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Editorial

Kawasaki Disease: Complex Long-term Issues for Pediatric and Adult Cardiologists

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See article by Manlhiot et al. pages 1598–1607 of this issue.

Kawasaki disease (KD) is a systemic inflammatory vasculitis[1] that affects medium-sized vessels and is characterized by a complex response with elevated plasma cytokines. Although the etiology of KD remains uncertain, epidemiological studies suggest a probable role of infection in a patient with a genetic predisposition. Most children respond to intravenous immunoglobulin (IVIG) and aspirin,[1] but there are data showing KD that is resistant to initial IVIG therapy, in which both inflammatory (TNF-α, IL-6, IL-8, IL-17, IFN-γ, G-CSF, MCP-1 and sIL-2Rα) and anti-inflammatory (IL-10, sTNFR1, and sTNFR2) cytokine levels are simultaneously elevated.[2] At present the standard treatment is IVIG (2 gm/kg) as soon as diagnosis is made and aspirin at either a moderate dose of 30 to 50 mg/kg per day or a high dose of 80 to 100 mg/kg per day. In the case of failure of response, many clinicians would give a second dose of IVIG plus or minus a 3-day pulse of intravenous methyl prednisolone at a dose of 20 to 30 mg/kg per day. Other drugs, such as infliximab, anakinra, and cyclosporine, have been tried.[1]

Although every organ can be affected, it is rare for any organ other than the heart to be involved. Untreated coronary artery aneurysms (CAAs) classically occur in 20% to 30% of cases;[3,4] the incidence has significantly decreased to 5% to 10% of children with the use of IVIG. It is important to measure the size of CAA accurately,[5] as treatment and prognosis depend on this; a simple classification for coronary artery (CA) injury is mild dilatation, moderate aneurysm, and severe giant CA.[4] At an International Kawasaki Disease Symposium, Manlhiot[6] described the 10- and 40-year outcomes and mortality of children diagnosed with KD at Hospital for Sick Children, Toronto, between 1974 and 2013. There were 2623 patients diagnosed, of whom 410 had a CA injury: 215 had CA dilation with z-scores > 2.5, <5; 56 had moderate CAA > 5, < 10; and 138 had giant CAA > 10 (or a CA size of > 8 mm). A z-score is a numerical measurement that relates a single measurement to the average and standard deviation of all measurements in any group; therefore, a z-score of 0 is the average, and a z-score of 2 is 2 standard deviations from the mean.

The average follow-up of these patients varied in relation to patient age and date of diagnosis, but 63% had follow-up data into adult programs. Some children had follow-up of 6.7 years for CAA and 13.3 years for giant CAA; 57 patients had >15 years of follow-up, and 34 had > 25 years of follow-up. Importantly, there were no complications in patients without giant CAA.

The interesting long-term cardiac results are as follows:

- No revascularization at 5, 20, and 40 years in 95%, 87%, and 80% of subjects, respectively
- No occlusive/symptomatic CA thrombus at 5, 20, and 40 years in 90%, 85%, and 82% of subjects, respectively
- No acute myocardial infarction at 5, 20, and 40 years in 94%, 92%, and 89% of subjects, respectively

The long-term mortality of patients with and without CAA

- Three deaths without CA involvement (1 due to macrophage activation syndrome in the acute phase of KD, 2 other deaths due to cancer)
- No deaths with CA dilatation or CAA
- Three deaths with giant CAA, 2 from acute myocardial infarction, 1 nonmedical

The mortality for patients with KD compared with the general population was 1.5% vs 0.7% at 10 years and 3.1% vs 2.3% at 40 years.

