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Adjunctive therapies for Kawasaki disease

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Summary Kawasaki disease (KD) is the most common cause of acquired heart disease in children in developed countries.[1,2] The primary goal of treatment is to prevent coronary artery aneurysms (CAA). Between 10 and 20% of KD patients are resistant to treatment with intravenous immunoglobulin (IVIG) and have an almost nine-fold increased risk of developing CAA.[3] In addition, approximately 80–90% of patients who go on to develop CAA have abnormal coronary artery dimensions on their first echocardiogram and can therefore be identified as high-risk patients. These two subsets of KD patients are candidates for adjunctive therapy, in addition to IVIG. Understanding the mechanism of action of IVIG may provide insight into IVIG resistance and guidance for choosing adjunctive therapies in KD. Therapeutic options in the treatment of refractory KD and patients with early CAA include additional IVIG, glucocorticoids, tumor necrosis factor inhibitors, calcineurin inhibitors and interleukin-1 (IL-1) blockers.[3–10] Animal studies suggest that the anti-inflammatory properties of statins may also be beneficial in blocking CAA progression.[6] It is unlikely that these therapies will be studied in large, randomized controlled trials in the future due to required sample size and funding constraints. Thus, data from the research laboratory may be helpful in guiding selection of the most promising adjunctive therapies.

Introduction

Kawasaki disease (KD) is the most common vasculitis of childhood for which the cause is unknown and severe sequelae may develop from coronary artery aneurysms (CAA).[11] CAA occur in up to 25% of untreated KD, making it the most common cause of acquired heart disease in children in developed countries.[1,2] Given the significant morbidity and mortality associated with CAA, the primary goal of treatment is prevention of irreversible damage to the coronary arteries.

Intravenous immunoglobulin (IVIG) resistance

Randomized controlled trials and meta-analyses have confirmed that IVIG plus aspirin compared with aspirin alone reduces the risk of developing CAA.[8] Between 10 and 20% of patients with KD have persistence or reoccurrence of

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fever at least 36 h after completion of initial IVIG treatment.[3] This is generally thought to be the result of failure to halt the inflammatory process and is commonly referred to as refractory or resistant KD. The danger of persisting fevers in KD was highlighted in a retrospective observational study of 378 patients, which demonstrated that those who remained febrile had an almost nine-fold increased risk of developing coronary artery abnormalities compared to those who responded to the initial IVIG infusion (12.2% versus 1.4%, respectively).[3] Timely diagnosis and treatment of KD, along with aggressive therapy for patients who are IVIG-resistant or have early CAA despite IVIG, are critical steps to improve outcomes in KD.[3]

The choice of therapy for refractory KD could be better guided if the mechanism of action of IVIG were completely understood. Natural regulatory T cells (nTreg) are selected in the thymus during early development, recognize self-antigens, and play a critical role in maintaining immunological regulation.[12] Current data suggests that boosting T cell regulation is one of the most important functions of IVIG in the setting of KD.[13] Franco and colleagues recently demonstrated that a subset of nTreg that recognizes the heavy constant region of immunoglobulins (Fc), regulates vascular inflammation in KD.[13] Expansion of unique Fc-specific nTreg after IVIG was associated with favorable clinical outcomes and the absence of CAA, while failure to expand despite IVIG was associated with CAA.[13] The expansion of tolerogenic myeloid dendritic cells (mDC) that secrete IL-10 is another proposed mechanism of action of IVIG in the setting of KD.[14] Thus, both T cell regulation and IL-10 secretion appear important in the recovery from KD without CAA.

