Scratching the surface of allergic transfusion reactions

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Allergic transfusion reactions (ATRs) are a spectrum of hypersensitivity reactions that are the most common adverse reaction to platelets and plasma, occurring in up to 2% of transfusions. Despite the ubiquity of these reactions, little is known about their mechanism. In a small subset of severe reactions, specific antibody has been implicated as causal, although this mechanism does not explain all ATRs. Evidence suggests that donor, product, and recipient factors are involved, and it is possible that many ATRs are multifactorial. Further understanding of the mechanisms of ATRs is necessary so that rationally designed and cost-effective prevention measures can be developed.

Allergic transfusion reactions (ATRs) are the most common adverse events associated with platelet (PLT) and plasma transfusion, and ATRs are second in incidence to febrile reactions among red blood cell (RBC) transfusions.[1] Reported incidence rates depend on the degree of active surveillance versus passive reporting to the blood bank. Best estimates using active surveillance of transfusions show that ATRs are associated with approximately 2% of PLT transfusion.[2,3] There is less active surveillance data for RBC transfusion, but the incidence rate is approximately 0.1% to 0.5%.[1]

ATRs most commonly manifest with urticaria, pruritus, erythematous rash, angioedema, bronchospasm, and/or hypotension. These manifestations occur on a spectrum of severity and most commonly are mild, involving localized pruritus and/or urticaria only. More severe reactions involving angioedema, bronchospasm, or hypotension occur in less than 10% of ATRs.[4,5]

Regardless of severity, all ATRs cause patient morbidity and incur costs of transfusion reaction evaluation and possible product wastage.[6] The high incidence of these reactions makes them a cumulative burden on transfusion medicine specialists and patients, particularly chronically transfusion-dependent patients with recurrent reactions. A more comprehensive understanding of the mechanisms of ATRs will lead to strategies that reduce the incidence of these reactions. The goal of this review is to summarize our limited understanding of ATR mechanisms and their prevention.

THE SCOPE OF OUR UNDERSTANDING OF ATRs

Because ATRs are characterized by the development of allergic symptoms, it has been assumed that the mechanism of immunoglobulin (Ig)E-mediated, Type 1 immediate hypersensitivity reactions to a specific allergen (discussed below) explains ATRs. Indeed, it has been established that ATRs can occur due to 1) the passive transfer of specific antibody to a transfusion recipient and subsequent allergen exposure or 2) the development in a transfusion recipient of antibody specific to donor protein. These mechanisms are conceptually elegant, and there is a long list of reports consistent with these mechanisms.[7-27] However, most of these reports describe severe reactions, and there are no data that support the generalization of these mechanisms to the most common pruritic and urticarial reactions that occur almost daily in large centers. Furthermore, ATRs typically occur in a small proportion of transfusions for a given patient, if they are recurrent at all,[28] leaving uncertainty as to why some products seem to cause ATRs and others do not.

ABBREVIATIONS: ATR(s) = allergic transfusion reaction(s); PAS = platelet additive solution.

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The clinical manifestations of ATRs are similar to the signs and symptoms of other allergic reactions. Although the intravenous (IV) route of administration differs from most allergic exposures, for example, topical, inhalational, or gastrointestinal, the manifestations are similar. Data available from allergic reactions to radiocontrast media, which is another exclusively intravascular exposure, demonstrate the same spectrum of signs and symptoms as seen in ATRs and nonvascular allergic exposures: pruritus, urticaria, flushing, bronchospasm, emesis, abdominal pain, and hypotension.[29,30] The diagnosis of ATRs is complicated by the overlapping manifestations of hypotensive, fluid overload, transfusion-related acute lung injury, and septic reactions. The presence of cutaneous signs, the absence of fever, and the clinical and radiologic differences between pulmonary edema and bronchospasm usually make the diagnosis apparent among the differential diagnosis of transfusion reactions. Among anaphylaxis cases in an emergency room setting, cutaneous findings of pruritus, urticaria, edema, and flushing were present in the majority of patients with allergic reactions.[31] Isolated hypotension or bronchospasm is unusual among allergic reactions in general. The distribution of ATR signs and symptoms according to standardized criteria or a comparison of anaphylaxis from transfusion to anaphylaxis from other exposures has not been specifically studied.

