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EDITORIAL

Revisiting Once Again Steroids for the Treatment of Acute Kawasaki Disease

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The first physician to use steroids in the treatment of acute Kawasaki disease (KD) was Dr Tomisaku Kawasaki himself. In his epic description of his first 50 patients with mucocutaneous lymph node syndrome, he described 21 patients who received various forms of parenteral or oral steroids.[1,2] He concluded that, "Clearly intravenous infusion of prednisolone was effective in terminating the fever and improving the general condition, but it is not clear that it helped to shorten the overall course of this syndrome, since we did not see a significant difference when compared with the other treatment groups. We need to be cautious in judging the effect of this therapy."[2] It must be appreciated that Dr Kawasaki was unaware of the potential cardiovascular complications of KD at the time of his original publication, and so his conclusions were based solely on his clinical observation of his patients.

See Article by Ae et al.

The next appearance of steroids in the KD literature was the report by Kato and colleagues in 1979 of 92 patients with KD treated with 5 different combinations of antibiotics, aspirin, and steroids.[3] All patients underwent coronary angiography 1 to 2 months after the acute illness. Overall, 67.4% of patients who had received some combination, including steroids, developed coronary artery aneurysms (CAAs) compared with 20% who received antibiotics alone and 11% who received aspirin alone. Although the study would not meet the clinical trial standards of today, steroid treatment of KD fell into disrepute until it was revived 3 years later by a Japanese group using pulse steroids.[4] In a trial including 60 patients with KD, the authors described a benefit in reduction of aneurysm size in 62% of patients treated with pulse methylprednisolone compared with 33% of untreated patients. With this suggestive evidence in hand, there ensued 3 decades of debate about the role of steroids in the treatment of acute KD.[5,6]

With the adoption of intravenous immunoglobulin (IVIG) as the gold standard treatment for KD in 1986, it became difficult to adequately power a clinical trial that could demonstrate an improvement over and above the CAA rates of 3% to 5% that were seen with IVIG treatment.[7] It was shown that children who failed to become afebrile after IVIG had an increased risk of CAA, but identifying those patients before they failed IVIG proved difficult. Many of the clinical trials during this era were being conducted in Japan, and interest emerged in targeting intensification of initial IVIG therapy to patients who were predicted to fail to respond to IVIG. To that end, 3 different Japanese clinical scoring systems emerged to identify this population of patients.[8–10] The RAISE (Randomized Controlled Trial to Assess Immunoglobulin plus Steroid Efficacy for Kawasaki Disease) study that selected patients based on the Kobayashi score to predict IVIG resistance revived interest worldwide in the use of steroids.[11] This randomized, placebo-controlled, blinded end point study excluded patients with CAA on the initial echocardiogram and randomized 248 high-risk scoring patients with KD to receive prednisolone or placebo in addition to IVIG. The incidence of CAA was significantly lower in the IVIG plus prednisolone group compared with the IVIG alone group (4 patients [3%] versus

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28 patients [23%]; risk difference, 0.20; 95% CI, 0.12–0.28; $P<0.0001$). However, a subsequent study, the Post-RAISE study, failed to show a benefit in reduction of CAA with steroid therapy.[12] There were, however, important differences in study design between the 2 studies. In the Post-RAISE study, patients with incomplete KD and those with initial coronary artery Z scores ≥2.5 were included and reading of echocardiograms was not centralized or blinded.

