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Adjunctive therapies in Kawasaki Disease

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Abstract

Despite the administration of intravenous immunoglobulin (IVIG) at a dose of 2 g/kg, approximately 3-5% of children with acute KD may develop coronary artery aneurysms. IVIG-resistance, defined as recrudescence of fever more than 36 hours after IVIG completion, is a risk factor for coronary artery abnormalities. Thus, several adjunctive therapies are being evaluated for use in IVIG-resistant KD patients and in patients with coronary artery abnormalities. In this review we have discussed the role of some of these adjunctive therapies in treatment of children with KD.

Keywords

Anakinra; Atorvastatin; Cyclosporine; Etanercept; Infliximab; Methylprednisilone

Of the acute KD patients treated with IVIG, there are certain subpopulations that are most at risk for coronary artery damage and thus may benefit from adjunctive therapies. IVIG-resistant patients have an increased risk of coronary artery abnormalities (CAA) when compared with single dose IVIG responders, (15% vs. 5%).¹ In Japan, where scoring systems can predict who will be IVIG-resistant, this population of at-risk children can be identified at the time of diagnosis and targeted with additional treatment.²⁻⁴ A recent study demonstrated that 80% of coronary artery abnormalities are identified on the initial echocardiography examination in the first 10 days of illness.⁵ Nearly 50% of infants below 6 months of age treated for acute KD in first 10 days of illness end up developing CAA.⁶ These at-risk populations may benefit from early, adjunctive treatment to prevent or attenuate the progression of coronary artery damage.

Several clinical trials have addressed the intensification of initial therapy in an attempt to reduce recrudescence fever and achieve better cardiovascular outcomes. The most studied anti-inflammatory therapies for KD are corticosteroids. Corticosteroids are mainstay of treatment in various vasculitis, but their use in KD has remained controversial.^{7,8} A Phase III, randomized trial of single dose intravenous pulse methylprednisolone (30 mg/kg) as adjunctive therapy in the primary treatment of KD did not improve coronary artery outcomes at week 1 or 5 after therapy.⁷ However, a *post hoc* subgroup analysis showed that children with highest risk of IVIG-resistance had fewer CAA with primary corticosteroid therapy. In Japan, where multiple scoring systems have been developed that can accurately predict who

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is at high likelihood of being IVIG-resistant,^{3,9,10} several clinical studies of steroids have been performed in the high-risk population. The RAISE study in Japan was a 74-hospital, randomized, open-label, blinded endpoint study of intravenous prednisolone 2 mg/kg/day for 5 days followed by tapering oral regimen. High-risk patients had been identified through a scoring system and randomized them to receive either prednisolone or placebo with standard IVIG therapy for 4 to 5 weeks until the normalization of C-reactive protein.¹¹ Patients showing CAA in initial echocardiography were excluded. The results showed that patients in the steroid arm had less fever and greater reduction in coronary artery Z score. Similarly, one multicenter and two single-center randomized trials have assessed single-dose methylprednisolone (30 mg/kg/day) for children predicted to be IVIG-resistant, and found that the steroid group had a lower incidence of treatment resistance and CAA.^{3,12,13} However, the scoring systems used to identify Japanese study subjects at risk for IVIG resistance are not effective in populations of Western children or even children of other Asian ethnicities.^{1,14-16} A recent meta-analysis of use of corticosteroids in KD revealed that the combination of corticosteroid with IVIG as an initial treatment could reduce the risk of CAA. This benefit, however, was limited to those KD patients who had risk of IVIG-resistance. The findings, therefore, cannot be extrapolated to all patients with KD.¹⁷

Patients with KD in the acute phase have elevated level of the pro-inflammatory cytokine, tumor necrosis factor (TNF)- α . This observation led investigators to study the role of anti-TNF- α agents (i.e. infliximab) in IVIG-resistant patients.^{18,19} Infliximab, a chimeric monoclonal antibody that specifically binds TNF- α , and etanercept, a TNF- α receptor blocker, have both been evaluated in intensification of initial therapy and as rescue therapy for patients with treatment-resistant KD.^{20,21} Infliximab has been shown to be safe in a Phase III, randomized, double-blind, placebo-controlled study of primary treatment intensification in acute KD.²² In this study, combination of infliximab and IVIG resulted in fewer days of fever, a rapid decrease in CRP and a faster reduction in the Z-score of the left anterior descending artery when compared with IVIG therapy alone. Although addition of infliximab to IVIG as primary treatment did not decrease the IVIG resistance, it was found to be safe even in babies below 6 months.

