Published in final edited form as:

Transplantation. 1989 June ; 47(6): 993–995.

LOW RATE OF RHESUS IMMUNIZATION FROM RH-INCOMPATIBLE BLOOD TRANSFUSIONS DURING LIVER AND HEART TRANSPLANT SURGERY

Glenn Ramsey^{1,2,3}, Linda F. Hahn², Frank W. Cornell², David J. Boczkowski², Sandee Staschak⁴, Roxann Clark⁴, Robert L. Hardesty⁴, Bartley P. Griffith⁴, and Thomas E. Starzl⁴

²Central Blood Bank, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania

³Department of Pathology, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania

⁴Department of Surgery, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania

Abstract

Transfusion of one unit or more of Rh-positive red blood cells normally causes circulating anti-D antibody to appear 2–6 months later in 80–95% of Rh[−] persons. We asked whether transplant immunosuppression with cyclosporine and corticosteroids affects Rh immunization. Nineteen Rh[−] liver, heart, and heart-lung transplant recipients received 3–153 (median: 10) units of Rh⁺ RBCs at surgery and were tested for anti-D >2 months later. Three patients developed anti-D at 11–15 days; one may have had an unusually rapid primary immune response and two were secondary to previous exposure by pregnancy. None of the other 16 patients had anti-D when tested 2.5–51 months later (13 patients, >11.5 months). This low rate of Rhesus immunization in association with cyclosporine immunosuppression allows greater flexibility in meeting the transfusion needs of Rh[−] liver and heart transplant patients. Caution is still advised in young females and in patients who may have been previously exposed to Rh⁺ RBCs by transfusion or by pregnancy prior to the availability of perinatal Rh immune globulin twenty years ago. Other humoral immune responses to some vaccines or infectious agents may also be impaired in transplant patients.

The D antigen on red blood cells is highly immunogenic. As little as 30 µl of RBCs has caused Rh immunization, and after a single 1-ml injection of Rh⁺ RBCs, 10–40% of Rh[−] subjects develop anti-D (1). After transfusions of one or more Rh⁺ units, anti-D appears 2–6 months later in 80–95% of Rh[−] persons (2–4). Hemolytic disease of the newborn (HDN)* or hemolysis of Rh-incompatible RBC transfusions may then ensue.

Transplantation of livers, hearts, and heart-lungs can require large amounts of blood (5,6). Because only 15% of white and 7% of black patients are Rh[−], sufficient Rh[−] blood may not always be available for Rh[−] patients. In view of the setting of transplant immunosuppression, we studied our Rh[−] organ transplant recipients who received Rh⁺ RBCs during surgery to determine whether they subsequently formed anti-D at the normal high rate. The results are of interest with regard to both transplant transfusion management and the pathogenesis of Rhesus immunization.

MATERIALS AND METHODS

Standard serologic methods (7) were employed in Central Blood Bank's transfusion service at the University of Pittsburgh, which supports adult organ transplants at Presbyterian-University Hospital and pediatric transplants at Children's Hospital of Pittsburgh. Blood bank records were reviewed for Rh⁻ liver, heart, and heart-lung transplant patients from 1981 to early 1987, and all who received Rh⁺ RBCs during surgery were assessed in retrospect for evidence of subsequent anti-D. None of these patients had anti-D at our center prior to surgery. We then sought new samples from survivors for RBC antibody testing, including use of ficin-treated screening RBCs to enhance reactivity of Rh antibodies. We also reviewed a second group of patients with anti-D prior to surgery in order to assess the subsequent persistence of antibody. As is customary, we tested blood donors, but not patients, for the weak Rh⁺ D^u phenotype present in 0.23–0.56% of all people (1), or about 1.5–3% of apparently Rh⁻ patients.

For immunosuppression, our transplant programs have employed cyclosporine, corticosteroids, adjunctive rabbit antilymphocyte globulin, and—in recent years—OKT3 monoclonal antibody (8–12).

RESULTS

The proportions of Rh⁻ transplant patients receiving intra-operative Rh⁺ RBCs because of rapid need and/or low Rh⁻ inventory were as follows: liver, 19 of 109; heart, 8 of 51; and heart-lung, 2 of 8. None received Rh immune globulin (RhIG).

Eight of the 29 patients given Rh⁺ RBCs died within 2 months; three of these 8 had no anti-D by 7 weeks. Two other patients were not tested for RBC antibodies beyond one month after surgery. Thus, a total of 19 patients had sufficient follow-up for analysis.

Three liver transplant patients developed anti-D 11–15 days after receiving Rh⁺ RBCs. Two were women 64 and 53 years old, each with 3 past pregnancies and thus presumably immunized prior to the licensure of perinatal RhIG in the U.S.A. in 1968. One received 29 Rh⁺ units during two liver transplants over 12 days. Three days later, anti-D was present in the serum and on circulating RBCs; concurrently, the hematocrit dropped from 34% to 26%, and the total and indirect bilirubin levels rose from 8.1 and 3.4 mg/dl to 19.0 and 8.6 mg/dl. The other woman received 3 Rh⁺ units, the last of 13 in total. Anti-D appeared in the serum, but not on circulating RBCs, at 11 days, along with a hematocrit change from 28% to 18% and a rise in total and indirect bilirubin from 8.9 and 3.7 mg/dl to 20 and 6.2 mg/dl. Thus, both of these patients had evidence of mild delayed hemolysis at times when no bleeding was apparent.

The third patient was a 61-year-old man who was never known to have received Rh⁺ RBCs or platelets and had no RBC antibodies detected elsewhere 6 months before transplant. (24); however, several of these instances were associated with graft rejection, suggesting that immunosuppression might have been insufficient. In bone marrow transplantation, Rh⁻ recipients of Rh⁺ grafts seldom form anti-D, although Rh⁻ grafts sometimes do so to an Rh⁺ host or transfused RBCs (25,26).

Our results in RBC transfusions may be related to experimental evidence in rats and dogs that cyclosporine can prevent transfusion-induced humoral alloimmunization to antigens of the major histocompatibility complex (27,28). In humans, this drug has been reported to impair T cell-dependent antibody responses in bone marrow transplant recipients immunized with keyhole limpet hemocyanin (29), and also in renal transplant patients who were given influenza vaccine (30). Further work to determine whether the RBC Rh protein might also

be a T cell-dependent antigen would be of interest. Besides cyclosporine, the other immunosuppressive measures employed in our patients could have played a role in the effect we observed. Primary antibody responses to other antigens such as vaccines or infectious agents may also be impaired at the time of organ transplantation.

Acknowledgments

We thank Jean Girdwood and Donna Zanger for manuscript preparation.

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