There has been much debate about what level of antiplatelet drugs and anticoagulation should be given; antiplatelet agents, such as aspirin or clopidogrel, are useful for vascular injury and inflammation, whereas anticoagulation is useful if turbulent blood flow or stasis occurs. Su et al. performed a

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meta-analysis reviewing the safety and efficacy of the combination of warfarin plus aspirin for therapy for giant CAAs secondary to Kawasaki disease.[7] The combination decreased the incidence of CA occlusion, cardiac infarction, and death in children with giant CAA secondary to KD. There was no evidence of change in the rate of regression of CAA, CA stenosis, or thrombus formation.[7] However, their review consisted of 6 studies, and the longest patient follow-up was only 8 years. In an excellent editorial commenting on this paper,[8] Levin et al. performed a review of relevant literature and concluded that the combination of warfarin and aspirin was, at that time, the best treatment for children with KD and CAA.

In this issue of the *Canadian Journal of Cardiology*, Manlhiot et al. review data from an international Kawasaki Disease Registry (IKDR), which has information on children and adolescents < 18 years of age with KD, diagnosed between 1999 and 2017.[9] This excellent review was designed to look at the relationships among anticoagulant use, patients, and CA outcomes. CAAs were diagnosed and risk stratified according to American Heart Association recommendations.[1] Ninety-six percent of patients received aspirin after diagnosis; 383 of 440 patients with CAA z-scores greater than or equal to 10 were included in this study. Patients were excluded because of missing data (24), treatment < 14 days (17), and delayed diagnosis > 6 weeks (16). Of the 383, 189 received no anticoagulation, 114 received low-molecular-weight heparin (LMWH), and 80 received warfarin. Two and a half years later, CA thrombosis occurred in 20.6% of those with no anticoagulation, 5.7% with LMWH, and 6.7% in those with warfarin; CA thrombosis occurred in 63 patients, and 51 of these received secondary anticoagulation with LMWH (27) and warfarin (24). Of note, clopidogrel offered no advantage when used in combination with aspirin in prevention of thrombosis. In relation to safety, 361 courses of anticoagulation were reviewed: 187 with LMWH and 174 with warfarin. Two years after treatment, 10.9% of patients on LMWH had bled, and 5.5% of patients on warfarin had bled; however, severe bleeding events were rare. Risk factors for bleeding included higher CAA z-scores, concomitant treatment with clopidogrel, and previous bleeding episodes.

Warfarin treatment can be difficult in small children because of the frequent blood testing and the effects of diet on international normalized ratio. The therapeutic range is often uncertain in children because the risk of falls and minor trauma with normal activity. A major advantage is the reversibility and long-term clinical experience with warfarin. On the other hand, LMWH necessitates injection and is not easily reversed but is often more stable in dosing. Direct oral anticoagulants appear to be ideal for children except that experience is limited, only some can be easily reversed, and clear dosing and therapeutic ranges are not yet established. An excellent review of the current challenges and emerging issues of anticoagulation in children are well discussed in more detail in the review by Newall et al.[10] There is still significant variation in clinical practice as shown by an international survey[11] that was completed by 603 physicians from 63 countries. Briefly, with normal CA, 95 recommended 3 months of aspirin; for nongiant CAA,121 recommended dual antiplatelet drug therapy, and 72 recommended anticoagulation; for giant CAA, dual antiplatelet drug therapy was favoured by 39, and 285 preferred full anticoagulation. When compliance of survey responders was compared with Japanese college guidelines of 2014 and American Heart Association (AHA) guidelines of 2017, which are identical except for medium CAA (AHA dual platelet, Japanese anticoagulation), compliance was as follows: for normal CA, 82%; for persistent CA dilatation, 94%; for small CAA, 84%; for medium CAA, 32% using AHA and 19% using Japanese guidelines; and for giant CAA, 74% compliance. These results are concerning, particularly because 26% of physicians do not follow guidelines recommending anticoagulation of patients with giant CAA.

Manlhiot et al. show the benefit and safety of anticoagulation of children, with minimal difference between LMWH and warfarin. They clearly provide sufficient data on which to base a randomized controlled trial, should it be thought necessary. However, given the small numbers and the small differences, if any, between LMWH and warfarin, it would appear an randomized controlled trial is unlikely, and the final decision of which anticoagulant to use will remain a choice among patient, family, and physician. Further work is needed on direct oral anticoagulants, which have revolutionized oral anticoagulation in adults but for which there are insufficient data in children.

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