HISTORY OF ATRs

Modern observations of hypersensitivity responses to blood components began at the end of the 19th century when immediate hypersensitivity reactions and serum sickness were noted after immunizations in humans and animals. The first theories about the mechanisms of sensitization with foreign antigen were proposed separately in 1903 by Nicolas Arthus[32] and Bela Schick and Clemens von Pirquet.[33] Indeed, the introduction of the term "allergy" (Greek *allos* "other" + *ergon* "reaction") was borne out of the work of von Pirquet and Schick.[34] While the work is not specifically identified as transfusion specific, many of the experiments involved transfusion of serum IV. Von Pirquet noted that upon rechallenge of horse serum into children, there was sometimes an "immediate reaction" that consisted of urticaria, redness, and edema, and the reaction was "sometimes accompanied by collapse."[35] Their work helped lay the framework for the landmark 1963 Gell and Coombs[36] classification of the four types of hypersensitivity reactions, with Type 1 reactions being immediate hypersensitivity reactions, which include anaphylaxis.

The first reported ATRs were identified as passive transfer of horse allergy into previously nonallergic recipients.[7,8] Human experiments investigating passive sensitization to food and aeroallergens began in 1939.[10] Remarkably, the initial experiments accurately depict the same time course of passive sensitization that was observed in experiments done 66 years later with specific IgE kinetic studies,[10,22] suggesting passive transfer of IgE as a mechanism of allergy. As early as 1944, it was reported that some transfusion recipients who had experienced ATRs to serum had less severe reactions upon repeat exposure to the same product. The author concluded that it was possible to desensitize subjects to blood products,[37] as is often done for treatment of other hypersensitivity reactions, although other mechanisms may have been involved.

A major breakthrough in the modern understanding of ATRs came in the late 1960s with reports by Vyas and colleagues[12] and Schmidt and colleagues[11] of IgA deficiency and anti-IgA as a specific mechanism for ATRs. These were the first molecular descriptions of a specific hypersensitivity that caused allergic reactions through transfusion. The paradigm of protein-antibody reactions is the most extensively described model for ATRs. Associations of other protein deficiencies or polymorphisms, for example, C4[15] and haptoglobin,[21] with ATRs followed. Unusual antibody-mediated mechanisms of anti-CD36[23] and multimeric IgE in donor plasma[25] have been described recently. While many of these reports support a causal role for protein-specific antibodies in ATRs, they do not explain all ATRs.

Of note, the literature of ATRs to date reflects the terminology used in the fields of allergy and immunology. Historically, the terms allergic, anaphylactoid, and anaphylactic have been applied to describe hypersensitivity reactions to transfusion. "Anaphylactoid" has been used variably to describe reactions of moderate severity that do not qualify as anaphylaxis or reactions that are not mediated by IgE. Some allergy experts suggest that the term "anaphylactoid" is confusing and discourage its use.[38,39] Newer terms of "immunologic" and "nonimmunologic" hypersensitivity have been proposed.[38] Immunologic mechanisms refer to specific antigen recognition by antibody or T cells. Nonimmunologic mechanisms are thought to directly increase the susceptibility of mast cells to release histamine and other mediators of anaphylaxis. Nonimmunologic mechanisms are thought to be involved with radiocontrast media[40] and opioid[41] reactions, for example. Anaphylaxis is currently defined as an acute, life-threatening reaction involving skin, mucosal tissue (e.g., lips), or both, and at least one symptom of respiratory compromise or hypotension (≥30% decrease from baseline or symptom consistent with hypotension).[42]

GENERAL MECHANISMS OF ALLERGIC REACTIONS

Because urticaria, pruritus, angioedema, bronchospasm, and shock are familiar allergic manifestations, it is assumed that the same allergic pathophysiologic

mechanisms that underlie other allergic diseases are responsible for ATRs. Therefore, a basic understanding of the pathophysiology of immediate (Type 1) hypersensitivity reactions provides a context in which to discuss the pathophysiology of ATRs. The pathophysiology of Type 1 hypersensitivity reactions is most relevant because most allergic reactions to transfused blood products occur immediately or within a few hours of exposure and present clinically with symptoms similar to Type 1 hypersensitivity reactions. Type 1 hypersensitivity reactions are classically mediated by allergen-specific IgE, which can be quantified.

