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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