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Blood, 15 February 2003, Vol. 101, No. 4, pp. 1658-1659

CORRESPONDENCE

To the editor:

IVIG induces dose-dependent amelioration of **ITP** in rodent models

We have read with interest the paper from Hansen and Balthasar¹ regarding the amelioration of thrombocytopenia in a rat model of immune thrombocytopenia (**ITP**). The authors induce thrombocytopenia with a monoclonal antiplatelet antibody and find that pretreatment with IVIG (intravenous immunoglobulin) successfully prevents thrombocytopenia. They also find that IVIG increases the clearance rate of the antiplatelet antibody and suggest that this occurs via IVIG saturation of FcRn, the salvage receptor for IgG, as may be responsible for the protective effect of IVIG. Based upon their work, the authors state that "...decreases in plasma antibody levels would lead to decreases in the degree of platelet opsonization."^{1(p2092)} We have published, however, that 48 hours after IVIG injection, platelet-associated antiplatelet IgG remained at the same levels as seen in mice receiving antiplatelet antibody alone^{2(fig1)}; this suggests, at least in the short term, that IgG catabolism does not result in a decrease in the platelet-bound antibody, which is thought to mediate immune thrombocytopenia.

In an accompanying commentary, Dr John Kelton asked what the effect of IVIG would be if the pathological antibody was produced under steady-state conditions as it is in **ITP**.³ In fact, a recent study from a group in the Netherlands achieved a steady-state level of thrombocytopenia.⁴ We also find that preinjection of mice with an antiplatelet antibody induces a stable low platelet count (< 20% of normal levels) and that treatment with 2 g/kg body weight of IVIG (Gamimune; Bayer, Elkhart, IN) successfully reverses the thrombocytopenia.² This demonstrates that a single dose of IVIG is effective in steady-state thrombocytopenia in an animal model.

Hansen and Balthasar state that, to their knowledge, "no reports have shown dose dependencies in IVIG effects"^{1(p2091)} in animal models of thrombocytopenia. In fact, we have reported² that in passive murine **ITP**, a dose response is seen; for instance, IVIG treatment at 0.125 g/kg, 0.5 g/kg, and 2.0 g/kg doses increased the platelet count 0%, 170%, and 306%, respectively.

Hansen and Balthazar also indicate that IVIG did not neutralize the 7E3 antibody. Both our work² and that of Teeling et al⁴ reported in 2001 that preincubation of IVIG with the antiplatelet

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antibody used to induce **ITP** does not diminish the antibody's ability to bind to platelets in vitro or in vivo. We also found that IVIG depleted of mouse IgG-reactive components and of antibodies reactive with the antiplatelet antibody (ie, anti-idiotypic antibodies) was able to prevent thrombocytopenia as successfully as unmanipulated IVIG.

The publication by Hansen and Balthasar raises some interesting points regarding the ability of IVIG to promote the clearance of antiplatelet antibodies in murine **ITP**. Both their work¹ and ours² indicate that anti-idiotypic antibody interference of antiplatelet antibody binding does not appear to be responsible for the amelioration of **ITP** by IVIG (or at least is not solely responsible). We suggest that IVIG ameliorates immune thrombocytopenia via either competitive reticuloendothelial system blockade or reticuloendothelial system inhibition via an Fc γ RIIB-dependent mechanism.⁵

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Response:

IVIG effects on antiplatelet antibody levels and on platelet opsonization in **ITP**

Dr Crow and coworkers raise several interesting points in discussing our recent paper.¹ Our work showed that intravenous immunoglobulin (IVIG) attenuated thrombocytopenia and led to dose-dependent increases in the clearance of antiplatelet antibody in a passive rat model of immune thrombocytopenia (**ITP**) (eg, antibody clearance was increased by 140% following 2 g/kg of IVIG). Due to our observation that IVIG therapy decreased antiplatelet antibody concentrations, we had commented that this effect of IVIG "would lead to decreases in the degree of platelet opsonization"^{1(p2092)} and, thus, may contribute to the attenuation of thrombocytopenia observed following IVIG administration.

During the course of the review of our manuscript, 2 interesting papers were published. Bleeker et al² published a study demonstrating that administration of IVIG to mice could increase the clearance of endogenous IgG and could also increase the clearance of a murine monoclonal antibody (where the monoclonal antibody was not reactive with murine antigens). Although Bleeker et al did not use a model of autoimmunity, their results are consistent with our pharmacokinetic data and support the hypothesis that IVIG administration leads to a decrease in autoantibody concentrations.

Second, Crow and coworkers³ published an article that demonstrated dose-dependent effects of IVIG in a passive murine model of **ITP**. Included within this study were flow cytometry results that suggest that IVIG treatment did not alter the amount of antiplatelet antibody associated with platelets (assessed 48 hours after IVIG administration). Citing these results, Crow et al indicate here that "in the short term... IgG catabolism does not result in a decrease in the platelet-bound antibody," thereby suggesting that IVIG effects on antiplatelet antibody elimination may not contribute to the acute effects of IVIG in **ITP**.

A few points are worth noting. First, it is well appreciated that antibody binding to antigen is monotonic (ie, decreases in antibody concentration lead to decreases in antibody binding). As such, our comment regarding antiplatelet opsonization of platelets is well grounded in theory. Nonetheless, antibody binding to antigen is saturable and, thus, nonlinear. The impact of a change in antiplatelet antibody concentration on platelet-associated antiplatelet antibody may be expected to differ from model to model and from patient to patient because of differences in the determinants of antiplatelet antibody binding (ie, antibody concentration, platelet count, the number of antibody binding sites per platelet, the affinity of antiplatelet antibody for platelet-binding sites, etc). As such, while Crow et al find no difference in platelet-associated antiplatelet antibody assessed 48 hours after IVIG administration, this may not be representative of results observed in our model or of results observed in patients (eg, where several studies have found that IVIG therapy leads to reductions in platelet-associated antiplatelet antibody⁴⁻⁶).

In addition, it is important to note that small changes in antiplatelet antibody binding may lead to large changes in antiplatelet antibody-induced thrombocytopenia. Indeed, in our rat model, we predict steep relationships between antiplatelet antibody binding and antibody-mediated platelet elimination (ie, inferred from previous work where we measured 7E3 binding to rat platelets in vitro and assessed 7E3-induced thrombocytopenia in vivo⁷). As such, although Crow et al failed

to detect a change in platelet-associated antiplatelet antibody, this may be because their analytical method (flow cytometry) did not have sufficient power to detect small yet significant changes in antibody binding to platelets.

Crow et al also comment that the results of our studies and their studies indicate "...that anti-idiotypic antibody interference of antiplatelet antibody binding does not appear to be responsible for the amelioration of **ITP** by IVIG (at least not solely responsible)." Although our results are consistent with their statement, we feel that it is important to caution readers that our work and the work of Crow et al are performed in passive rodent models of **ITP** rather than in patients. In the models studied, anti-idiotypic effects do not appear to be important; however, much more work must be conducted before conclusions may be made about anti-idiotypic mechanisms of IVIG action in human **ITP**.

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Acknowledgments

Supported by grant HL67347 from the National Heart, Lung, and Blood Institute.

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