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Synthesis and Effects of Transfusion-Related Red Blood Cell Alloantibodies

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ABSTRACT

In hospitals around the US, blood transfusions are the most frequently performed procedure. Transfusions carry some danger even though they often save lives. The emergence of alloantibodies is one complication that affects a portion of red blood cell (RBC) transfusion patients. Given alloantibody induction and evanescence patterns, lost chances for alloantibody detection, and record fragmentation, it is expected that only 30% of induced RBC alloantibodies are recognized. Future transfusion situations involving alloantibodies may be clinically relevant, with the possibility for immediate or delayed hemolytic transfusion responses or trouble sourcing compatible RBC units. Additionally, alloantibodies may have a clinically significant impact on next pregnancies, with the potential to cause hemolytic illness in the fetus and infant. Developing broad or specific preventive interventions may be made possible by a better knowledge of the variables that affect the production of RBC alloantibodies. Blood donor, blood product, and transfusion recipient characteristics, as well as genetic and innate/adaptive immune factors, may all determine which transfusion recipients may develop alloimmunization, according to animal and human research. The main method used to avoid alloimmunization at the moment is the prudent transfusion of RBCs. Other mitigating techniques include matching the RBC antigens of blood donors and transfusion recipients or giving immunomodulatory treatments to a limited group of recipients who have a history of potentially fatal alloimmunization before they are exposed to blood products. To comprehend RBC alloimmunization and improve preventive measures, multidisciplinary partnerships between healthcare professionals with competence in transfusion medicine, hematology, cancer, transplantation, obstetrics, and immunology, among other fields, are required.

Introduction

Transfusion is the most frequent operation carried out during a particular hospitalization in the United States, where over 11 million red blood cells (RBCs) are transfused yearly.

Restrictive hemoglobin thresholds are as safe as or safer than liberal hemoglobin thresholds for many patient demographics and indications, according to transfusion threshold studies, which has resulted in a decrease in transfused RBC units during the past ten years. 3 Alloantibody development to transfused blood products, however, continues to be a clinically relevant issue despite decreasing transfusion loads. This review will concentrate on alloimmunization to RBC antigens, sometimes referred to as non-ABO blood group antigens.

RBC alloantibodies may be clinically relevant in future transfusion or pregnancy situations, as is covered in greater length in this article. These antibodies may cause hemolytic illness in the pregnancy and newborns as well as acute or delayed transfusion responses. Delays in obtaining appropriate RBC units for upcoming transfusions as well as time-consuming and expensive blood bank assessments may result from them. Given RBC alloantibody induction and evanescence kinetics in conjunction with other factors addressed in this study, only a portion of RBC alloantibodies generated are recognized. The impact of RBC alloimmunization's morbidity and death is thus probably underestimated.

Features of RBC antigen

From a structural and functional standpoint, RBC antigens are many and varied. Since some antigens are proteins and others are carbohydrates4, it's likely that certain antigens will be affected by the factors addressed in this study differently than others. For instance, it is often seen that carbohydrate antigens prefer to produce IgM-class antibodies, with the highest reactivity at 22°C, whereas polypeptide antigens tend to produce alloantibodies of the immunoglobulin G (IgG) class (reactive at 37°C) (also referred to as immediate spin reactivity). 5 Additionally, some

antigens exhibit high levels of expression, while others exhibit "dosage," with more antigen present in the homozygous form than the heterozygous one. Animal and human studies indicate that RBC antigens with extremely low densities (such as KELlo or weak RhD) have relatively low levels of immunogenicity, while studies on animals suggest that RBC antigens with extremely high densities (such as KELhi)6 may be less immunogenic than those with a more moderate density. 7,8 White blood cells (WBCs) and tissue may potentially express antigens, in addition to RBCs. During the formation of RBCs, certain antigens are expressed extremely early while others are expressed later. Most clinically relevant antigens (like K1/K2) show single amino acid polymorphism changes between donors and recipients, however other key antigens (like RhD) show multiple amino acid differences and may be completely absent in receivers while absent entirely in donors (or vice versa). Additionally, complex variations of the antigens encoded by RHD and RHCE—discussed in more detail below—are more likely to be found in people of African heritage than in those of European descent. With the development of high-throughput genotyping tools and developing next-generation sequencing research over the last ten years, the scientific community's knowledge of RBC antigens has significantly grown. 11 These innovations have an effect on obstetrical practices, hospital transfusion medicine services, and blood donation facilities.

