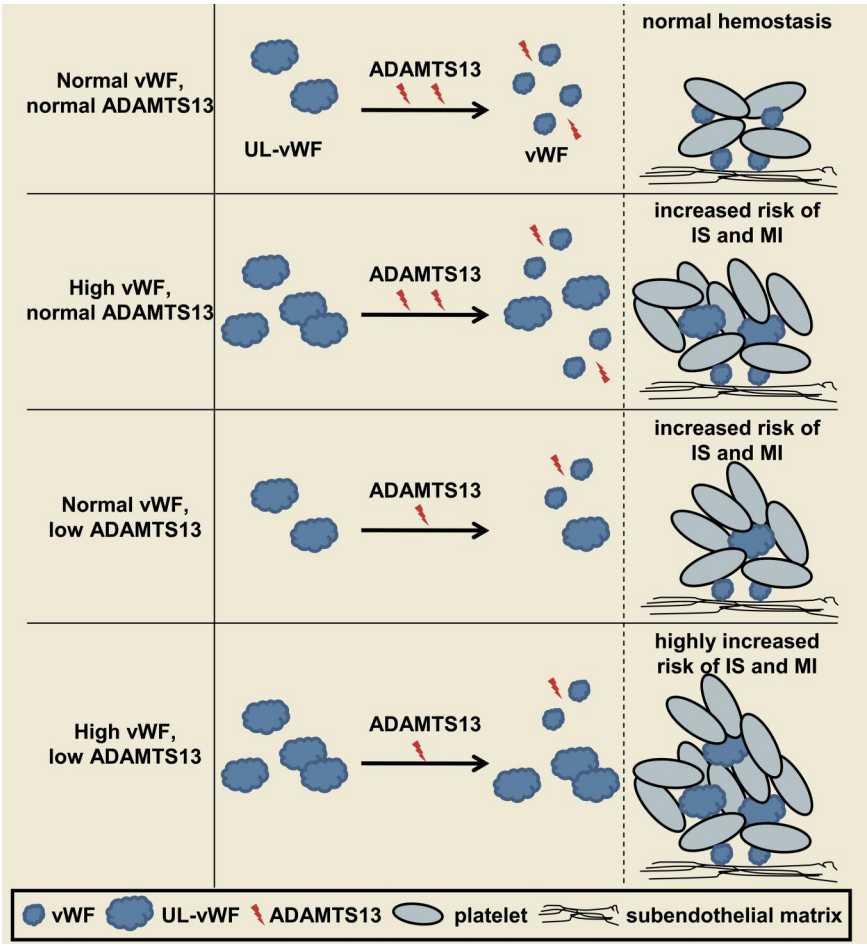


**Simplified model of VWF and ADAMTS13 plasma levels and their contribution to thrombotic events. At sites of injury, VWF becomes immobilized on the damaged vessel wall allowing platelet tethering by the GPIb-VWF interaction (not depicted), which in turn enables platelet activation and thrombus growth to seal a wound (normal hemostasis). Released ultra-large (UL)–VWF can be cleaved by ADAMTS13 into less-reactive smaller VWF multimers to limit thrombus growth. High VWF or low ADAMTS13 plasma levels are each a risk factor for the development of ischemic stroke (IS) and myocardial infarction (MI). The combination of both high VWF and low ADAMTS13 plasma levels further increases the risk of a thrombotic event.**


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that these substances increase plasma levels of activated procoagulant proteins as shown by Siegerink et al.[10] In that study, the risk of ischemic stroke conferred by a combination of high levels of activated intrinsic coagulation proteins and the use of oral contraceptive was found to be higher than expected based on the single effects.

The results of the current report suggest that it will be important to study VWF and ADAMTS13 plasma levels of young women who want to start using oral contraceptives. If VWF and/or ADAMTS13 turn out to be good indicators, screening of these proteins could decrease the number of young patients suffering from thrombo-inflammatory or thrombotic events such as ischemic stroke and myocardial infarction, respectively.

*Conflict-of-interest disclosure: The author declares no competing financial interests.* ■

● ● ● TRANSFUSION MEDICINE

Comment on Smith et al, page 1566

# Tolerant heaven or mHEL trouble

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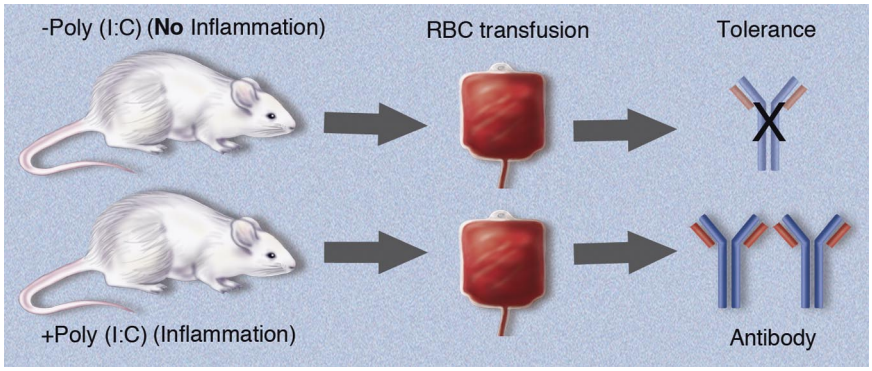
In this issue of *Blood*, Smith and colleagues find that an RBC transfusion can induce tolerance to the foreign antigens on the surface of transfused erythrocytes if the animal has not been given an inflammatory stimulus.[1]

A risk associated with every RBC transfusion is the development of alloantibodies directed against erythrocyte antigens. While anti-RBC antibodies do not develop after most transfusions, these antibodies can be dangerous for subsequent transfusions and pregnancies. Hence, patients at higher risk for harm from these antibodies are premenopausal females and patients likely to receive multiple RBC transfusions, such as patients with sickle cell disease.

