

Resistance to intravenous immunoglobulin (IVIG) in Kawasaki disease: no influence of different IVIG lot utilisation

Sirs,

Kawasaki disease (KD) prognosis has greatly improved after introduction of intravenous immunoglobulin (IVIG), but resistance to IVIG has been described in several reports (1, 2). Administration of IVIG and aspirin during the acute phase of disease lowers the incidence of coronary abnormalities and shortens the duration of fever (3). However, 11% to 38% of patients continue to have persistent or recrudescent fever at least 36 hours after IVIG treatment. These patients with so-called "IVIG-resistance" are at higher risk for the development of coronary artery abnormalities, and up to now there are no risk-scoring system to predict resistance to therapy, except for Japanese cohorts. Moreover, therapy in case of re-treatment remains controversial (1).

In the last 6 months we have admitted to the Meyer Children Hospital, Florence, Italy, 21 patients with KD; of these, 38% (8/21) were IVIG-resistant, a significant increase over the previous years, and we have tried to explore possible reasons. All 8 IVIG-resistant patients (3 M, 5 F) were caucasians, whose age ranged from 6 months to 3y 6m. All met the standard definition for KD (4), and there were no differences in clinical, epidemiological, or laboratory parameters between responders and non-responders. We wondered whether there could have been an association of IVIG resistance with particular IVIG brand or lot. However, our hospital pharmacy has not changed the

brand of IVIG (Kedrion) in the last few years. All patients were treated with the standard dosage of 2 g/kg infusion. A *post-hoc* power analysis of our sample showed a 0.80 (1- β probability) power value, therefore an 80% chance to detect a true difference in our population.

Regarding the lots, we have analysed their numbers: 12 different lots, corresponding to 27 administrations for 21 KD children (4 children received 2 different lots during the first IVIG administration, 1 child 3 different ones) have been used. Twelve (44.4%) out of 27 lot administrations were associated to a non-responder outcome. However, regarding the different lot use, we could not find differences between responders and non-responders: chi-squared test for trend, Mantel-Haenszel linear-by-linear association chi-squared test: 0.31, p 0.86.

In 3/8 patients a second IVIG cycle was not sufficient to control the disease, and intravenous corticosteroids (with infliximab in one case) were necessary. The second IVIG cycle was administered to the same patient with the same or with different lots than the previous one, and again no statistical difference between responders and non-responders to this second cycle was found (chi-squared test for trend 0.75, p 0.38).

Considering that the mechanism of action of IVIG is still unknown (5) but different immunoglobulin could have different effects on immune activation, we suspected that IVIG brands or lots could influence response to therapy. However, in agreement with Tremoulet *et al.* (6), we found that IVIG-resistance was not associated with a particular brand or lot of IVIG. Risk factors for IVIG resistance have yet to be fully defined; the identification of patients who are

likely to be IVIG-resistant should continue, in order to allow the early use of additional therapies.

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References

1. SON MB, GAUVREAU K, BURNS JC *et al.*: Infliximab for intravenous immunoglobulin resistance in Kawasaki disease: a retrospective study. *J Pediatr* 2011; 158: 644-9.
2. SLEEPER LY, MINICH LL, MCCRINDLE BM *et al.*: Evaluation of Kawasaki disease risk-scoring systems for intravenous immunoglobulin resistance. *J Pediatr* 2011; 158: 831-5.
3. NEWBURGER JW, TAKAHASHI M, BURNS JC *et al.*: The treatment of Kawasaki syndrome with intravenous gamma globulin. *N Engl J Med* 1986; 315: 341-7.
4. NEWBURGER JW, TAKAHASHI M, GERBER MA *et al.*: Diagnosis, treatment, and long-term management of Kawasaki disease: a statement for health professionals from the Committee on Rheumatic Fever, Endocarditis and Kawasaki Disease, Council on Cardiovascular Disease in the Young, American Heart Association. *Circulation* 2004; 110: 2747-71.
5. GALEOTTI C, BAYRY J, KONE-PAUT I, KAVERI SV: Kawasaki disease: aetiopathogenesis and therapeutic utility of intravenous immunoglobulin. *Autoimmun Rev* 2010; 9: 441-8.
6. TREMOULET AH, BEST BM, SON S *et al.*: Resistance to intravenous immunoglobulin in children with Kawasaki disease. *J Pediatr* 2008; 153: 117-21.