

A patient-centric approach to preventing allergic reactions to platelet transfusions

Allergic transfusion reactions (ATRs) are the most common transfusion complications. Although usually they are not serious, cumulatively they can amount to significant morbidity for the multiply transfused hospitalized patients who are the sickest of all patients. ATRs are attributed to a Type I hypersensitivity reaction mediated by preformed recipient antibody directed to an “allergen” in the transfused product. In practice, however, there is usually no identified culprit(s), and the ATR appears to involve an interaction between unspecified recipient and product (including donor) factors.¹⁻³ To prevent ATRs, diphenhydramine is administered before more than half of the transfusions given in the United States, despite the fact that pretransfusion medication with 25 mg of diphenhydramine was found not to prevent ATRs in two randomized controlled trials (RCTs).^{4,5} Thus, although ATRs accompany 1% to 3% of all transfusions, the pathogenesis of ATRs remains poorly understood and effective prevention of ATRs eludes us.

In this issue of **TRANSFUSION**, two important studies^{1,2} by the same group of investigators from the Johns Hopkins Hospital and Cancer Center examine ATRs from two different perspectives. Savage and colleagues¹ set out to distinguish between recipient, donor, and product factors that predict the occurrence of ATRs. They find that recipient factors are paramount in predicting ATRs, although there is also some (minor) role for donor factors and their study¹ was not designed to investigate some product-related (such as storage) factors. Over 10 years in the Johns Hopkins Oncology service, a minority (30.0%) of platelet (PLT) recipients accounted for a majority (62.1%) of ATRs.¹ A total of 630 ATRs occurred when apheresis PLTs (APs) split from the same plateletpheresis collection were transfused to two or more recipients. However, ATRs were observed in two or more different recipients of the same collection only 6 of 630 times (0.95%), that is, as frequently as it would have been expected from the overall incidence of ATRs (1.7%) in all clinical services of the Johns Hopkins hospital.¹ Tobian and coworkers² set out to determine to what extent removal of donor plasma from APs and red blood cells (RBCs) can reduce the risk of ATRs. They find that concentrating APs (to remove 73% of the donor plasma with ≥ 100 mL of plasma remaining in the product

to resuspend the PLTs) reduces the risk of ATRs by more than threefold (from 5.5% [in this selected population of patients prone to ATRs] to 1.7%), while washing APs (to remove 95% of the donor plasma) reduces the risk of ATRs by an additional more than threefold to 0.5%. Similarly, washing RBCs (to remove 89% of the donor plasma) reduces the risk of ATRs from 2.7% to 0.3%.²

Since recipient factors are primarily responsible for ATRs,¹ it is for the minority of patients who have already had severe ATRs that Tobian and coworkers² recommend removal of donor plasma to reduce the risk of ATRs. Concentrated APs should be used first, and washed PLTs and RBCs should be used for patients who fail to respond to concentrated APs (as was the case for one-third of the patients of Tobian et al.²). Washing APs and RBCs does reduce the risk of ATRs; however, it also: 1) shortens the shelf life of the product; 2) decreases the number of PLTs transfused to the patient because 15% of the PLTs are lost during washing; and 3) may reduce the survival of the transfused PLTs in vivo.² Accordingly, patients chronically transfused with washed PLTs should be monitored with daily PLT counts so that (if necessary) they can receive increased PLT transfusions to maintain adequate PLT counts.²

Both the administration of concentrated APs when a transfusion medicine specialist has determined their appropriateness as Tobian and coworkers² recommend and the daily monitoring of PLT counts for patients chronically receiving washed PLTs after their ATRs have failed to respond to concentrated APs² are attributes of a patient-centric approach⁶ to meeting patient transfusion needs. An alternative approach is the use of PLT additive solutions (PASs) for replacing approximately the same volume of donor plasma as that removed from the concentrated APs of Tobian and coworkers.² PASs have indeed been shown to reduce the risk of adverse reactions to PLTs,^{7,8} but these alternative approaches to the management of ATRs underlie different philosophies about how we can best meet patient transfusion needs.^{6,9,10}