In the study by Ae and colleagues in this issue of the *Journal of the American Heart Association* (*JAHA*), the authors report an analysis of steroids combined with IVIG for Japanese patients with KD using data from the nationwide epidemiologic surveys in Japan that are performed every 2 years.[13] A control group of 1593 patients with KD not treated with steroids from an earlier time period was matched 1:1 to cases treated with steroids from a later time period and the matching was repeated 1000 times. CAAs were defined according to the Japanese Ministry of Health criteria, not Z scores. The median proportion of patients who developed CAAs in the steroid treatment and control groups was 4.6% (95% CI, 3.8%–5.8%) and 8.8% (95% CI, 7.5%–10.0%), respectively, with an estimated risk ratio of 0.53 (95% CI, 0.41–0.67). There was also a benefit in reducing the need to administer additional treatment for IVIG resistance by an estimated 35% (95% CI, 25%–44%). The authors attempted to deal with confounding by indication by matching patients from a more recent survey in which steroids were used for high-risk scoring patients to controls from an earlier survey during which time period steroid use was uncommon. The criteria on which these controls were matched included age, sex, recurrence status, and day of illness but did not include other important risk factors for CAA. The only way to do the matching correctly would have been to apply the Kobayashi score retrospectively and use it as a matching criterion. Unfortunately, the data to perform the Kobayashi score did not exist in the epidemiologic surveys, so this was an insurmountable problem and a weakness of the analysis. It is possible, for example, that the 2 groups could have been mismatched for severity of inflammation, which is a major risk for CAA development. The authors concluded that these epidemiologic data from Japan suggest that a prospective, randomized trial of adjunctive therapy with steroids for a high-risk, multiethnic population with KD is warranted. Although a retrospective study can only be hypothesis generating, this conclusion seems justified when considered in the context of the RAISE study.

Unfortunately, numerous studies in Western, multiethnic populations of patients with KD have failed to show sufficient sensitivity or specificity of the various Japanese scoring systems to predict IVIG resistance, and attempts to devise robust, novel scoring systems tailored to this population have largely failed.[14–16] Instead of focusing on IVIG resistance as a risk factor for CAA, attention in the United States has turned to intensification of therapy for patients predicted to develop CAA based on observations that Z scores ≥2.5 for the right or left anterior descending coronary arteries on the first echocardiogram were strong predictors of CAA.[17–19] An analysis of retrospective data from 3 clinical centers suggested that intensification of initial therapy with either steroids or infliximab for patients with Z scores ≥2.5 reduced the risk of CAA progression.[20] However, to date, no prospective clinical trial data in a multiethnic population are available to inform whether steroids or alternative anti-inflammatory therapies are effective in reducing the risk of CAA. With the addition of these latest data from Ae and colleagues[13] from the Japanese national surveys, perhaps enthusiasm will mount for conducting such a trial in the United States.

ARTICLE INFORMATION

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Disclosures

None.

REFERENCES

1. Kawasaki T. Acute febrile mucocutaneous syndrome with lymphoid involvement with specific desquamation of the fingers and toes in children [in Japanese]. *Arerugi*. 1967;16:178–222.
2. Shike H, Burns JC, Shimizu C. English translation of Dr. Tomisaku Kawasaki's original report of fifty patients in 1967 (Japanese). *Pediatr Infect Dis J*. 2002;21:993.
3. Kato H, Koike S, Yokoyama T. Kawasaki disease: effect of treatment on coronary artery involvement. *Pediatrics*. 1979;63:175–179.
4. Kijima Y, Kamiya T, Suzuki A, Hirose O, Manabe H. A trial procedure to prevent aneurysm formation of the coronary arteries by steroid pulse therapy in Kawasaki disease. *Jpn Circ J*. 1982;46:1239–1242.
5. Burns JC. Revisiting steroids in the primary treatment of acute Kawasaki disease. *J Pediatr*. 2006;149:291–292.
6. Shulman ST. Is there a role for corticosteroids in Kawasaki disease? *J Pediatr*. 2003;142:601–603.
7. Newburger JW, Takahashi M, Burns JC, Beiser AS, Chung KJ, Duffy CE, Glode MP, Mason WH, Reddy V, Sanders SP, et al. The treatment of Kawasaki syndrome with intravenous gamma globulin. *N Engl J Med*. 1986;315:341–347.
8. Fukunishi M, Kikkawa M, Hamana K, Onodera T, Matsuzaki K, Matsumoto Y, Hara J. Prediction of non-responsiveness to intravenous high-dose gamma-globulin therapy in patients with Kawasaki disease at onset. *J Pediatr*. 2000;137:172–176.
9. Egami K, Muta H, Ishii M, Suda K, Sugahara Y, Iemura M, Matsuishi T. Prediction of resistance to intravenous immunoglobulin treatment in patients with Kawasaki disease. *J Pediatr*. 2006;149:237–240.
10. Kobayashi T, Inoue Y, Takeuchi K, Okada Y, Tamura K, Tomomasa T, Kobayashi T, Morikawa A. Prediction of intravenous immunoglobulin unresponsiveness in patients with Kawasaki disease. *Circulation*. 2006;113:2606–2612.
11. Kobayashi T, Saji T, Otani T, Takeuchi K, Nakamura T, Arakawa H, Kato T, Hara T, Hamaoka K, Ogawa S, et al. Efficacy of immunoglobulin plus prednisolone for prevention of coronary artery abnormalities in severe Kawasaki disease (RAISE study): a randomised, open-label, blinded-endpoints trial. *Lancet*. 2012;379:1613–1620.

