



# Importance of predicting non-response to intravenous immunoglobulin therapy in non-Asian patients with Kawasaki disease

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Kawasaki disease (KD) is an acute systemic inflammatory disease of unclear aetiology, primarily diagnosed in young children under the age of five. KD can affect medium and small-sized arteries and the risk of definite damage to the coronary vessels represents the main concern. Presently, KD is the leading cause of acquired heart disease during childhood in developed countries.<sup>1</sup>

Although the immunomodulatory treatment of patients with intravenous immunoglobulin (IVIG) before the 10th day of fever has reduced the overall risk of coronary aneurysms (CAA) from 25% to 5%, this therapeutic strategy is insufficient to some patients for several reasons. First, the propensity to develop coronary artery lesions and non-coronary cardiac involvement (myocarditis, valve involvement, pericardial effusion, aortic root involvement, systemic arterial aneurysm) is different from one patient to another, and the youngest (<1 year) are most at risk (up to 48% and 22% respectively in children under 6 months of age).<sup>2</sup> Second, IVIG does not yield complete response and the 20% non-responders have an increased risk of cardiac complications.<sup>1</sup>

In a retrospective study including 363 consecutive children with KD admitted to two tertiary hospitals in France and Italy, Ouldali et al, have demonstrated that the presence of fever 2 days post IVIG treatment was significantly associated with CAA at week 6; a point which should be considered for a more homogeneous definition of IVIG-resistance within international recommendations.<sup>3</sup> Altogether, stratifying treatment according to each patient's individual risk may improve long-term prognosis. Targeting risk factors is challenging when there is a lack of agreement for a definitive

diagnosis and when the evolution of the disease is swift requiring treatment in an emergency setting. Furthermore, the affected population and the disease course and outcome are heterogeneous.

As the Japanese population is 20 to 35 times more affected by KD than Caucasian peers,<sup>4</sup> the first developed scores aimed to identify early on patients at risk of resistance to IVIG treatment were developed in the former group.<sup>5-7</sup> Their good performance has been a pedestal for building therapeutic trials for KD.<sup>8</sup> Unfortunately, these scores are of little use in non-Asian populations, where they lack sensitivity and specificity; i.e. sensitivity was 14 to 61% in the French Kawanet cohort.<sup>9</sup>

To fulfil this unmet need in routine practice and clinical research, our team has developed the Kawanet score using a French multicenter cohort of 425 patients from which Asians were excluded for analyses. We identified hepatomegaly, ALT level  $\geq 30$  IU/L, lymphocyte count  $< 2400/\text{mm}^3$  and time to treatment  $< 5$  days, as predictors of secondary treatment after initial IVIG. The best sensitivity (77%) and specificity (60%) of this model were obtained with 1 point per variable and cut-off  $\geq 2$  points.<sup>9</sup> Ouldali et al, made a first attempt at reproducing the Kawanet score in an independent multi-ethnic cohort including Asian children.<sup>3</sup> The performance of the Kawanet score was lower in their cohort compared to the training cohort. As presence of coronary dilations and myocardial dysfunction were associated with the risk of non-response to IVIG, it made sense to combine them in a scoring system. Therefore, they implemented cardiac ultrasound data (presence of either coronary artery maximal Z-score  $\geq 2.0$ , pericarditis, myocarditis and/or ventricular dysfunction) into the Kawanet score items. Consequently, they obtained an overall sensitivity of 76% and a specificity of 54%, which was higher than the Kawanet score in their cohort. In multivariate analyses of Kawanet cohort, cardiac involvement at initial ultrasound was also statistically associated with unresponsiveness to IVIG. Since in many centres, cardiac ultrasound cannot be obtained before the initiation of treatment, our team proposed a score that can be used in the absence of echocardiographic information. However, when available, the inclusion of cardiac data

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seems to us perfectly justified as they are decisive for the individual prognosis of patients.

Finding a predictive risk score for treatment resistance and cardiac complications is imperative for the non-Asian populations and is among the highest unmet needs for KD.<sup>10</sup> The possibility of adding echocardiographic parameters to it to improve its performance is progress, but may be limited by its feasibility in an emergency setting. The Kawanet score is a recently developed tool that needs polishing for perfect complete accuracy in clinical trials. For such, it is necessary to use larger cohorts of patients and prospective evaluations.

### Contributors

MP and IKP drafted, reviewed and edited this commentary and agree to be accountable for its content.

### Declaration of interests

MP and IKP are co-inventors of the Kawanet score. IKP was a consultant for SOBI, Novartis, CHUGAI, LFB and Pfizer. IKP received support for meeting attendance by Pfizer, Novartis and SOBI. IKP participated in a Data Safety Monitoring Board or advisory board for cell gene therapeutical trial (Use of Apremilast for pediatric Behçet and juvenile psoriatic arthritis).

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### References

- 1 McCrindle BW, Rowley AH, Newburger JW, et al. Diagnosis, treatment, and long-term management of Kawasaki disease: a scientific statement for health professionals from the American Heart Association. *Circulation*. 2017;135(17):e927–e999.
- 2 Cakmak F, Demir F, Cakan M, et al. Is it all about age? Clinical characteristics of Kawasaki disease in the extremely young: PeRA research group experience. *Postgrad Med*. 2022;134(4):429–434.
- 3 Ouldali N, Dellepiane RM, Torreggiani S, et al. Development of a score for early identification of children with Kawasaki disease requiring second-line treatment in multi-ethnic populations in Europe: a multicentre retrospective cohort study. *Lancet Reg Health Eur*. 2022. <https://doi.org/10.1016/j.lanepe.2022.100481>.
- 4 Piram M. Epidemiology of Kawasaki disease in Europe. *Front Pediatr*. 2021;9:673554.
- 5 Kobayashi T, Inoue Y, Takeuchi K, et al. Prediction of intravenous immunoglobulin unresponsiveness in patients with Kawasaki disease. *Circulation*. 2006;113(22):2606–2612.
- 6 Egami K, Muta H, Ishii M, et al. Prediction of resistance to intravenous immunoglobulin treatment in patients with Kawasaki disease. *J Pediatr*. 2006;149(2):237–240.
- 7 Sano T, Kurotobi S, Matsuzaki K, et al. Prediction of non-responsiveness to standard high-dose gamma-globulin therapy in patients with acute Kawasaki disease before starting initial treatment. *Eur J Pediatr*. 2007;166(2):131–137.
- 8 Kobayashi T, Saji T, Otani T, 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(9826):1613–1620.
- 9 Piram M, Darce Bello M, Tellier S, et al. Defining the risk of first intravenous immunoglobulin unresponsiveness in non-Asian patients with Kawasaki disease. *Sci Rep*. 2020;10(1):3125.
- 10 de Graeff N, Groot N, Ozen S, et al. European consensus-based recommendations for the diagnosis and treatment of Kawasaki disease - the SHARE initiative. *Rheumatology (Oxford)*. 2019;58(4):672–682.