Activation of mast cells and basophils, the primary allergic effectors of immediate hypersensitivity reactions, typically occurs after cell surface high-affinity IgE receptors (FcεRI) aggregate in response to cell surface IgE binding with specific antigen (Fig. 1). Details of the cell signaling in this context have been recently reviewed.[43-45] IgE–antigen interactions lead to a signal transduction cascade that results in the immediate release of preformed mediators such as histamine. There is also de novo synthesis of lipid mediators such as leukotrienes and PLT-activating factor. Changes in gene expression and cytokine and chemokine generation are consistent with the onset time of the so-called "late phase" of an allergic reaction, which peaks 6 to 8 hours after exposure.[46]

IgE-independent mechanisms that can lead to clinical manifestations of immediate hypersensitivity reactions have also been described. IgG can directly induce anaphylaxis by binding the low-affinity IgG receptor FcγRIII in mouse models.[47] The significance of IgG in anaphylactic reactions in humans is not well established but limited case series provide evidence for this mechanism, which may involve direct complement activation.[48-50] Iodinated, hyperosmolar radiocontrast compounds can cause IgE-independent reactions. Investigations into the mechanism of these reactions show that they may be mediated by anaphylatoxin (complement component C3a, C4a, or C5a) activation; hyperosmolar effect on mast cells; or direct, osmolarity-independent induction of histamine release, as with opioids.[40,41] Evidence for nonimmunologic mechanisms also comes from studies of direct injection of allergic agonists, for example, bradykinins, leukotrienes, and PLT-activating factor, which stimulate histamine release from human basophils and mast cells.[51-54]

CLINICAL OBSERVATIONS THAT GIVE INSIGHT INTO THE MECHANISMS OF ATRs

Clinical studies have helped define in broad strokes the recipient and product factors that are involved in the