A phase I, randomized, multicenter clinical trial in IVIG-resistant KD patients with a single dose infusion of 5 mg/kg of infliximab has shown that the drug is safe and is not associated with significant infusion reactions or serious adverse events.²³ More recently, a retrospective review of two centers that administered either a second dose of IVIG or infliximab to IVIG-resistant patients showed that KD patients receiving infliximab had fewer days of fever and hospitalization but coronary artery outcomes were similar.²⁴ A Phase III randomized, multicenter, open-label study is currently underway in the United States to compare the effectiveness of a second dose of IVIG versus infliximab in treating IVIG-resistant KD (NCT03065244). Although there is always a concern regarding re-activation of latent tuberculosis with the use of anti TNF- α therapies, this has not been reported in KD patients receiving a single dose of infliximab as adjunctive therapy.

Etanercept has been used in infants with refractory KD with significant improvement in inflammation and fever resolution.^{21,25} An open-label trial of etanercept (0.4–0.8 mg/kg subcutaneous weekly for 3 doses) in 15 KD patients (age, 6 months to 5 years) revealed that

addition of etanercept to IVIG as primary therapy and aspirin was safe, well-tolerated, and not associated with recrudescence of fever.²⁶ A phase III randomized, placebo-controlled trial to assess use of etanercept (0.8 mg/kg subcutaneous weekly for 3 doses) as adjunctive therapy to IVIG is currently in progress (NCT00841789).

Use of cyclosporine has also been studied as rescue therapy in patients with refractory KD.^{27,28} The use of cyclosporine is supported by the genetic evidence that the nuclear factor activated T cells (NFAT)-calcineurin pathway is implicated in disease susceptibility and cyclosporine inhibits the dephosphorylation of NFAT and the translocation of this transcription factor to the nucleus. A, multicentre, Phase III, randomized, open-label study of cyclosporine as adjunctive therapy for KD patients with predicted IVIG resistance has recently completed enrolment in Japan.²⁹

Atorvastatin, a HMG co-A reductase inhibitor commonly used as a cholesterol-lowering drug, has pleiotropic anti-inflammatory and anti-oxidant effects that promote healing of the endothelium.³⁰ Given the endothelial damage in KD, using atorvastatin to interfere with this process would be reasonable. The role of atorvastatin has been studied in 20 KD patients (median age 2.3 years) with giant coronary aneurysms. Atorvastatin was prescribed for a median duration of 2.5 years.³¹ The authors concluded that atorvastatin was safe to use in young children but close monitoring is warranted if it is used for prolonged period of time. Atorvastatin inhibited the secretion of matrix metalloproteinase 9 (MMP-9) in a mouse model of KD as well as attenuated MMP-9 gene expression *in vitro* in human endothelial cells.^{32,33} Genetic variation in MMP genes have also been shown to influence KD susceptibility and aneurysm formation.³⁴ Genetic studies have demonstrated the importance of the transforming growth factor-beta (TGFβ) pathway in the pathogenesis of coronary artery damage in KD, which is thought to lead to myofibroblast-like cells that invade the vascular wall of the coronary arteries.^{35,36} Myofibroblast formation, via MMP-9- dependent and –independent mechanisms, is inhibited by statins.³⁷ In an *in vitro* human umbilical vein endothelial cell (HUVEC) system, sera from KD patients induced an increase in markers of myofibroblast formation that was reduced by treatment *in vitro* with atorvastatin.³⁸ In addition, sera from acute KD patients treated with atorvastatin showed restoration of markers of endothelial cell homeostasis in the HUVEC model compared to matched KD controls. In view of above mentioned evidence, an open-label, two-center, Phase I/IIa dose escalation clinical trial of atorvastatin for patients with acute KD and coronary artery damage was designed and is currently enrolling subjects (NCT01431105).³⁹

More recently, the importance of IL-1 signaling pathway has been highlighted in patients with KD. Elevated level of IL-1β levels in *Lactobacillus casei* cell wall extract was seen in KD mouse model. Anakinra, an IL-1 receptor antagonist, successfully blocked the development of vasculitis in this KD mouse model.^{40,41} In addition, IL-1 related genes are upregulated in the peripheral blood from acute KD patients.⁴² On the basis of these findings, a Phase I/IIa, open-label, dose-escalation, two-center trial of anakinra for acute KD patients with CAA is in progress (NCT02179853). This study will assess the safety, pharmacokinetics, anti-inflammatory and endothelial-repairing properties of anakinra administered for six weeks in this high-risk population.

To summarize, adjunctive therapy is often necessary for KD patients with the highest risk of IVIG-resistance and those with CAA. The results of clinical trials currently in progress in Japan, the U.S., and Western Europe should help to build an evidence base for the most effective therapies and help to guide physicians in the care of high-risk KD patients.

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