Currently, two approaches are routinely used to minimize the development of anti-RBC antibodies. One approach, minimizing transfusion of foreign antigens, is widely used for a limited number of antigens. Indeed, most




**Transfusion in the absence of an inflammatory stimulus induces tolerance to future transfusions while transfusion in the absence of inflammation often induces an immune response, not tolerance, as reported by Smith et al.[1] Professional illustration by Marie Dauenheimer.**

blood banks transfuse RhD− RBCs for RhD− patients and some blood banks provide RBCs lacking Kell and sometimes a few other antigens for select patient populations. The other approach to prevent antibody development, administering Rh immune globulin to prevent the development of anti-RhD antibodies, is a passive immunization used to prevent an active immune response and is frequently used for pregnant women. These approaches are limited by the fact that supplies of RBC units lacking a specific antigen may be in short supply and Rh immune globulin is only effective in preventing development of antibodies to RhD.

An alternate approach suggested by Smith et al would be to tolerize patients to specific antigens by transfusing RBCs with those antigens.[1] They have found that mice transfused with RBCs expressing human glycophorin A (hGPA) or membrane-bound hen egg lysozyme (mHEL) become tolerant of the transfused antigens if the initial transfusions occurred in the absence of inflammation (see figure).[1] This is the first model in which the investigators have been able to modify transfusion procedures to determine whether a transfusion induces tolerance or an antibody response. If such an approach were to work in humans, then transfusion with a small number of RBC units could protect against alloimmunization from future transfusions. This could be especially beneficial for patients with hemoglobinopathies who are frequently transfused.

While the report of Smith et al is promising, several issues need to be studied before this approach can be used clinically. It is not clear whether this approach will work for humans and if it does, it is not clear if all patients can be tolerized and, if they can be tolerized, for how long.

Part of the difficulty in predicting the answers to these questions lies in the fact that the mechanism by which tolerance is induced is not known. Under somewhat different conditions, murine tolerance to hGPA is known to be associated with increased functioning of regulatory T cells (Tregs).[2] However, it is not known whether tolerance induced by transfusion in the absence of inflammation augments Treg functioning.

One finding in humans suggests that RBC transfusion may tolerize patients to RBC antigens. Some reports have found that the younger thalassemia major patients are when they start their chronic transfusion programs, the lower their chances of developing antibodies to RBC antigens.[3,4] Taken together, these reports suggest that patients first transfused before the age of 1 year had the lowest chance of alloimmunization, patients first transfused when they were less than 3 years old had an intermediate alloimmunization risk, and patients first transfused at older ages had the highest alloimmunization risk. These findings suggest that tolerance may be inducible in humans but that tolerance induction is more likely to occur at younger ages.

Other human studies have found induction of tolerance to ABO antigens. If an infant is transplanted with a heart expressing foreign ABO antigens, that child will become tolerant to those ABO antigens.[5] Indeed, that tolerant patient will have no B cells producing antibodies against the heart's ABO antigens. However, such antibodies will develop if the patient is re-transplanted with a heart that does not express the foreign ABO antigens.

While studies of human thalassemia and heart transplant patients suggest that tolerance to antigens expressed on RBCs can be induced in humans, they also suggest some limitations to the process. Tolerance may only be inducible at young ages, may depend on continued presence of the foreign antigen, and may not last indefinately. Indeed, clinical experience would suggest that human tolerance to RBC antigens is neither complete nor permanent because chronically transfused patients sometimes make an antibody to an antigen that they would have been exposed to from multiple prior transfusions.

In addition, to translate to clinical use, one would need to know how to determine whether a person is in an inflamed state making him or her more likely to mount an immune response or in a noninflamed state in which he or she would be likely to become tolerant. Future studies using the murine transfusion model used by Smith et al could help identify characteristics of the noninflamed state conducive to transfusion induced tolerance.

*Conflict-of-interest disclosure: The author declares no competing financial interests.* ■

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● ● ● TRANSPLANTATION

Comment on Srinivasan et al, page 1570

# Exciting new murine model of cGVHD

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In this issue of *Blood*, Srinivasan et al report that mice conditioned for allogeneic hematopoietic stem cell transplantation with cyclophosphamide and total body irradiation develop wide-spectrum manifestations of chronic graft-versus-host disease (cGVHD).[1] This represents an exciting new preclinical model that can be used to uncover mechanisms of cGVHD and test interventional therapies.