immunosuppressive therapies, including cyclophosphamide,[36] methotrexate,[37] and plasma exchange,[38] have been used in the treatment of refractory KD. No definite conclusions can be reached from these rare individual cases. Prospective clinical trials are warranted to determine the role of these therapies.

6. Statins

Therapeutic regimens in the chronic stage of KD depend on the severity of coronary artery involvement and include antiplatelet therapy with aspirin, with or without dipyridamole or clopidogrel, anticoagulant therapy with warfarin or low-molecular-weight heparin.[1] Ongoing low-grade inflammation and endothelial dysfunction persist in patients with a history of KD.[39] Some studies also demonstrated that subclinical atherosclerosis develops early in KD patients,[40,41] which makes early initiation of therapy to improve chronic inflammation an important issue. Statins are well-known lipid-lowering agents, but have so-called pleiotropic, cholesterol-independent effects that are believed to include anti-proliferative, anti-inflammatory, and antioxidant actions; they also upregulate eNOS activity.[42−44] Our pilot study has shown that statin therapy seems to significantly improve chronic vascular inflammation and endothelial dysfunction in children with coronary arterial abnormality in the chronic stage of KD.[45] A recent animal study also demonstrated that atorvastatin can inhibit critical pathogenic steps in the development of coronary artery damage in KD.[46] Further study is needed to determine the safety and efficacy of statins in children with KD.

In conclusion, high-dose IVIG in the acute phase of KD is the accepted treatment guideline. Anti-inflammatory high doses of aspirin are recommended in conjunction with IVIG, but the efficacy of aspirin may be limited to its anticoagulant

and antipyretic actions, which can be achieved at a low dose. Additional treatments after initial IVIG treatment failure, including corticosteriod therapy, are controversial. Management in the chronic stage of KD, especially for patients without evidence of CALs, is still an issue under debate. Future multicenter studies may help to define the optimal management for KD patients.