Formation, detection, and disappearance of RBC alloantibodies

Only a small percentage of transfusion patients will ever acquire detectable RBC alloantibodies, despite the fact that every transfused RBC unit contains hundreds of non-self RBC antigens. A person must, at the very least, have an HLA-binding motif that can present a piece of the non-self antigen, experience exposure to a non-self RBC antigen, and produce an alloantibody. A fraction of the examined RBC antigens may be presented by a number of distinct HLA types. Human platelet glycoprotein antigen 1a (HPA1a), which is strongly related with HLA class II DRB3*01:01.20, is the only examined antigen for which HLA restriction is restricted.

However, since virtually all transfused RBC units have non-self antigens and virtually all transfused recipients have HLA-binding motifs capable of presenting some portion of these antigens, there are additional factors to take into account in figuring out which transfused recipients may develop RBC alloantibodies. For instance, based on donor/recipient RBC antigen mismatches and average RBC antigen prevalence rates, it has been anticipated that >99 percent of transfused persons should be able to produce at least two RBC alloantibodies. Once a person has been exposed to the majority of "non-self" blood type antigens, the fraction of alloimmunized individuals plateaus, albeit it initially rises with transfusion load. Despite this capacity, research from the past show that only 2 to 5 percent of people who get regular transfusions acquire detectable RBC alloantibodies. 5 The 11 million RBC units that are transfused each year must be taken into account when analyzing this alloimmunization prevalence. Studies of patient populations or the inflammatory settings that surround a transfusion, as well as prospective studies, show increased levels of RBC alloimmunization (described in more detail later in this review).

The "screen" part of the type and screen method is used to identify alloantibodies to RBC antigens. This screening procedure, commonly referred to as an indirect antiglobulin or indirect Coombs test, looks for widespread, clinically significant RBC alloantibodies. In the US, the antibody screen is often carried out utilizing a solid-phase or gel card platform and normally entails evaluating the patient's plasma against reagent RBCs with established antigen specificities21. These tests make it simple to identify individual antibodies, such as anti-D or anti-K. Since there are presently no "single bead/single antigen" techniques for RBC alloantibody detection like there are for HLA antibody detection owing to the structural complexity and variety of RBC antigens, the identification of numerous alloantibodies becomes more difficult and time-consuming. Additionally, low titer antibodies may be undetected by current blood-banking methods, yet antibodies of unknown relevance may be found. Anti-human IgG is the detecting antibody employed in the screen, and specialist reference laboratory testing may be necessary to identify antibodies belonging to distinct classes or specific subtypes.

Alloantibody identification is followed by a crossmatch, which combines the patient's plasma with the antigen-negative donor RBCs to be transfused. This acts as a final compatibility check. If the low-incidence antigen was absent from the reagent screening cells, alloantibodies against it may be discovered for the first time during the crossmatch. For alloimmunized pregnant women, transfusion services may do additional testing, such as serial RBC alloantibody titers. In certain nations, further testing to determine the clinical importance of found alloantibodies may be carried out, such as functional antibody analysis by chemiluminescence or monocyte monolayer assay. RBC alloantibody glycosylation patterns have also been linked in various contexts to clinical importance, according to research findings.

For maximum transfusion safety, it is essential to get the patients' past transfusion histories. There is no national antibody registry in the United States. This leads to the problem known as transfusion record fragmentation, where a patient may get treatment at one hospital after receiving a transfusion where an RBC alloantibody is found but later at a different hospital where the antibody is unknown. A apparently compatible RBC transfusion might cause a quick anamnestic RBC alloantibody reaction if the antibody discovered at the first hospital had vanished2 or dropped below

the level of detection by conventional blood banking methods by the time the patient is seen at the second hospital. A delayed hemolytic transfusion reaction (DHTR), where an anamnestic antibody response results in hemolysis and premature clearance of the transfused RBCs, or a delayed serologic transfusion reaction, where an anamnestic antibody is identified by the transfusion service but may not result in hemolysis, may result from such a response.

