ABSTRACTS FROM CURRENT LITERATURE

Pharmacologic interventions for Kawasaki disease in children: A network meta-analysis of 56 randomized controlled trials

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Background : Although the current consensus recommends a standard treatment of high-dose intravenous immunoglobulin with high-dose aspirin to manage Kawasaki disease (KD), the use of different adjunctive therapies remains controversial. The aim of the current network meta-analysis (NMA) was to compare the efficacy and tolerability of different existing interventions for the initial and refractory stages of KD.

Methods: An NMA of randomised controlled trials (RCTs) was conducted using the frequentist model applied after electronic searches in PubMed, Embase, ScienceDirect, ProQuest, ClinicalTrials.gov, ClinicalKey, Cochrane CENTRAL, and Web of Science. The main outcomes were reduced fever duration/diminished severity of fever subsided. The initial stage of KD was defined as the first stage to treat patients with KD; the refractory stage of KD represents KD patients who failed to respond to standard KD treatment. The cut-off points for intravenous immunoglobulin (IVIG) were low (100–400 mg), medium (1 g), and high (at least 2 g).

Findings: A total of fifty-six RCTs with 6486 participants were included. NMA demonstrated that the medium-dosage IVIG + aspirin + infliximab [mean difference="1.76 days (95% confidence intervals (95% CIs): "3.65 to 0.13 days) compared to high-dosage IVIG + aspirin] exhibited the shortest fever duration; likewise, the medium-dosage IVIG + aspirin + infliximab [odds ratio (OR)=0.50, 95% CIs: 0.18–1.37 compared to high-dosage IVIG + aspirin] exhibited the smallest incidence of coronary artery lesion (CAL) in the initial-stage KD.

In the refractory-stage KD, the high-dosage IVIG + pulse steroid therapy (OR=0.04, 95% CIs: 0.00–0.43 compared to the high-dosage IVIG only) had the best rate of decline of fever; likewise, the high-dosage IVIG + ciclosporin [OR=0.05 (95% CIs: 0.00–1.21) compared to the high-dosage IVIG only] exhibited the smallest incidence of CAL. Infliximab significantly improved resolution compared to the high-dosage IVIG only group (OR=0.20, 95%CIs: 0.07–0.62) in refractory-stage KD.

Interpretation: The NMA demonstrated that the combination therapy with the standard therapy of IVIG and aspirin might have an additional effect on shortening the duration of fever and lowering the CAL incidence rate in patients with acute KD. Moreover, the combination therapy with high-dose IVIG and pulse steroid therapy or cyclosporine therapy might have an additional effect on improving the rate of decline of fever and lowering the incidence rate of CAL in children with refractory KD. Because some of the findings of this NMA should be considered hypothesis-generating rather than confirmatory, further evidence from *de novo* randomised trials is needed to support our results.

Identifying children with Kawasaki disease at high risk for coronary aneurysms

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Kawasaki disease, a childhood vasculitis manifested by symptoms of high fever, mucocutaneous inflammation, and unilateral cervical adenopathy, can cause lasting damage to the coronary arteries, and more rarely, other medium-sized muscular arteries. Most children respond well to prompt treatment with high-dose intravenous immunoglobulin (IVIG). However, coronary artery aneurysms, defined by internal lumen diameter at least 2.5 SDs above the population mean for body surface area (Ze"2.5), occur in <"25% of affected children and are the principal cause of long-term morbidity and mortality in Kawasaki disease. Several

risk scores have attempted to predict which children are likely to develop coronary aneurysms.

In previous studies in North America, baseline risk factors for coronary artery aneurysms on echocardiography performed 2-8 weeks after Kawasaki disease onset have included higher coronary artery dimensions on baseline echocardiography, IVIG resistance (the persistence or recrudescence of fever after a single dose of IVIG), young age (<12 months or <6 months depending upon the risk score), Asian race, and late diagnosis and treatment with IVIG. Japanese risk scores based upon clinical and laboratory variables have been highly accurate in predicting IVIG resistance, one of the strongest risk factors for coronary artery aneurysms. In Japanese children predicted to have high risk of IVIG resistance, primary adjunctive therapy with corticosteroids or cyclosporine has been shown in randomized clinical trials to reduce the incidence of coronary artery aneurysms. However, Japanese children predicted to be at low risk for aneurysms on the basis of laboratory measures may still develop coronary abnormalities. Understanding the risk factors for aneurysm development thus requires further refinement.

In this volume of *The Journal*, Iio et al analyze independent risk factors for development of coronary artery aneurysms in 1632 Japanese children with Kawasaki disease who were predicted to be at low risk for resistance to primary IVIG treatment. In this low-risk group, 5.5% of patients developed any coronary artery aneurysms and 1%, medium or large coronary aneurysms. In multivariable analysis, baseline coronary artery Z score >2.5, age <12 months at fever onset, and IVIG resistance were independent risk factors for diagnosis of coronary artery aneurysms on echocardiography one month after disease onset. Among these risk factors, coronary artery Z score e"2.5 was most strongly associated with aneurysm development. Taken together with previous literature, these data suggest that enlarged coronary Z scores measured on baseline echocardiography can be used to select children at high risk for subsequent coronary artery aneurysms and thus who may benefit from adjunctive therapy.

The study of Iio et al adds weight to the concept that a high-risk cohort for randomized clinical trials of primary adjunctive therapy in Kawasaki disease may be most simply selected through findings on baseline echocardiography. The ability to select such a high-risk cohort is critical to the design of trials to answer remaining questions in Kawasaki disease therapy: In children of all races and ethnicities, who should receive treatment with adjunctive therapies? How do antiinflammatory therapies compare with each other, and what is the cost/benefit ratio for these therapies?