A clinical response to IVIG in KD usually occurs rapidly in the first 12–24 h after receiving treatment and is characterized by defervescence, fading of the rash and other mucocutaneous signs, and a reduction in C-reactive protein level.[8] A historical example that may have some striking parallels to the clinical response seen in KD is the rapid resolution of rash seen in scarlet fever when patients were treated with anti-streptococcal horse serum in the pre-antibiotic era. Dochez found that when the horse serum was given subcutaneously to patients with scarlet fever, it produced complete resolution of the rash surrounding the injection site.[15] When it was given systemically to 12 patients with scarlet fever, it produced complete recovery within 12–36 h, presumably by neutralizing the streptococcal toxin.[15–17] The similarities in observations support the theory that direct antibody-mediated mechanisms play a role in the dramatic and rapid clinical improvement associated with IVIG infusion. Possible antibody-mediated mechanisms include neutralizing etiological agents, superantigens, or toxins and provision of anti-cytokine and anti-idiotype antibodies.[15]

Risk of CAA

Multiple studies have illustrated that patients with IVIG resistance have a much higher rate of CAA (15% versus 5% in responders).[3,18] Data suggest that the initial echocardiogram is often abnormal in KD patients who go on to develop CAA. In a study from Denver, Colorado, 46 of 57 children (81%) who ultimately developed CAA had CA abnormalities noted on their initial echocardiogram.[19] In unpublished data on 943 consecutive KD patients from Burns and colleagues at Rady Children's Hospital in San Diego, 73 (7.7%) were classified as having an aneurysm and of these, 65 (89%) had an abnormal first echocardiogram. Thus, both patients with IVIG resistance and patients with early CA abnormalities, based on the high-risk of progression to CAA, should be targeted with more aggressive therapy to halt the progression of coronary artery inflammation.

Choosing adjunctive therapies for KD

Second infusion of IVIG

One approach to treating IVIG resistance and early CAA has been to administer a second infusion of IVIG.[20] This approach has never been studied in an adequately powered, prospective, randomized, controlled clinical trial. In a recent meta-analysis of published small trials, steroids were more effective than second IVIG in reducing fever, but neither retreatment had an impact on preventing CAA, the primary goal of treatment.[21] Two recent case series have raised an important safety concern of hemolytic anemia following a second infusion of IVIG in patients with either A or B blood groups.[22,23] This newly emergent problem may be related to changes in antibody screening of donor blood for IVIG lots, but the cause for the higher anti-A and anti-B titers has not yet been definitively identified.

Glucocorticoids

Although some studies have suggested that adjunctive therapy with glucocorticoids in patients with high-risk KD may be beneficial, the role of glucocorticoids in initial therapy remains controversial.[7,10] The RAISE study was a randomized trial examining the efficacy of IVIG plus steroids compared with IVIG alone for prevention of CAA in 248 Japanese children.[10] High-risk patients were identified by the Kobayashi score and were predicted to have IVIG resistance based on this scoring system.[24] The incidence of coronary artery abnormalities during the study period was significantly lower in the IVIG plus prednisolone group compared to the IVIG alone group (3% versus 23%, relative risk 0.20, 95% CI 0.12–0.28).[10] Important issues to consider in this study include the exclusion of patients with coronary artery abnormalities before enrollment (12 patients), the prolonged hospitalization for three to five days of IV methylprednisolone, and patient selection using a scoring system that does not perform well in multi-ethnic populations outside Japan.[18,24–26] Further studies are required to clarify the role of glucocorticoids in KD in multi-ethnic populations and in patients with early coronary artery changes.

Tumor necrosis factor (TNF) inhibitors

TNF-alpha is elevated in the acute phase of KD, and levels are highest in children who subsequently develop CAA.[14] This observation provided the foundation for exploring

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whether TNF-alpha blockade with monoclonal antibodies (e.g. infliximab) or with soluble decoy receptors (e.g. etanercept) could be an effective adjunctive therapy in children with acute KD.[4,27] A trial was conducted involving 196 children randomized to a single intravenous infusion of infliximab (5 mg/kg) versus placebo, in addition to standard initial therapy with IVIG and aspirin.[27] The addition of infliximab to primary treatment in acute KD did not reduce the incidence of coronary artery abnormalities, but was safe and reduced fever duration and left anterior descending coronary artery *Z* scores by two-fold.[27] In a two-center retrospective study comparing second IVIG infusion versus infliximab for IVIG-resistant KD patients, administration of infliximab was associated with a more rapid decrease in CRP, fewer days of fever, reduced cost, and shortened hospitalization.[4] These data support the use of infliximab for refractory KD, but randomized, controlled trials are needed.