RBC alloimmunization's clinical importance

Alloimmunization is a factor in transfusion-related death, albeit it is uncommon for alloimmunization to be the only cause of such mortality. The most frequent transfusion-related side effects of RBC alloimmunization are (1) transfusion delays since it takes time to identify new alloantibodies, (2) trouble finding suitable blood for highly alloimmunized people, and (3) postponed hemolytic or serologic responses. Even though they are uncommon, alloimmunized individuals might have acute hemolytic transfusion responses. RBC alloantibodies are not always harmful if there are no more transfusions, pregnancies, or transplants.

Depending on the circumstance, transfusing RBCs that express an antigen that the recipient possesses alloantibodies against might have different clinical effects. For the duration of the transfusion recipient's life, some RBCs that first seemed to be incompatible may continue to circulate. Other RBCs, however, may undergo a DHTR and be entirely cleansed a few days after the transfusion. The clinical team can notice a fever, black urine, or a hemoglobin that returns to its pretransfusion level in DHTRs. A supposedly novel antibody that was likely present pretransfusion but undetectable may be discovered during the blood bank workup. Both the direct antiglobulin test (DAT) result and the apparent new antibody eluate result might be positive. It is now often incompatible to do a repeat crossmatch utilizing a current plasma sample combined with RBCs from a remaining portion of the unit that was first transfused. The blood bank technologists, not the clinical staff, are the ones who often suspect new or anamnestic alloantibodies. According to the preceding description of these alloantibodies, the patient may be experiencing a delayed serologic transfusion response.

RBC alloantibodies put certain patient groups, especially those with SCD, at higher risk for transfusion-related problems. In this patient group, DHTRs with bystander hemolysis, also known as hyperhemolysis, or the destruction of both the patient's own RBCs and transfused RBCs, are a particularly dreaded and sometimes fatal consequence. It's conceivable that the mortality caused by transfusions due to RBC alloimmunization and DHTRs is significantly higher than was previously thought. The majority of DHTRs with bystander hemolysis occur in patients with a history of RBC alloimmunization, and the majority are connected to the acute onset of reticulocytopenia. However, some but not all DHTRs with bystander hemolysis are associated with newly detectable RBC alloantibodies (e.g., no new RBC alloantibody may be detected in some reactions). Recent research has examined this complication's risk factors and prevention measures. For instance, it is well known that individuals who have had DHTRs with bystander hemolysis are more likely to have this problem once again when exposed to RBCs in the future. Excessive eryptosis has been suggested as one possible reason for the increased phosphatidyl serine expression on foreign RBCs in individuals with SCD who are undergoing bystander hemolysis.

Bystander hemolysis has also been linked to complement activation, and a stop-gain mutation in MBL2 (mannose-binding protein C) has been found in certain individuals with both SCD and bystander hemolysis, according to a recent genome-wide association analysis. A role for complement activation in bystander hemolysis is further supported by case reports of the effectiveness of eculizumab in the treatment of life-threatening bystander hemolysis cases, albeit it is important to be mindful of the increased risk of meningococcemia after eculizumab therapy. A new case report describing elevated C5a, C5b-9, and Bb levels after an incident of bystander hemolysis in a young child with repeated episodes of bystander hemolysis provides evidence of activation of the alternative complement pathway.

Clinically significant RBC alloantibodies occur during pregnancy as well as in transfusion circumstances. When maternal alloantibodies against fetal RBC antigens produced from the father cross the placenta, they result in hemolysis and/or the inhibition of erythropoiesis in the developing baby. Maternal RBC alloimmunization may affect up to 1 in every 600 pregnancies, while the main prophylactic measure (i.e., Rh immune globulin) solely targets the RhD antigen. D-alloimmunization continues to be a major contributor to HDFN despite the availability of prophylaxis against the RhD antigen. Many clinically significant HDFN cases are caused by alloantibodies against antigens in the C/c, E/e, Kell, Duffy, Kidd, and MNS blood groups in addition to anti-D alloantibodies. It is noteworthy that maternal RBC alloantibodies often cause worry and need repeated assessments, even when the infant is finally shown to not express the corresponding RBC antigen (s). When the mother and fetus have ABO compatibility, maternal alloantibodies are substantially less likely to form. This is most likely because maternal isohemagglutinins quickly eliminate

fetal RBCs from the body. Intrauterine transfusion is a substantial risk factor for the development of RBC alloantibody induction during pregnancy, in addition to blood exchange between the mother and fetus. 48