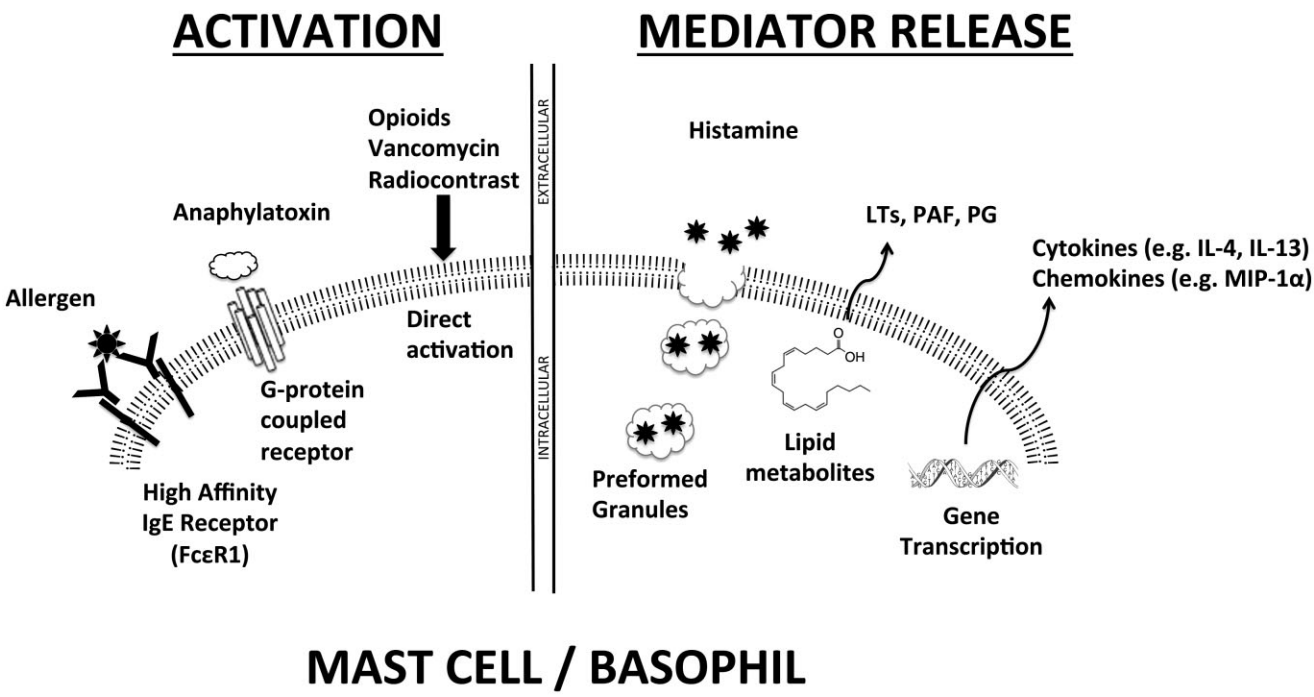

Fig. 1. Summary of mast cell/basophil activation and mediator release. The best understood mechanism for activation is the aggregation of high-affinity IgE receptor on the cell surface after exposure to allergen, but IgE-independent mechanisms of activation have also been described. After activation, mediators may be released immediately via preformed granule release or immediate synthesis of lipid mediators; products of gene transcription may be synthesized within hours. LT = leukotriene; PAF = PLT-activating factor, PG = prostaglandin; MIP-1α = macrophage inflammatory protein-1α.

mechanisms of ATRs. Notable observations are listed below.

Plasma as the culprit

It has been known for decades that plasma reduction of products is associated with a lower incidence of ATRs.[55,56] There appears to be a dose–response relationship between the amount of plasma and the incidence of ATRs. Tobian and coworkers[57] showed that in a selected cohort of PLT recipients with recurrent ATRs, the ATR incidence rates of unmanipulated, concentrated, washed PLT components were 5.5, 1.7, and 0.5%, respectively. Furthermore, PLT components prepared with PLT additive solution (PAS) have a reduced plasma component and are associated with a lower incidence of ATRs.[58-60] It is not known whether the plasma agents responsible for ATRs are present in the donor at the time of collection or arise during PLT processing and storage, but there is not an obvious association between storage time and ATRs.[3] A recent study suggests that ABO-incompatible PLT transfusion results in higher rates ATRs,[61] but the contributions of incompatible plasma versus incompatible PLTs were not described.

Plasma proteins are obvious suspects for the etiology of antibody-mediated ATRs, as a limited number of examples demonstrate that antibody-mediated hypersensitivity to proteins underlies some ATRs. This mechanism requires an initial exposure to develop antibody and subsequent sensitization. Ahmed and colleagues[62] evaluated the incidence of ATRs to first RBC transfusion in multiparous women, who are known to be to be exposed and sensitized to a variety of antigens during pregnancy. This suggestive study found that the incidence of mild ATRs to first transfusion increased from 0% with zero or one prior pregnancy to 3.8, 8.3, 21.7, and 37.5% with two, three, four, and five prior pregnancies, respectively. Thus, the frequency of fetal exposure directly correlates with the risk of ATR on initial transfusion. Sensitization to specific allergen can occur with prior transfusion, but autoantibodies can be formed in the absence of identifiable exposure, as has been demonstrated with anti-IgA.[63] Nevertheless, prior sensitization does not necessarily lead to reactions.[64] Sensitization can rarely occur through passive transfer of plasma containing specific antibody, as demonstrated by cases of passively acquired food and drug allergy.[14,24,65] It has been considered that food allergen could be consumed by a donor and transmitted via plasma to a sensitized recipient,[26] but this hypothesis has not been proven yet.[66]

No apparent role of white blood cells

White blood cells (WBCs) in blood components do not appear to be directly involved with the pathogenesis of ATRs, even though they are capable of producing several mediators that could produce symptoms of ATRs. First, there is the observation that acellular plasma components are a common cause of ATRs.[67] Second, as universal leukoreduction became universally adopted in certain centers, reductions in febrile, but not allergic, reactions were noted.[68-70]

Atopic predisposition of recipients, not donors

Allergic individuals tend to have multiple manifestations of allergic disease, and it is reasonable to suspect that an atopic predisposition is a risk factor for ATRs. Maunsell[37] experimentally found that an atopic history to environmental allergens is associated with an increased risk of an ATR. Wilhelm and coworkers[71] found that 91% of PLT recipients tested positive for IgE specific to environmental allergens, and Savage and coworkers[4] reported that median total IgE, a crude measure of atopic predisposition, was 6.7-fold higher in subjects who experienced an ATR compared to controls who never had an ATR, and IgE specific to common environmental allergens was 58% higher than controls. It does not seem plausible that the IgE specific to environmental allergens is causing the ATR per se, but the general atopic predisposition of the patient that increases susceptibility to an ATR. The lack of concordance of ATRs in two different recipients of the same apheresis PLT collections also supports the concept that a recipient, not an intrinsic product characteristic, increases susceptibility to ATRs.[28] These clinical observations are corroborated by in vitro data that show the threshold and magnitude (i.e., priming) of histamine release from mast cells and basophils varies among individuals[72] and that transfusion recipients who experience ATRs have plasma factors that increase susceptibility to mast cell calcium influx and histamine degranulation.[73] Of note, an atopic predisposition may be acquired,[22] as in a case of passively transferred peanut-specific IgE.[24] Genetic predispositions to ATRs have not been studied, as they have in other allergic diseases.[74]