The approach of Tobian and coworkers² is *patient-centric*, because it *selects* the patients to whom concentrated APs should be administered. Only a minority of patients prone to ATRs will receive concentrated APs, with the majority of the PLT transfusion recipients still benefiting from any hemostatic contribution of two-thirds of the donor plasma. PLTs stored in PAS-II result in lower corrected count increments (CCIs) than PLTs stored in

plasma.⁷ It was subsequently demonstrated that PLTs stored in PAS-III result in CCIs equivalent to, and prevent bleeding as effectively as, PLTs stored in plasma.¹¹ However, several international blood operators had moved to PLTs stored in PAS-II to prevent ATRs without adequate documentation of the efficacy of this PAS to raise posttransfusion CCIs and prevent bleeding. Moreover, as Tobian and coworkers² point out, theirs² is the first study to demonstrate that plasma removal can indeed prevent ATRs, thereby retrospectively justifying the decisions of international blood operators to use PASs to prevent ATRs. Before the study of Tobian and coworkers,² the actual evidence demonstrating that effecting a 95% plasma reduction through washing of APs can reduce the risk of chronic ATRs had consisted of two studies^{12,13} including only 10 patients.

The manufacturing of PLTs stored in PAS for transfusion to *all* PLT transfusion recipients is *component-centric*, because it treats all patients for a complication to which some of them are prone, thereby depriving the majority of the patients (who are not predisposed to ATRs) from any benefit to their hemostasis contributed by two-thirds of the donor plasma.^{7,11} A reason for favoring such a component-centric approach is that the transfusion medicine knowledge required to select the patients who need concentrated APs is not yet available everywhere and that the history of prior ATRs to make this selection may not be available to the clinicians or the blood bank. Nonetheless, a transfusion recipient receiving APs stored in PAS has already been subjected to the infectious and immunologic (including transfusion-related acute lung injury [TRALI]) risks from that allogeneic collection, making the rationale for removing two-thirds of the same donor's plasma debatable if the recipient is not prone to developing ATRs. Importantly in this respect, untoward effects of ABO-incompatible plasma in ABO-incompatible APs can be avoided by other means.¹⁴

It is possible, however, to use APs stored in PAS in a "patient-centric" manner: that is, to administer them solely to patients prone to ATRs, substituting APs stored in PAS-III for the concentrated APs of Tobian and coworkers.² Patients who continue to have ATRs after receiving concentrated APs and/or APs stored in PAS-III will have to be managed thereafter with washed APs, and it is important that the patient-centric aspects of their management recommended by Tobian and coworkers² (daily monitoring of PLT counts to increase PLT transfusions if necessary) be maintained in settings where a component-centric approach is used. A completely patient-centric approach to PLT transfusion would combine: 1) transfusing APs (rather than pooled whole blood-derived PLTs) to reduce the risk of transfusion-transmitted infections (TTIs) and PLT transfusion-associated sepsis by at least twofold;¹⁵ 2) reserving the PLTs and plasma and/or RBCs from the same multicomponent apheresis collection for transfusion to

the same recipient to reduce the risk of TRALI^{16,17} in addition to TTIs; and 3) concentrating (or washing if necessary) APs—or, alternatively, using APs stored in PAS-III—for patients prone to ATRs.²

The greater frequency of ATRs in association with PLT and plasma (rather than RBC) transfusions is the basis for the prevailing belief that implicates a mediator(s) present in donor plasma in the pathogenesis of ATRs. However, there are likely both donor and recipient attributes that are needed concurrently to elicit an ATR, and their relative contribution to an ATR may change with time and circumstances.¹ It is thus possible for a patient's predisposition to ATRs¹ to be transient,² and for this reason the efficacy of plasma removal in reducing the risk of ATRs cannot be established¹⁰ by the retrospective cohort study of Tobian and coworkers.² Although it can be inferred that the risk of ATRs increased with increasing dose of plasma in the 179 patients included in that study² (since the risk declined as unmanipulated components were replaced by concentrated APs and then by washed PLTs and RBCs in accordance with the hospital's policy²), it is also possible that the recipients' own predisposition to ATRs decreased over time, so that the reduction in the recipients' predisposition coincided with the removal of plasma from the transfused products. Establishing that plasma removal is causally related to a decrease in the risk of ATRs will thus require RCTs.¹⁰ Because the etiology of ATRs is likely multifactorial,¹⁻³ prevention of ATRs will ultimately require a combination of multiple approaches to address various factors.² Hopefully, the studies of Savage and colleagues¹ and Tobian and colleagues² will spearhead this long-awaited research.

CONFLICT OF INTEREST

The author has no conflict of interest of any kind.

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