To the editor:

A closer look at intravascular hemolysis (IVH) following intravenous anti-D for immune thrombocytopenic purpura (ITP)

Gaines has recently highlighted the risks of intravascular hemolysis (IVH) associated with intravenous infusion of anti-D in patients with ITP.[1] Collectively, we have seen uncomplicated IVH detected by routine clinical monitoring in 10 otherwise healthy patients with ITP among the more than 900 patients we have treated with anti-D. Nonetheless, the seriousness of the very rare occurrence of IVH accompanied by disseminated intravascular coagulation (DIC) and renal failure makes it important to clarify its frequency, pathophysiology, and prevention. Of the 6 patients reported by Gaines,[1] 5 had evidence of a prothrombotic state, diagnosed either before or after death. What is not clear is whether any or all might have had preexisting DIC or an underlying predisposition to develop DIC. Pretreatment reticulocyte counts or direct antiglobulin tests (DATs) were not reported in all. Although not pathognomonic, a positive DAT might have predicted exaggerated IVH in some of the patients. Also, 3 of the 6 patients had comorbid conditions, including chronic lymphocytic leukemia, disseminated cytomegalovirus infection, myelodysplastic syndrome, viral myocarditis, and 2 had cirrhosis (M. Genereux, Cangene Corporation, personal communication, May 2006).

Only 2 patients shared one lot of anti-D in the 2 reported series.[1,2] Therefore, it seems unlikely that high titers of a single additional alloantibody, found in only specific lots of WinRho-SDF, would explain all cases. In theory, a rare patient may express a single polymorphic determinant at a very high density or sufficient copies of several relevant red cell antigens to show lot-dependent hemolysis. Also, IVH may be more prevalent in patients with preexisting hemolysis (eg, Evans syndrome or infection with Epstein-Barr virus) and unusually high levels of residual red cell antibodies from prior treatment.[3-5] None of the patients treated in our centers were known to have underlying hemolytic conditions, and we would choose alternative modalities in patients with such findings.

IVH/DIC/renal failure after anti-D infusion could also result from a "2-hit" phenomenon (ie, IVH may have serious sequelae only when there are aggravating conditions, such as coexisting antiphospholipid antibodies, pre-existing renal insufficiency, or after marked cytokine release after infusion of anti-D, which has been associated with certain FcγR polymorphisms).[6]

It should also be noted that the diagnostic criteria for IVH in the setting of anti-D treatment are imprecise. Patients not uncommonly experience fever and chills after infusion of IV anti-D,[3] and most cases of marked hemolysis in the authors' experience are due to robust extravascular hemolysis. Moreover, incidental hemoglobinuria may occur in an unexpectedly large proportion of children with ITP,[7] and likely adults, at presentation.

Based on our collective expertise and medical judgment, we propose 4 recommendations: (1) encourage clinicians to monitor patients closely for systemic complaints and macroscopic hematuria/hemoglobinuria in the 48 hours after infusion; (2) consider alternative therapies in patients with evidence of underlying hemolysis (ie, reticulocytosis greater than 3%) and in those at high risk for hemolysis (eg, positive DAT not attributable to previous anti-D); (3) similarly, consider alternatives to anti-D in those with comorbid conditions, including compromised renal function; and (4) obtain a complete blood count, reticulocyte count, DAT, and a dipstick urinalysis prior to treatment with anti-D and monitor for IVH/renal failure after treatment in patients experiencing untoward side effects.

Anti-D is an important and useful option in the treatment of ITP in adults and children and one not to be overlooked because of very rare, albeit serious, complications. All alternative forms of management, including no treatment, are also associated with major complications in some patients. We anticipate that a comprehensive prospective surveillance study of anti-D infusion reactions will soon be initiated to identify the incidence of IVH and the factors that predispose to its occurrence.

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