There is limited evidence that certain donors are associated more frequently with ATRs than the general donor population.[25,28] However, there are no reported estimates of the frequency of suspect donors in a large donor population. Atopic disease in donors does not appear to confer a risk of ATRs,[4,75] even though atopy is prevalent in donor populations.[76] Nevertheless, if it is confirmed that some donors are particularly associated with ATRs independent of the recipient, it remains unknown to what extent the increased risk is intrinsic to the donor, as reported in rare cases,[23,25] or a susceptibility that is unmasked during component processing and storage.

RELATIONSHIP OF SPECIFIC MEDIATORS AND PREDISPOSITIONS TO ATRs

Histamine

The fact that nearly all ATRs occur during or very soon after transfusion suggests that preformed or quickly syn-

thesized mediators contribute to the clinical manifestations of ATRs. A primary mediator of these Type 1 hypersensitivity manifestations is histamine. It is also important to understand the role of histamine in allergic reactions because antihistamines are the most widely used drugs to treat ATRs.

Histamine is a histidine-derived small molecule for which there are four histamine receptor subtypes. Clinical manifestations attributable to histamine include bronchospasm, headache, flushing, palpitations, angioedema, hypotension, and rhinitis.[77] Histamine is stored preformed in mast cells and basophils and can be released after IgE aggregation or other antibody-independent stimuli, for example, opioids[41] or activated complement.[78] Histamine increases vascular permeability and activates sensory neurons in conjunction with other mediators.[79] Histamine has a half-life of minutes in blood and is released into blood almost immediately after allergen challenge or mast cell or basophil activation.[80,81]

Histamine is present in blood components. Levels of histamine in blood components depend on the number of WBCs and duration of storage; however, leukoreduction markedly reduces plasma concentrations in blood components.[82-86] The lack of an effect of leukoreduction on incidence rates of ATRs argues against a role for passive transfer of histamine as a cause of ATRs. One study found higher in vivo plasma histamine in recipients who experience ATRs, but it is not clear if this elevation precedes or is a consequence of ATRs.[84]

Complement

The complement system is a coordinated set of plasma proteins that has a primary role in attacking extracellular pathogens. Dysregulated and maladaptive complement activation is an inflammatory pathway commonly involved in anaphylaxis and many diseases. Anaphylatoxins are activated cleavage products of the complement pathway.[87] Among the anaphylatoxins C3a, C4a, and C5a, C5a is the most potent; they cause increases in vascular permeability, bronchospasm, and histamine release. Mast cells and basophils express complement receptors for C3a (which also binds C4a) and C5a.[88,89]

The extensive literature on the PLT storage lesion[90] leads to the hypothesis that complement component accumulation during storage could lead to ATR development. C3a and C4a, but not C5a, have been demonstrated to increase during storage.[91-94] C3a increases markedly during blood collection but is apparently rapidly degraded and/or adsorbed.[93] Accumulation of anaphylatoxins during storage is a possible mechanism of ATRs in PLT concentrates, but there does not appear to be an association between storage time of PLTs and the development of ATRs.[3] Although levels of C5a remain low, there is an association of products that contain higher C5a levels with ATRs.[95]

Specific protein deficiencies and polymorphisms

Exposure of a transfusion recipient to a foreign protein is a known mechanism of sensitization. IgA[12] and haptoglobin[21] deficiencies are classic examples; however, protein deficiency is not a universal set-up for ATRs. There is extensive experience with coagulation factor replacement that shows a low rate of allergic reactions, approximately 1 in 10,000 doses[96] or 3% of recipients.[97] Other experience of plasma and plasma protein replacement in subjects with severe α1-antitrypsin deficiency shows a similarly low incidence.[98,99] Reports of C4 polymorphisms and ATRs raise the possibility that differences in protein polymorphisms between donors and recipients could be a common source of intermittent ATRs in recipients when given donor products mismatched for a polymorphic protein. Indeed, in the report from Shimada and colleagues on haptoglobin deficient patients, one was noted to have "relatively mild reactions." Antibodies appear to be made frequently to transfused proteins, for example, albumin, fibrinogen, C2, and C4, but the formation of these antibodies has not been studied in the context of ATRs.[100]

