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 in AITP, and recent work has shown that these responses are due to several mechanisms including monocyte-phagocyte FcR 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 so 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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RESPONSE

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 Wintrobe
showed that it contained less than either of two unmodified
intravenous gammaglobulins.3

The well-documented in vitro Fc blocking effect of IgG aggre-
gates has lead Boughton et al to speculate that IgG aggregates
mediate the effect of anti-D. The clearest data supporting opsoniza-
tion 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.12 However, neither
patient provides clear proof of response to anti-D. The patient in
Smith et al10 received IMIG, not anti-D. The patient described by
Moise et al10 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,8 Oksenhend-
ler et al,9 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 al9 were subsequently treated with plasma
containing anti-“e” and anti-“e” and all three responded, con-
firming 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 199010: “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, a
few systematic,11,12 but no controlled studies of whether gammaglob-
ulin 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.13 We believe that there may also be 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,14 have
seen profound changes in neutrophil and lymphocyte FcRII
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.15 The relationship of changes in
FcR expression, in vitro Ig production, and anti-idiotypic antibod-
ies 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.

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