IL-1 blockade

Lee and colleagues recently showed in a mouse model for KD that IL-1 is involved in coronary artery inflammation and that CAA development can be prevented by IL-1R blockade.[28] Elevated levels of IL-1 have also been reported in acute KD patients and have correlated with vascular wall damage. A large genomic study of paired whole blood samples from 142 KD subjects showed that the IL-1 related pathways were markedly up regulated at the transcriptional level during the acute phase.[29] Case reports have demonstrated that the use of the IL-1 receptor antagonist, anakinra, may be effective for the treatment of refractory Kawasaki.[9,30] Both case reports detail patients 2 years and under, requiring intensive care, who failed to respond to standard IVIG therapy and had a dramatic clinical improvement with the addition of anakinra and subsequent resolution of CAA.[9,30] Two clinical trials are currently underway to examine the efficacy and safety of anakinra. An open-label Phase 1, multicentre trial for KD patients who fail to respond to IVIG is currently recruiting in Europe. Subjects receive anakinra 2 mg/kg/day escalated to 4 mg/kg/day if no response by day 3 (NCT02390596). In the U.S., a Phase 1/2a two-center, dose-escalation study (4—8 mg/kg/day) of anakinra in infants and children at least 8 months of age with coronary artery abnormalities is currently enrolling subjects (NCT02179853) (see Table 1).

Calcineurin inhibitors

Epidemiological data that suggests an important role for genetics in influencing disease susceptibility to KD includes the increased incidence in children of Asian ancestry and increased incidence among family members of affected individuals. Onouchi and colleagues studied candidate genes using a genome wide approach.[31] Inositol-Triphosphate 3-Kinase C (ITPKC) encodes an enzyme that negatively regulates T cell activation through the calcineurin/NFAT pathway. A risk allele for KD susceptibility and CAA in ITPKC was associated with reduced enzyme activity that may lead to enhanced T cell activation.[31] Cyclosporin A (CyA) is strong suppressor of T cell activation and may be a potential treatment for refractory KD. A pilot trial was conducted in 28 Japanese children who were resistant to two doses of IVIG and were then treated with oral CyA.[32] Eighteen of these 28 children (64.3%) responded promptly to treatment and became afebrile within three days, while an additional four subjects became afebrile within five days.[32] The small sample size and non-randomized study design precluded an analysis of the effect of CyA on the development of CAA. The lower rate of treatment response may have also been influenced by the use of oral therapy initially. Another observational study reviewed 10 U.S. patients treated with either CyA or tacrolimus, initially given intravenously and then orally.[5] Treatment resulted in resolution of fever and inflammation in all 10 patients.[5] A randomized clinical trial of CyA for high-risk KD patients chosen by the Kobayashi score is currently in progress in Japan.[33]

Statins

Atorvastatin is a selective competitive inhibitor of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase. The anti-inflammatory and endothelial-healing properties of statins may be beneficial in blocking CAA progression.[6] Statins have been shown to increase the number of circulating regulatory T cells, thought to be crucial in recovery from KD and to prevent CAA. In a mouse model of KD, atorvastatin reduced the secretion of matrix metalloproteinase-9, reduced T cell activation, and inhibited the release of TNF-alpha, all of which reduced vasculitis in the mice.[6] Atorvastatin is currently being evaluated in a Phase I/IIa dose-escalation study in children at least 2 years of age with acute KD and dilated CA (NCT01431105). This study will assist in defining the potential role for atorvastatin in the acute phase management of KD to prevent progression of CAA.

Conclusion

Therapeutic options that have demonstrated effectiveness in the treatment of refractory KD include additional IVIG, glucocorticoids, tumor necrosis factor inhibitors and other immunosuppressive agents including calcineurin inhibitors and IL-1 blockers.[3—10] None of these therapies have been subjected to rigorous, adequately powered, randomized, controlled trials.[7] Barriers to studying adjunctive treatment options for refractory KD include challenges with small sample size, inadequate statistical power, high costs and the nature of KD as a self-limiting vasculitis in which response to therapy may represent natural resolution of the disease process. It is therefore unlikely that large randomized controlled trials will be conducted in this area in the future. Alternative novel solutions will need to be sought including pragmatic clinical trials without randomization or comparative effectiveness trials with randomization. The limitations of these study designs include the potential for introduction of bias and confounders influencing results. Clinicians must be alert to the dangers of the persistently febrile child with KD despite standard therapy, since the risk of CAA is increased with a longer duration of fever and IVIG resistance. Children with early