Other product-derived factors

PLTs are a rich source of several molecules that have been demonstrated to either prime allergic effector cells or directly activate these cells to release allergic mediators.[101] The observation of ATRs after autologous transfusion suggests a product-specific mechanism in some cases.[5] CCL5 (RANTES) is one such candidate because it is abundant in PLTs, is released during storage,[102,103] and can activate allergic effector cells.[104] Three studies have evaluated CCL5 concentrations in PLTs: two found minimally higher levels in products associated with ATRs[95,105] and the third study, which was augmented by in vitro functional assays, did not find a role for CCL5.[106] The literature that describes molecules released by PLTs during storage may serve as a list for candidate mediators of ATRs.[107] While little is known about the role of molecules like CCL5 in ATRs, even less is known about potential direct allergic agonists in RBC and plasma transfusion.

A non–blood-derived product source of allergen is ethylene oxide, which has been described as a cause for allergic reactions in apheresis donors,[16,17] but the applicability of ethylene oxide antibodies to transfusion recipients has not been published. Some transfusion recipients may develop IgE antibodies against plasticizer

compounds.[108] The relationship of these antibodies to transfusion reactions has yet to be demonstrated.

SYNTHESIZING THE DATA: A TWO-PRONG MODEL OF ATRs

The current evidence summarized in this review supports the concept that both atopic susceptibility in the recipient as well as particular donor and product characteristics are unique risk factors for the development of ATRs. Thus, we propose a model in which the frequency and possibly even the severity of ATRs would depend on the combination of how strong the recipient predisposition and specific donor or product factors (Fig. 2).

The concept of recipient, product, and donor contributions to the development of an ATR has implications for research. Studies that evaluate only one part of the recipient, product, or donor aspects of transfusion may miss key aspects of the process compared to those that control for the other parts of the donor–product–recipient chain.

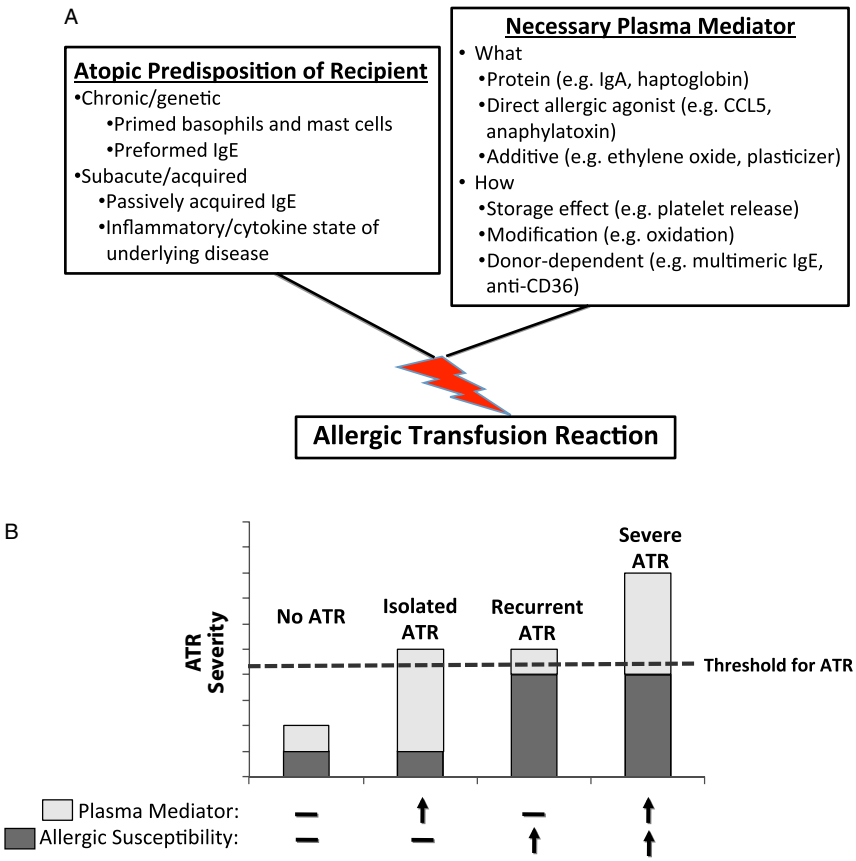

Fig. 2. Conceptual model of ATRs. (A) ATRs may result from a combination of recipient atopic predisposition and a necessary plasma mediator in the blood component. Known and speculative factors are listed. (B) The degree of recipient susceptibility at the time of transfusion and magnitude of the plasma mediator(s) may determine the severity of an ATR.