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References

1. Newburger JW, Takahashi M, Gerber MA, Gewitz MH, Tani LY, Burns JC, 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**:2747−71.
2. Kato H, Ichinose E, Yoshioka F, Takechi T, Matsunaga S, Suzuki K, et al. Fate of coronary aneurysms in Kawasaki disease: serial coronary angiography and long-term follow-up study. *Am J Cardiol* 1982;**49**:1758−66.
3. Kato H, Ichinose E, Kawasaki T. Myocardial infarction in Kawasaki disease: clinical analyses in 195 cases. *J Pediatr* 1986;**108**:923−7.
4. Suzuki A, Kamiya T, Kuwahara N, Ono Y, Kohata T, Takahashi O, et al. Coronary arterial lesions of Kawasaki disease: cardiac catheterization findings of 1100 cases. *Pediatr Cardiol* 1986;**7**:3−9.
5. Senzaki H. Long-term outcome of Kawasaki disease. *Circulation* 2008; **118**:2763−72.
6. Hsieh KS, Weng KP, Lin CC, Huang TC, Lee CL, Huang SM. Treatment of acute Kawasaki disease: aspirin's role in the febrile stage revisited. *Pediatrics* 2004;**114**:e689−93.
7. Huang WC, Huang LM, Chang IS, Chang LY, Chiang BL, Chen PJ, et al, and the Kawasaki Disease Research Group. Epidemiologic features of Kawasaki disease in Taiwan, 2003−2006. *Pediatrics* 2009;**123**:e401−5.
8. Nakamura Y, Yashiro M, Uehara R, Sadakane A, Chihara I, Aoyama Y, et al. Epidemiologic features of Kawasaki disease in Japan: results of the 2007−2008 nationwide survey. *J Epidemiol* 2010;**20**:302−7.
9. Park YW, Han JW, Hong YM, Ma JS, Cha SH, Kwon TC, et al. Epidemiological features of Kawasaki disease in Korea, 2006−2008. *Pediatr Int* 2011;**53**:36−9.
10. Juan CC, Hwang B, Lee PC, Lin YJ, Chien JC, Lee HY, et al. The clinical manifestations and risk factors of a delayed diagnosis of Kawasaki disease. *J Chin Med Assoc* 2007;**70**:374−9.
11. Newburger JW, Takahashi M, Beiser AS, Burns JC, Bastian J, Chung KJ, et al. A single intravenous infusion of gamma globulin as compared with four infusions in the treatment of acute Kawasaki syndrome. *N Engl J Med* 1991;**324**:1633−9.
12. Shulman ST. IVGG therapy in Kawasaki disease: mechanism(s) of action. *Clin Immunol Immunopathol* 1989;**53**:S141−6.
13. Takatsuki S, Ito Y, Takeuchi D, Hoshida H, Nakayama T, Matsuura H, et al. IVIG reduced vascular oxidative stress in patients with Kawasaki disease. *Circ J* 2009;**73**:1315−8.
14. Lau AC, Duong TT, Ito S, Yeung RS. Intravenous immunoglobulin and salicylate differentially modulate pathogenic processes leading to vascular damage in a model of Kawasaki disease. *Arthritis Rheum* 2009;**60**: 2131−41.
15. Sundel RP, Burns JC, Baker A, Beiser AS, Newburger JW. Gamma globulin re-treatment in Kawasaki disease. *J Pediatr* 1993;**123**:657−9.
16. Burns JC, Capparelli EV, Brown JA, Newburger JW, Glode MP. Intravenous gamma-globulin treatment and re-treatment in Kawasaki disease. *Pediatr Infect Dis J* 1998;**17**:1144−8.
17. Fukunishi M, Kikkawa M, Hamana K, Onodera T, Matsuzaki K, Matsumoto Y, et al. Prediction of non-responsiveness to intravenous high-dose c-globulin therapy in patients with Kawasaki disease at onset. *J Pediatr* 2000;**137**:172−6.
18. Durongpisitkul K, Soongswang J, Laohaprasitiporn D, Nana A, Prachuabmoh C, Kangkagate C. Immunoglobulin failure and retreatment in Kawasaki disease. *Pediatr Cardiol* 2003;**24**:145−8.
19. Sano T, Kurotobi S, Matsuzaki K, Yamamoto T, Maki I, Miki K, et al. Prediction of non-responsiveness to standard high-dose gamma-globulin therapy in patients with acute Kawasaki disease before starting initial treatment. *Eur J Pediatr* 2007;**166**:131−7.
20. Tremoulet AH, Best BM, Song S, Wang S, Corinaldesi E, Eichenfield JR, et al. Resistance to intravenous immunoglobulin in children with Kawasaki disease. *J Pediatr* 2008;**153**:117−21.
21. Shulman ST. Is there a role for corticosteroids in Kawasaki disease? *J Pediatr* 2003;**142**:601−3.
22. Oishi T, Fujieda M, Shiraishi T, Ono M, Inoue K, Takahashi A, et al. Infliximab treatment for refractory Kawasaki disease with coronary artery aneurysm: a 1-month-old girl. *Circ J* 2008;**72**:850−2.
23. Hashino K, Ishii M, Iemura M, Akagi T, Kato H. Retreatment for immune globulin-resistant Kawasaki disease: a comparative study of additional immune globulin and steroid pulse therapy. *Pediatr Int* 2001;**43**:211−7.
24. Okada K, Hara J, Maki I, Miki K, Matsuzaki K, Matsuoka T, et al. Pulse methylprednisolone with gammaglobulin as an initial treatment for acute Kawasaki disease. *Eur J Pediatr* 2009;**168**:181−5.
25. Shirley DA, Stephens I. Primary treatment of incomplete Kawasaki disease with infliximab and methylprednisolone in a patient with a contraindication to intravenous immune globulin. *Pediatr Infect Dis J* 2010;**29**:978−9.
26. Dajani AS, Taubert KA, Gerber MA, Shulman ST, Ferrieri P, Freed M, et al. Diagnosis and therapy of Kawasaki disease in children. *Circulation* 1993;**87**:1776−80.
27. Kusakawa S, Tatara K. Efficacies and risks of aspirin in the treatment of the Kawasaki disease. *Prog Clin Biol Res* 1987;**250**:401−13.
28. Furusho K, Kamiya T, Nakano H, Kiyosawa N, Shinomiya K, Hayashidera T, et al. High-dose intravenous gammaglobulin for Kawasaki disease. *Lancet* 1984;**2**:1055−8.
29. Kato H, Koike S, Yokoyama T. Kawasaki disease: effect of treatment on coronary artery involvement. *Pediatrics* 1979;**63**:175−9.
30. Okada Y, Shinohara M, Kobayashi T, Inoue Y, Tomomasa T, Kobayashi T, et al. Effect of corticosteroids in addition to intravenous gamma globulin therapy on serum cytokine levels in the acute phase of Kawasaki disease in children. *J Pediatr* 2003;**143**:363−7.
31. Newburger JW, Sleeper LA, McCrindle BW, Minich LL, Gersony W, Vetter VL, et al. Randomized trial of pulsed corticosteroid therapy for primary treatment of Kawasaki disease. *N Engl J Med* 2007;**356**:663−75.
32. Song MS, Lee SB, Sohn S, Oh JH, Yoon KL, Han JW, et al. Infliximab treatment for refractory Kawasaki disease in Korean children. *Korean Circ J* 2010;**40**:334−8.
33. Son MB, Gauvreau K, Burns JC, Corinaldesi E, Tremoulet AH, Watson VE, et al. Infliximab for intravenous immunoglobulin resistance in Kawasaki disease: a retrospective study. *J Pediatr* 2011;**158**:644−9.
34. Weng KP, Hsieh KS, Ho TY, Huang SH, Lai CR, Chiu YT, et al. IL-1B polymorphism in association with initial intravenous immunoglobulin treatment failure in Taiwanese children with Kawasaki disease. *Circ J* 2010;**74**:544−51.
35. Abbate A, Salloum FN, Vecile E, Das A, Hoke NN, Straino S, et al. Anakinra, a recombinant human interleukin-1 receptor antagonist, inhibits apoptosis in experimental acute myocardial infarction. *Circulation* 2008; **117**:2670−83.
36. Wallace CA, French JW, Kahn SJ, Sherry DD. Initial intravenous gammaglobulin treatment failure in Kawasaki disease. *Pediatrics* 2000;**105**: E78.
37. Lee TJ, Kim KH, Chun JK, Kim DS. Low-dose methotrexate therapy for intravenous immunoglobulin-resistant Kawasaki disease. *Yonsei Med J* 2008;**49**:714−8.
38. Mori M, Imagawa T, Katakura S, Miyamae T, Okuyama K, Ito S, et al. Efficacy of plasma exchange therapy for Kawasaki disease intractable to intravenous gamma-globulin. *Mod Rheumatol* 2004;**14**:43−7.

