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A platelet cover-up

Donald M. Arnold1,2
1MCMASTER UNIVERSITY; 2CANADIAN BLOOD SERVICES

In this issue of Blood, Bakchoul et al explore a novel approach to the treatment of neonatal alloimmune thrombocytopenia (NAIT) in utero: shielding fetal platelets from maternal alloantibodies.

Neonatal alloimmune thrombocytopenia (NAIT) is typically first discovered when an otherwise healthy infant is unexpectedly found to have severe thrombocytopenia and bleeding immediately after birth. Once a mother has become immunized by fetal platelet antigens, maternal antiplatelet alloantibodies can cross the placenta, bind fetal platelets, and target them for destruction by phagocytosis in reticuloendothelial tissues. Without a method for preventing the initial maternal immunization, better antenatal treatments are needed to improve fetal and neonatal outcomes during subsequent pregnancies.

NAIT is the platelet equivalent of hemolytic disease of the newborn (HDN). In HDN, maternal alloantibodies against red blood cell antigens, typically RhD, cause hemolysis in the fetus. In NAIT, maternal alloantibodies, typically against human platelet antigen (HPA)-1a, cause fetal thrombocytopenia, which can lead to intracranial hemorrhage. A few important differences between HDN and NAIT are noteworthy. First, HDN generally occurs in second or subsequent pregnancies or after an initial immunizing fetal-maternal hemorrhage, whereas NAIT frequently occurs in first pregnancies (although many women become immunized at the time of delivery). Second, HDN, which was once a leading cause of neonatal death, has virtually been eliminated by Rh immunoglobulin
No prevention strategy exists for NAIT, and progress in management has been comparatively slow.

A screening program designed to identify women at risk before the initial event was evaluated in a study of over 100,000 women who were tested for HPA-1a and anti–HPA-1a alloantibodies. Women with positive serology were offered additional follow-up and early cesarean section delivery. The results suggested that such a program is feasible and may eventually have a role in reducing severe neonatal outcomes; but universal screening may not be sensible in the absence of an effective intervention.

Until such time as platelet immunization can be prevented, mothers with a history of NAIT will require treatment during subsequent pregnancies to reduce the risks to the fetus. The current mainstay of therapy is antenatal intravenous immune globulin administered to the mother in high doses (1–2 g/kg) at weekly intervals from the second trimester until delivery, with or without corticosteroids. While this approach appears to be effective at preventing intracranial hemorrhage in the infant, it is costly and cumbersome, and may be associated with significant side effects.

Bakchoul et al move us 1 step closer to targeted therapy for women with NAIT. These investigators produced a modified monoclonal anti–HPA-1a antibody with preserved Fab-binding capacity but impaired Fc-mediated phagocytic potential. This type of modified monoclonal could eventually be used to shield fetal platelets from destruction by maternal alloantibodies (see figure).

Bakchoul et al began with the monoclonal mouse anti-human platelet glycoprotein IIIa antibody SZ21 and chemically removed the carbohydrate moiety from the Fc portion to create a deglycosylated version (called NMG-SZ21). In a mouse model, they showed that their designer antibody crosses the placenta, binds to HPA-1a in pups, and rescues platelets from anti–HPA-1a alloantibody-mediated destruction. This study provides important lessons on how to deliver an effective treatment directly to the fetus. Its clinical application will require a humanized form of the antibody.

A similar approach was developed by another group of investigators using the human anti–HPA-1a monoclonal B2G1. This group substituted IgG1 residues of the Fc domain to create a modified antibody (B2G1Δnab), whose Fab binding ability and Fc effector functions have also been dissociated. The antibody’s kinetics across the placenta, an Fc-dependent process itself, will need to be tested.

The prevention of maternal immunization to fetal platelet antigens is the panacea. Short of that, therapy with a specific shielding antibody would represent a major advance.
in therapy. The continuous exposure of maternal antiplatelet alloantibodies to fetal platelets and the expression of HPA-1a antigens on endothelial cells and placental tissue imply that high doses of any monoclonal would be necessary if it were to be used as a therapeutic intervention. Nevertheless, even a small increment in fetal platelet count would likely be sufficient to avoid intracranial hemorrhage. Clinical studies in this area will require the testing of pregnant women and large collaborative trials, which should not impede this important program of research.

NAIT is a common and devastating illness. The investigations described by Bakchoul et al breathe new life into this field of study designed to protect our most vulnerable population. This line of research brings renewed hope that NAIT will eventually follow in the shadow of HDN and become a thing of the past.

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REFERENCES


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