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Table 1 Adjunctive therapies for refractory Kawasaki disease.[a]

Adjunctive therapy	Rationale and proposed mechanism of action	Evidence	Summary of findings
Additional IVIG	Dose-response effect documented with first infusion Expanding regulatory T cell and tolerogenic myeloid dendritic cell population ? Antibody-mediated mechanisms	Retrospective observational studies by Burns, JC. 1998[3] and Sundel, RP. 1993[20] Meta-analysis by Yang, X. 2015[21]	Majority will respond to IVIG retreatment with refractory KD. Glucocorticoids more effective in controlling fever compared with IVIG retreatment in refractory KD (but no difference between treatments in CA outcome).
Glucocorticoids e.g. oral prednisolone	Anti-inflammatory effects	Randomized open-label blinded-endpoints trial (RAISE study) Kobayashi, T. 2012[10] Meta-analysis by Yang, X. 2015[21]	Lower incidence of CAA for primary treatment of KD with IVIG plus prednisolone versus IVIG alone group (3% versus 23%, relative risk 0.20, 95% CI 0.12—0·28). Unknown applicability to multi-ethnic populations outside Japan. Glucocorticoids more effective in controlling fever compared with IVIG retreatment in refractory KD (but no difference between treatments in CA outcome).
TNFα inhibitors e.g. infliximab, etanercept	TNFα levels are elevated in acute KD and highest in those who develop CAA	Retrospective observational study Son, M. 2011[4] Randomized double-blind, placebo controlled trial Tremoulet, AH. 2014[27]	Comparing second IVIG versus infliximab for refractory KD, infliximab was associated with fewer days of fever, reduced cost, and shortened hospitalization; no difference in CA outcome. Addition of infliximab to primary IVIG treatment reduced fever duration and left anterior descending coronary artery Z scores by two-fold; did not prevent IVIG resistance.
Calcineurin inhibitors e.g. cyclosporin, tacrolimus	A risk allele for KD susceptibility and CAA in ITPKC was associated with reduced enzyme activity that may lead to enhanced T cell activation	Prospective and retrospective small observational studies Suzuki, H. 2011[32] Tremoulet, AH. 2012[5]	Resolution of fever in 18/28 (64.3%) of refractory Japanese KD patients with oral CyA. Resolution of fever in all of 10 IVIG refractory U.S. patients treated with IV followed by oral CyA or tacrolimus.
Interleukin-1 blockers e.g. anakinra	In a mouse model for KD; CAA prevented by IL-1R blockade Increased expression of IL-1 pathway genes in acute KD	Case reports Cohen, S. 2012 and Shafferman, A. 2014 Clinical trials in progress: (NCT02390596) (NCT02179853)	Resolution of fever and reversal of CAA in 2 severe, refractory KD patients.
Statins e.g. atorvastatin	In a mouse model of KD; atorvastatin reduces T cell activation, inhibited the release of TNF-alpha, decreased MMP-9 secretion; reduced vasculitis	Clinical trial in progress: (NCT01431105)	Trial results awaited.

IVIG: Intravenous immune globulin, KD: Kawasaki disease, CA: coronary artery, CAA: coronary artery aneurysm, TNFα: tumor necrosis factor alpha, ITPKC: Inositol-Triphosphate 3-Kinase C, pts: patients, CyA: cyclosporin, IL-1: interleukin-1, MMP: matrix metalloproteinase-9.

[a] Refractory Kawasaki disease defined as persistence or reoccurrence of fever (38.0 °C) at least 36 h after completion of initial IVIG treatment.

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abnormal echocardiograms and evidence of CAA are similarly in a high-risk group and should be targeted with aggressive therapy in the initial phase of treatment to prevent further disease progression. Evidence-based guidance for the best choice of therapy for these patients awaits further data from the clinic and research laboratory.

Conflicts of interest

The authors have no conflicts of interest to disclose.

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