KiDrug Alert Journal Club

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A Critical Review of: "Efficacy of immunoglobulin plus prednisolone for prevention of coronary artery abnormalities in severe Kawasaki disease (RAISE study): a randomized, open-label, blinded-endpoints trial"

Kobayashi T, Saji T, Otani T, Takeuchi K, Nakamura T, Arakawa H, et al. for the RAISE Study Group. Lancet 2012; 379:1613-20.

SUMMARY OF FINDINGS

The standard treatment of Kawasaki disease (KD) in the acute phase is intravenous immunoglobulin (IVIG) plus aspirin. Few researchers have investigated alternative and adjunct treatments as 'rescue' strategies for patients with KD who do not respond to the standard regimens. Corticosteroids have been investigated for several decades as a possible therapy for KD, with mixed results.

The RAISE study group conducted a randomized controlled trial to assess the efficacy of adjunct therapy with corticosteroids for KD. Specifically, they investigated whether addition of prednisolone to IVIG with aspirin reduces the incidence of coronary artery abnormalities. RAISE study was a multicenter, prospective, open-label, blinded end points trial conducted at 74 hospitals in Japan between September 2008 and December 2010. 248 patients were enrolled. All had severe disease with a Kobayashi[1] risk score ≥5, indicating a high risk of nonresponse to immunoglobulin therapy and subsequent coronary artery involvement. Participants were randomly assigned into two groups; the control group received standard therapy consisting of IVIG 2 g/kg over 24 h with aspirin 30 mg/kg per day until defervescence, followed by aspirin 3–5 mg/kg/ day for at least 28 days after fever onset (n = 123, IVIG group); the second group (corticosteroid group) received a similar regimen with the addition of intravenous prednisolone 2 mg/kg/day in three divided doses for 5 days, then orally, if fever resolved within 5 days, and followed by a 15-day dose taper period after C-reactive protein (CRP) levels normalized (n= 125). In addition, the corticosteroid group received 0.5 mg/kg per day of the histamine (H_2) receptor antagonist famotidine, for gastric protection. The primary outcome of the study was determined as the incidence of coronary artery abnormalities during the study period. A two- dimensional echocardiography exam was performed during drug treatment and four weeks after. In addition, clinical characteristics were recorded including fever duration, need for adjuvant therapy, and measurement of serum inflammatory markers.

There were no differences in the baseline characteristics between the two treatment groups. The mean age of cohort patients at enrollment was 31.5 months and 13% were younger than six months. The incidence of coronary artery anomalies was significantly lower in the prednisolone adjuvant group compared with the IVIG group. Four patients (3%) in the former developed coronary anomalies compared with 28 patients (23%) in the latter; risk difference 0.20, 95% CI 0.12–0.28, P <0.001) at 1-2 weeks after disease onset. At week 4 Only 4 of 120 patients (3%) receiving corticosteroids as adjuvant therapy compared with 15 of 120 patients (13%) in the IVIG group had coronary artery abnormalities (P = 0.014). Secondary outcomes included faster

resolution of fever (mean of 1 day vs of 2 days, in the corticosteroid vs. control group, respectively; P <0.0001), less use of rescue therapies (13% vs. 40%, respectively; P <0.0001), and greater reductions in inflammatory markers in the corticosteroid group.

There were no mortalities and no significant differences in adverse event risk between the groups. Transient adverse effects were noted in three patients in the corticosteroid group and two patients in the IVIG group, all resolved spontaneously. The authors concluded that the addition of prednisolone to the standard regimen of IVIG improves coronary artery outcomes in Japanese patients with resistant KD. They suggested that studies of intensified treatment for KD in a mixed ethnic population are warranted.

COMMENTS

Kawasaki disease is a systemic acute vasculitis of unknown etiology, first described in 1974.[2] It occurs commonly in children younger than 5 years and the disease is more prevalent in children of Asian descent.[3,4] KD is mainly a clinical diagnosis, based on recognition of the constellation of non-specific criteria comprising of fever of at least 5 days duration, non-purulent conjunctivitis, rash, cervical lymphadenopathy, oropharyngeal mucositis, and edema or erythema of the hands and feet.[5] Cases of incomplete KD (lacking enough criteria for definitive diagnosis) may occur.

KD is the most common cause of acquired heart disease in children in developed countries.[6] Vasculitis affecting the coronary arteries results in coronary artery aneurysms in 15-25% of untreated patients.[6,7] Thus, early identification and intervention is critical to prevent these complications. The standard of care is well established and consists of high dose IVIG plus aspirin as initial therapy. This regimen improves clinical symptoms and dramatically reduces the risk of coronary artery involvement.[7,8] Resistance to IVIG therapy is reported in 10% to 20% of patients, and manifests in persistent or recurrent fever after completion of IVIG administration.[9-11] Persistent and recurrent fever are considered the greatest risk factors for developing coronary artery lesions.[12]

The RAISE study identified high-risk KD patients randomized for standard vs. adjunct corticosteroid therapy at the onset of disease. All the children were of Japanese origin, as highlighted by the study investigators; the challenge remains in regards to the generalization of the study findings. Are the results applicable in non-Japanese patients? Does KD in Japan behave differently from the disease in other populations?

In addition, the RAISE study investigators employed the Kobayashi risk scoring to stratify patients and identify children with high risk for IVIG resistance coronary artery abnormalities. However, this scoring system has low sensitivity in other, such as the North American population.[13] The Kobayashi score failed to predict non-response to IVIG in American children[14], and more accurate methods to identify non-Japanese children with high-risk KD are warranted.

Treatment strategies for KD are varied among institutions, and guidelines for adjuvant or additional therapy have not been established. The role of corticosteroids in KD is controversial. The difference in treatment regimens of KD in terms of corticosteroid role is highlighted when one compares the RAISE study to the PHN (Pediatric Heart Network) study.[14] In contrast with the RAISE study, which included prolonged low-dose (2 mg/kg/day) of prednisolone, the PHN study assessed the efficacy of high-dose, intravenous pulse therapy of methylprednisolone (30 mg/kg) in unselected KD patients before IVIG administration. This study failed to show benefit of corticosteroid therapy in terms of coronary outcomes. Drs. Mary Beth Son and Jane Newburger, in an accompanying Editorial in the Lancet, pointed out that the discordance in outcomes between the two studies may stem from differences in patient selection and treatment duration and intensity. Interestingly, the PHN study, a subsequent analysis showed that corticosteroids

yielded benefit in patients unresponsive to IVIG. Further evaluation for the efficacy of the RAISE regimen in non-Japanese patients with high-risk for resistant KD is warranted.

Great challenges and many open questions remain in the care of children with Kawasaki disease. Future should be focused on exploring criteria for early identification of high-risk patients and optimization of therapy, especially in children from non-Japanese origin.

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