Refractory Kawasaki Disease: Infliximab or Methotrexate Therapy?

Sir,

We read with interest the article by Girish *et al.*¹ They reported a 4-yr-old boy with refractory Kawasaki disease (KD), who was resistant to additional IVIG and methylprednisolone pulse therapy, but successfully treated with anti-TNF- α agent (infliximab).¹

However, infliximab is very expensive to use as a second-line drug in refractory KD in developing countries. Therefore, one of our authors have previously used low-dose oral methotrexate as a treatment for patients with refractory KD.² In his study, methotrexate treatment resulted in rapid defervescence, improvement in clinical symptoms, normalization of acute-phase reactants, and no progression of coronary artery dilatation in severe KD patients resistant to additional IVIG and intravenous dexamethasone.² Methotrexate was also discontinued with no recurrence of fever in all patients.² Because methotrexate is cheap, easy to administer (oral, weekly), easily available and less toxic than infliximab, it could effectively be used before applying infliximab to KD patients refractory to additional IVIG or high-dose steroid therapy.

Also, we should think about the responsiveness to infliximab in patients with KD. Although not studied in KD, Martínez-Borra *et al.* reported that high serum TNF- α levels were associated with lack of response to infliximab in fistulizing Crohn's disease.³ Marotte *et al.* also demonstrated that the level of circulating TNF- α bioactivity was higher in good responders than in poor responders, although the TNF- α protein levels were not associated with the response to infliximab.⁴

In conclusion, because coronary artery aneurysm can develop within a relatively short time in young infants, low-dose oral methotrexate could be one of the useful drugs in refractory KD before considering infliximab. Further studies are also necessary to identify the factors predictive of the clinical response to infliximab in KD, and the relationship between the responsiveness to infliximab and the degree of increased serum TNF- α levels or circulating TNF- α bioactivity should be further elucidated in the future.

Jae Il Shin, Jae Seung Lee, Jae Young Choi, and Dong Soo Kim

Department of Pediatrics, Yonsei University College of Medicine, Severance Children's Hospital, Seoul, Korea
E-mail: dskim6634@yuhs.ac

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Author's Reply

We appreciate your comments on our article titled "Infliximab treatment in Refractory Kawasaki Disease". While all pediatricians all over the world continue to struggle with IVIG resistant KD, this topic has been discussed to engage the attention of researchers at many centers in the world. Hopefully soon pediatricians can look beyond isolated case reports or uncontrolled case series and be guided by randomized double-blind controlled studies. Your experience with methotrexate in IVIG resistant KD is indeed very interesting, but the small number and lack of control group make it difficult to draw any definite conclusions. Currently, a two-center, randomized, double-blind,

placebo controlled trial is in progress in the U.S (ref Jane C. Burns. "Kawasaki Disease Update". *Indian J Ped* 2009;76:71-76.) to evaluate the role of Infliximab in IVIG resistant KD.

Methotrexate could also be evaluated by you in a similar study, though at a conceptual level, I have my reservation about the use of a slowly acting anti-inflammatory drug in this condition.

Drs Meenakshi Girish and Subramaniam

Dept of Pediatrics, NKPSIMS
Nagpur, India. E-mail: min_gir@rediffmail.com