CORRESPONDENCE

ANTI-D IG FOR TREATMENT OF IMMUNE THROMBOCYTOPENIC PURPURA

To the Editor:

In a recent article on the treatment of autoimmune thrombocytopenia (AITP) with anti-D Ig, Bussel et al. make several assertions that we would question. Many preparations of anti-D Ig for intramuscular use contain substantial quantities of polymeric IgG, but this is responsible for most of the inhibitory activity against macrophage Fc receptors and we have shown that the platelet count responses to different anti-D and other therapeutic Igs are proportionate to their polymeric IgG content. Bussel et al. were unable to show this with the intravenous Winrho product. Most manufacturers of anti-D Ig calibrate the material by adding variable quantities of non-specific IgG, and recent evidence has shown that the responses in ITP are due to this material and not to the anti-D component. This theory is also supported by the reports of responses in AITP patients who are rhesus-negative, which is contrary to what Bussel et al. have stated. Short- and long-term responses to anti-D Ig are seen in AITP, and recent work has shown that these responses are due to several mechanisms including monocyte-phagocyte Fc receptor inhibition by polymeric IgG material, and the inhibition of autoimmune antibody synthesis by anti-idiotypic antibodies. The latter contrasts with the effects Bussel et al. describe on IgG synthesis in vitro.

Bussel et al. also make observations concerning the safety of the Winrho anti-D Ig that we think could be misleading. All the original IgG preparations for intramuscular use were manufactured by simple Cohn ethanol fractionation and contained polymeric IgG. Although these caused severe adverse reactions when administered intravenously to patients with hypogammaglobulinemia, this was not in subjects with normal levels of IgG. Most anti-Rh-D immunoglobulins are manufactured for intramuscular use, but we have now safely administered such preparations by slow intravenous infusion to over 50 patients with AITP without adverse reactions. This contrasts with the five severe reactions described by Bussel et al., who are clearly incorrect in their assertion that the Winrho anti-D is uniquely safe for use in AITP.

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Dr Boughton raises an interesting and unresolved issue: what effect do IgG aggregates in preparations of gammaglobulin have with regard to infusion reactions and mechanism of treatment effect. Although little definitive information exists, two points appear clear: (1) the IgG aggregates appear to cause significant reactions when administered intravenously, especially in hypogammaglobulinemic patients; and (2) in vitro studies show the greater efficacy of aggregates in inhibiting FcR function than comparable quantities of monomeric IgG. Definitive clinical studies have not been performed on the intravenous (IV) infusion of IgG aggregates but many clinicians feel strongly that this may be dangerous. The World Health Organization and the Food and Drug Administration require that IV gammaglobulin (IVIG) preparations have absent anticomplementary activity, i.e., a very low level of aggregates. All current IVIG preparations available in the United States fulfill this criteria. However, the use of anti-D in the treatment of immune thrombocytopenic purpura (ITP) has resurrected the possibility of infusion of IgG aggregates if intramuscular preparations are administered intravenously. It is interesting that Boughton et al. claim that they could safely administer such material albeit very slowly (over 2 to 4 hours?). In comparison with IVIG, after which headaches are common when high doses are infused, IV anti-D (Winrho) has a low...
incidence of serious reactions (2 in 344 or < 1%). Thus, it is a safe treatment of ITP with the advantage of being administered in only 3 to 5 minutes. Study of the IgG aggregate content of Winrho showed that it contained less than either of two unmodified intravenous gammaglobulins.1

The well-documented in vitro Fc blocking effect of IgG aggregates has lead Boughton et al to speculate that IgG aggregates mediate the effect of anti-D. The clearest data supporting opsonization of red cells as the cause of the postinfusion Fc blockade is the lack of efficacy of anti-D in Rh- recipients. If the antibody component directed against the D antigen was irrelevant and the clinical effects due solely to IgG aggregates, the blood type of the treated patient should be irrelevant. It clearly is not. Boughton et al cite two cases of "response" of Rh- patients.2,3 However, neither patient provides clear proof of response to anti-D. The patient in Smith et al received IMIG, not anti-D. The patient described by Moise et al4 was a pregnant woman who had had ITP diagnosed years before the pregnancy. At 26 weeks of gestation she was begun on 40 mg of prednisone per day; 4 weeks later she received anti-D IV 120 mcg. Three weeks later she was found to have a platelet count 30,000/μL higher that then returned to the preinfusion range for the next four counts until delivery. Platelet counts fluctuate considerably in ITP in pregnant women, and the lack of repeated responsiveness makes it difficult to attribute this patient's response to the coincidentally administered anti-D. In contrast, at least 7 Rh- ITP patients have been treated with anti-D to increase platelet counts and all of those patients of Salama et al,5 Oksenhendler et al,6 and ourselves had no platelet response at all, in contrast to the majority of Rh- patients. Of interest, the three Rh- patients of Oksenhendler et al were subsequently treated with plasma containing anti-"e" and anti-"c" and all three responded, confirming the requirement for specific anti-red cell antibody for therapeutic efficacy in ITP. This demonstrates that antibody-coated red cells are important for the efficacy of anti-D treatment of ITP, although it does not exclude an additional effect of the IgG aggregates. We assume that this is also the conclusion of Boughton et al because they stated in 19906: "There are, to our knowledge, five rhesus-negative patients who have been treated with anti-D and none has shown a therapeutic response. This supports the role of opsonized RBC's in the induction of MPS FcR blockade in ITP."

A final point addresses the issue of long-term response to treatment. As Boughton alludes to, there are many anecdotal, few systematic, but no controlled studies of whether gammaglobulin infusion has any curative effect in patients with ITP. In the cases of apparent long-term responses, it is currently fashionable to think that these are due to the development of (or infusion of) anti-idiotypic antibodies.7 We believe there may be also a role for FcR-mediated effects, so-called immunomodulatory effects of FcR stimulation. Boughton refers to the changes seen in FcRII expression by lymphocytes. We and Macey and Newland,8 have seen profound changes in neutrophil and lymphocyte FcRIII expression following infusions of IV gammaglobulin. This type of change is also seen following infusion of IV anti-D and of a monoclonal anti-FcRIII antibody.9 The relationship of changes in FcR expression, in vitro Ig production, and anti-idiotypic antibodies remains unclear. Pending the measurement of very precise and specific antiplatelet antibody levels and/or the performance of large appropriately controlled trials, the issue of "curative effect" for any treatment of ITP other than splenectomy remains uncertain.

REFERENCES

Anti-D Ig for treatment of immune thrombocytopenic purpura [letter; comment]

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