PREVENTION OF ALLERGIC REACTIONS

A primary motivation for understanding of the mechanisms of ATRs is to develop effective, rational prevention strategies. Vamvakas[109] summarized ATR prevention strategies as component-centered versus patient-centered approaches. As stated previously, plasma reduction is an intervention shown to reduce the incidence of ATRs. Based on available data, universal adoption of PAS PLTs might be expected to reduce the overall burden of ATRs, as ATRs are most commonly reported to PLTs. In the absence of PAS PLTs, plasma reduction is not always feasible, given the time and labor requirements of plasma-reducing individual products. Plasma reduction methods often come at a cost of reduced PLT yields and corrected count increments.[59,110,111]

Antihistamines are commonly used as pretransfusion medications in an attempt to reduce the incidence of ATRs.[1,112,113] The sedating H1 receptor antagonist diphenhydramine is the most frequently used antihistamine. A recent systematic review by Marti-Carvajal and colleagues evaluated three RCTs[114-116] and concluded no benefit of antihistamines.[117] Other studies also do not report a difference in ATR rates with pretransfusioon medication.[118,119] In spite of the lack of evidence for the practice, many hospitals have placed pretransfusion medication orders in their transfusion order sets, encouraging the continuing use of a wasteful practice.

Despite the lack of evidence for efficacy as a prophylactic agent, there is extensive, unpublished clinical experience of symptomatic benefit of antihistamines once an ATR manifests, which is consistent with studies demonstrating efficacy in other allergic diseases.[120] The combination of H1 antagonists with H2 receptor or other nonsedating antihistamines has not been studied in the setting of transfusion. In vivo data suggest a synergistic effect of H1 and H2 antagonists in the alleviation of symptoms during histamine infusion,[77] but the relevance of this to transfusion is not clear.

Using glucocorticoids for the prevention and treatment of severe ATRs has not been studied but is a common practice that is borrowed from experience from severe allergic reactions in other settings.[121] It is hoped that other antihistamines or other classes of medications will be able to prevent ATRs in

the future as we learn more about the mechanisms of ATR and perform rationally designed clinical research studies based on knowledge of these mechanisms.

CHALLENGES AND FUTURE DIRECTIONS IN ATR RESEARCH

Anaphylactic reactions understandably receive special attention in research, and certainly our understanding is relatively restricted to these reactions. It is not known to what extent the common, mild ATRs are less intense manifestations of severe forms or whether they represent a different pathophysiology altogether. Common ATRs tend to be studied in aggregate, and it is not known if there are patterns or clusters of certain manifestations (e.g., respiratory) with certain types of transfusion recipients (e.g., asthma). More detailed study of recipient susceptibility factors and the clinical manifestations of ATRs may help parse categories of ATRs beyond "mild" or "severe."

Studies of ATRs would appear to be at a disadvantage because any transfused allergic mediator is disseminated systemically and no one site is a target, as in allergic rhinitis or asthma. Furthermore, blood components represent complex, heterogeneous exposures to potential allergen. Nevertheless, the most common manifestations of ATRs are cutaneous,[4,5] and this distribution suggests involvement of cutaneous mast cells or basophils, which are amenable to direct study.[51,52,54,104,122]

After an initial transfusion, subjects can be actively and passively sensitized. That is, recipients may not only develop antibodies to transfused proteins, but they receive antibodies from donor plasma. Disentangling the contribution of passive sensitization from transfusion of different donors' plasma will not be possible until a more comprehensive understanding of ATR mechanisms is known. In vitro and animal models have been applied sparingly to questions about ATRs. Some of the limitations of clinical ATR research can be controlled for in laboratory settings. A combination of clinical and translational laboratory research is needed to enhance our understanding of ATRs.

In summary, ATRs are common, problematic transfusion reactions that cause morbidity and consume time and money. Only with a deeper understanding of the pathophysiology of ATRs will rationally designed prevention strategies be possible.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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