12. Miyata K, Kaneko T, Morikawa Y, Sakakibara H, Matsushima T, Misawa M, Takahashi T, Nakazawa M, Tamame T, Tsuchihashi T, et al. Efficacy and safety of intravenous immunoglobulin plus prednisolone therapy in patients with Kawasaki disease (Post RAISE): a multicentre, prospective cohort study. *Lancet Child Adolesc Health*. 2018;2:855–862.
13. Ae R, Abrams JY, Maddox RA, Schonberger LB, Nakamura Y, Kuwabara M, Makino N, Matsubara Y, Kosami K, Sasahara T, et al. Corticosteroids added to initial intravenous immunoglobulin treatment for the prevention of coronary artery abnormalities in high-risk patients with Kawasaki disease. *J Am Heart Assoc*. 2020;9:e015308. DOI: 10.1161/JAHA.119.015308.
14. Tremoulet AH, Best BM, Song S, Wang S, Corinaldesi E, Eichenfield JR, Martin DD, Newburger JW, Burns JC. Resistance to intravenous immunoglobulin in children with Kawasaki disease. *J Pediatr*. 2008;153:117–121.
15. Sleeper LA, Minich LL, McCrindle BM, Li JS, Mason W, Colan SD, Atz AM, Printz BF, Baker A, Vetter VL, et al. Evaluation of Kawasaki disease risk-scoring systems for intravenous immunoglobulin resistance. *J Pediatr*. 2011;158:831–835.e833.
16. Fabi M, Andreozzi L, Corinaldesi E, Bodnar T, Lami F, Cicero C, Tchana B, Landini C, Sprocati M, Bigucci B, et al. Inability of Asian risk scoring systems to predict intravenous immunoglobulin resistance and coronary lesions in Kawasaki disease in an Italian cohort. *Eur J Pediatr*. 2019;178:315–322.
17. Dominguez SR, Anderson MS, El-Adawy M, Glode MP. Preventing coronary artery abnormalities: a need for earlier diagnosis and treatment of kawasaki disease. *Pediatr Infect Dis J*. 2012;31:1217–1220.
18. Son MBF, Gauvreau K, Kim S, Tang A, Dedeoglu F, Fulton DR, Lo MS, Baker AL, Sundel RP, Newburger JW. Predicting coronary artery aneurysms in Kawasaki disease at a North American center: an assessment of baseline z scores. *J Am Heart Assoc*. 2017;6:e005378. DOI: 10.1161/JAHA.116.005378.
19. Son MBF, Gauvreau K, Tremoulet AH, Lo M, Baker AL, de Ferranti S, Dedeoglu F, Sundel RP, Friedman KG, Burns JC, et al. Risk model development and validation for prediction of coronary artery aneurysms in Kawasaki disease in a North American population. *J Am Heart Assoc*. 2019;8:e011319. DOI: 10.1161/JAHA.118.011319.
20. Dionne A, Burns JC, Dahdah N, Tremoulet AH, Gauvreau K, de Ferranti SD, Baker AL, Son MB, Gould P, Fournier A, et al. Treatment intensification in patients with Kawasaki disease and coronary aneurysm at diagnosis. *Pediatrics*. 2019;143:e20183341.