RBC alloantibodies may also be clinically relevant in hematopoietic stem cell transplant situations, while being less researched than in transfusion or pregnant contexts. RBC alloantibodies may have implications for the product infusion or donor RBC engraftment in situations where the donor expresses the cognate RBC antigen in question, just as isohemagglutinins are significant in major ABO mismatched transplant settings (e.g., blood group O recipient, blood group A donor). An adult with SCD who had a preexisting anti-Jka RBC alloantibody needed ongoing transfusion therapy for 18 months after a reduced-intensity conditioning transplant from a donor who was Jka positive because persistent recipient plasma cells continued to produce antibodies. Although it is unclear what role RBC alloantibodies may play in solid organ transplantation, alloantibodies against antigens that are expressed on both the transplanted organ and RBCs (such as those in the Jk family expressed on renal endothelial cells) may, at the very least, have an impact on the results of the transplant.

Prevention methods for RBC alloimmunization

One method of preventing RBC alloimmunization is prudent transfusion or transfusion avoidance. However, this is often not practical. To reduce the production of alloantibodies to matched immunogenic antigens like D, C/c, E/e, and K, matching for certain blood group antigens is advised for individuals with SCD. Patients at risk of developing anti-C alloantibodies have antigenic variations such the hybrid RHD*DIIIa-CE(4-7)-D allele, which encodes a partial C antigen but lacks the typical RHCE*Ce or *CE allele. However, genotyping must be finished before this variant may be identified.

Genotyping is increasingly being used to direct transfusion treatment for SCD patients since it has recently been shown to be more accurate than phenotyping. In addition to SCD, persons with thalassemia major and MDS are more prone than those with other blood group systems to develop alloantibodies to Rh antigens. For these at-risk patient categories, prophylactic matching for these antigens has also been advised. It has been suggested that extended matching for patients with RBC autoantibodies is an effective way to both stop the development of new RBC alloantibodies and find suitable RBC units for upcoming transfusions more promptly. The need for standard registries to record such complex data grows as more patients and donors are phenotyped or genotyped.

There hasn't been a thorough investigation of pharmacologic inhibition of RBC alloantibody production. Patients are less likely to develop an alloimmune response when receiving corticosteroids or chemotherapy for disease maintenance, as was previously mentioned. Type 1 interferon has been linked to RBC alloantibody production in animal models, and type 1 interferon receptor blockage can stop alloantibody development. Worldwide partnerships are required to identify the best treatments for this very uncommon but life-threatening condition. Pharmacologic intervention to attenuate or prevent life-threatening DHTRs with bystander hemolysis is also now being explored.

Animal models: Lessons learnt

Over the last 10–15 years, several mouse models have been created, enabling the research of reductionist topics that are just impractical to examine in humans. While a comprehensive discussion is beyond the scope of this article, recent mouse models include those that express model antigens specifically on RBCs (like HOD) or real human blood type antigens (such as KEL or human glycophorin A). The effects of recipient inflammation,1 type 1 interferon,6, CD4+ T cells, regulatory T cells, CD40/CD40L interactions, interleukin-6 receptor signaling, bridging channel dendritic cells, and complement on the induction of RBC alloantibodies have been highlighted in studies using these models, among others. The phenomena of RBC antigen modification, putative immunoprophylaxis treatment mechanisms, and, as was already noted, transfusion-associated tolerance induction have all been the subject of murine investigations. Animal studies have also shed light on the effects of transfusions of incompatible RBCs.

Conclusion

Clinically significant issues can arise from transfusion-associated alloimmunization against RBC antigens. Given the combination of

characteristics discussed in this analysis, it is probable that the identified RBC alloantibodies and reported problems linked to RBC alloimmunization reflect just one-third of the real issues. Because of this, it is likely that what is known about RBC alloimmunization is just the "tip of the iceberg." To comprehend risk factors for antibody formation, multidisciplinary investigations are required at the fundamental, translational, and clinical levels. Both preventative and protective measures against the risks posed by alloantibodies already in existence need to be improved. Alloantibodies related to transfusions and pregnancy have effects on a variety of fields, including hematology, oncology, transplantation, obstetrics, and immunology, in addition to blood banks and transfusion medicine.

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