Comparison of Cytokine Responses with Anti-D and Intravenous Immunoglobulin in Idiopathic Thrombocytopenia

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I read with interest the mechanistic paper by Oliver Meyer and colleagues [1] on the possible induction of endogenous thrombopoietin (eTPO) by IL-6 when using high-dose intravenous immunoglobulin (IVIG) in patients with idiopathic thrombocytopenia (ITP). As the authors rightly point out, it is difficult to characterize the actual mechanism in the absence of serial monitoring of cytokine levels (particularly IL-6) based on this small study. However, this study has similarity with two previous cytokine-based studies applying intravenous (i.v.) anti-D therapy.

The study by Cooper et al. [2] showed that monocyte chemoattractant protein-1 (MCP-1), IL-6, TNF- α and IL-10 levels were raised after treatment with i.v. anti-D within 2 h, while only IL-10 was seen to rise within 2 h after treatment with IVIG (the other cytokine that was raised was MCP-1 at 7 days) [2]. Higher IL-10 levels had correlated with a rise in platelet count at 24 h. The high cytokine responses (MCP-1, IL-6, TNF- α) were seen in patients with Fc γ RIIa-131HH genotype, supporting the concept of Fc γ RIIa interaction with IVIG and anti-D from a mechanistic point of view. The study by Malinowska et al. [3] showed that anti-D led to a significant increase in platelet count at 20 h, and to a significant and rapid increase in plasma IL-6, IL-8, TNF- α

within 1–20 h after anti-D infusion [3], supporting the concept of cytokine immunomodulation with anti-D therapy.

A recent paper by Del Vecchio et al. [4] showed that IL-10 levels at the onset may predict the course of patients with ITP, and higher levels have a positive outcome on disease remission within 1 year, while high thrombopoietin levels were not helpful in predicting the course of disease. This study however did not undertake serial monitoring of cytokine levels to assess whether a particular treatment and baseline high IL-10 contributed to the favorable outcome (i.e., remission within 1 year). In the era of monoclonal antibody therapy, and with advanced trials of symphoantibodies in ITP [5], cytokine-based studies in isolation will become increasingly difficult to interpret as these antibodies will interrupt various signaling pathways either directly or indirectly (downstream pathways). However, such preliminary studies are extremely important in advancing our knowledge and preventing untoward side effects in patients who enter into phase III clinical trials.

Disclosure Statement

The author declared no conflict of interest.

References

- 1 Meyer O, Winter O, Salama A: Influence of intravenous immunoglobulin treatment on thrombopoiesis. *Transfus Med Hemother* 2012;39:217–220.
- 2 Cooper N, Heddle NM, Haas M, Reid ME, Lesser ML, Fleit HB, Woloski BM, Bussel JB: Intravenous (IV) anti-D and IV immunoglobulin achieve acute platelet increases by different mechanisms: modulation of cytokine and platelet responses to IV anti-D by Fc γ RIIa and Fc γ RIIIa polymorphisms. *Br J Haematol* 2004;124:511–518.
- 3 Malinowska I, Obitko-Pludowska A, Buescher ES, Wasik M, Rokicka-Milewska R: Release of cytokines and soluble cytokine receptors after intravenous anti-D treatment in children with chronic thrombocytopenic purpura. *Hematol J* 2001;2:242–249.
- 4 Del Vecchio GC, Giordano P, Tesse R, Piacente L, Altomare M, De Mattia D: Clinical significance of serum cytokine levels and thrombopoietic markers in childhood idiopathic thrombocytopenic purpura. *Blood Transfus* 2012;10:194–199.
- 5 Stasi R: Rozrolimupab, symphobodies against rhesus D, for the potential prevention of hemolytic disease of the newborn and the treatment of idiopathic thrombocytopenic purpura. *Curr Opin Mol Ther* 2010;12:734–740.