39. Mitani Y, Sawada H, Hayakawa H, Aoki K, Ohashi H, Matsumura M, et al. Elevated levels of high-sensitivity C-reactive protein and serum amyloid-A late after Kawasaki disease: association between inflammation and late coronary sequelae in Kawasaki disease. *Circulation* 2005;**111**:38−43.
40. McCrindle BW, Mcintyre S, Kim C, Lin T, Adeli K. Are patients after Kawasaki disease at increased risk for accelerated atherosclerosis? *J Pediatr* 2007;**151**:244−8.
41. Pozza RD, Bechtold S, Urschel S, Kozlik-Feldmann R, Netz H. Subclinical atherosclerosis, but normal autonomic function after Kawasaki disease. *J Pediatr* 2007;**151**:239−43.
42. Massy ZA, Keane WF, Kasiske BL. Inhibition of the mevalonate pathway: benefits beyond cholesterol reduction? *Lancet* 1996;**347**:102−3.
43. Wierzbicki AS, Poston R, Ferro A. The lipid and non-lipid effects of statins. *Pharmacol Ther* 2003;**99**:95−112.
44. Rikitake Y, Liao JK. Rho GTPases, statins, and nitric oxide. *Circ Res* 2005;**97**:1232−5.
45. Huang SM, Weng KP, Chang JS, Lee WY, Huang SH, Hsieh KS. Effects of statin therapy in children complicated with coronary arterial abnormality late after Kawasaki disease. *Circ J* 2008;**72**: 1583−7.
46. Blankier S, McCrindle BW, Ito S, Yeung RS. The role of atorvastatin in regulating the immune response leading to vascular damage in a model of Kawasaki disease. *Clin Exp Immunol* 2011;**164**: 193−201.