

Letter to the Editor

Both patient characteristics and IVIG product-specific mechanisms may affect eosinophils in immunoglobulin-treated Kawasaki disease

Editor

Kuo et al. suggest that higher eosinophil counts post-intravenous immunoglobulin (IVIG) administration are an indicator of IVIG responsiveness in patients with Kawasaki disease (KD) (1). Both patient phenotype and choice of IVIG product may explain their findings. Polymorphisms in the PAF-AH gene have been shown to be associated with IVIG resistance in KD (2) and naturally occurring anti-Siglec-8 autoantibodies in IVIG preparations can lead to spontaneous apoptosis of eosinophils (3). These eosinophil-reducing factors should be considered before assuming that a low eosinophil count is enough to warrant a second course of IVIG therapy.

Platelet-activating factor (PAF) primes eosinophils and promotes the release of cysteinyl leukotrienes and cyclo-oxygenase products (PGE₂, PGD₂, TXB₂, PGF_{2α}) (4). PAF priming lowers the normal life span of eosinophils (5). The phospholipase A₂ enzyme, PAF acetylhydrolase (PAF-AH) hydrolyzes PAF and oxidizes phospholipids to biologically inactive molecules. Deficiency of PAF-AH has been shown to increase the risk of development of asthma (6) and atherosclerosis (7). The most prevalent loss-of-function mutation identified in the PAF-AH gene G994T abolishes the enzyme activity (8), and in 76 Japanese KD children significantly more patients with the GT (heterozygous)/TT (homozygous) genotype had longer duration of fever and higher C-reactive protein, and required additional IVIG (i.e., lower PAF-AH activity correlated with IVIG resistance) (2). There were no differences in total white cell or neutrophil counts or incidence of coronary arterial lesions between the two groups. It can be inferred that

the increased PAF activity in PAF-AH-deficient individuals lowers the viability of eosinophils and partly explains the low eosinophil count seen in the IVIG-resistant patients in Kuo's study (1).

Anti-sialic acid binding immunoglobulin-like lectin-8 (Siglec-8) autoantibodies are present in IVIG. In the presence of IL-5, GM-CSF, IFN-γ or TNF-α, anti-Siglec-8 leads to spontaneous apoptosis of eosinophils (3). These autoantibodies cause additional eosinophil death via a caspase-independent pathway dependent on reactive oxygen species that are elevated in KD. Changes in cell counts (i.e., lymphocytes, neutrophils, eosinophils, or platelets) observed after IVIG administration may be related to anti-Siglec-8 differences within the preparations. The significance of these autoantibodies in normal individuals is unclear at present, so correlation of the anti-Siglec-8 levels in KD patients and IVIG responses may reveal their role in the disease. Another important difference between IVIG products is varying amounts of IgG glycosylation, as post-translational modification with N-linked glycans at Asn297 of Fc portion of IgG alters the immunomodulatory potential by binding onto specific Fcγ receptors (9).

It is therefore important to consider these and other factors as contributing to the pathophysiological changes observed after IVIG administration. Hence, it would be useful to know the IVIG products that were used in Kuo's study. Even though various validated scoring systems may predict responsiveness to IVIG (10), it is important to realize that the efficacy of an IVIG product depends on the donor population, stabilizers, viral elimination techniques, and other aspects, and as such each IVIG product is unique in its own right.

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