

# Immune-Related Adverse Drug Reactions and Immunologically Mediated Drug Hypersensitivity



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## KEYWORDS

- Adverse drug reaction • Adenovirus vector • Allergy • Complement
- Cytokine storm • Gene transfer • Hypersensitivity • Hypogammaglobulinemia

## KEY POINTS

- Therapeutic agents used to treat immunologically mediated conditions can cause immunologically mediated adverse reactions because the immune system may recognize the therapeutic agent as not-self or because the therapeutic agent can have a disruptive effect on normal immune system function.
- The time to onset of the adverse reaction and the clinical characteristics of the reaction are the key features that help determine the mechanism of the adverse reaction, guide appropriate testing to confirm the mechanism, and then direct subsequent management.
- Reexposure to therapeutic agents used to treat immunologically mediated conditions that have been associated with an adverse reaction may be appropriate if there is no useful alternative for a potentially life-threatening condition, the patient is willing to experience another reaction of similar severity to the index reaction, and the treating physicians are able to manage subsequent reactions.
- Desensitization is only reliably useful in the setting of immunoglobulin E-mediated acute-onset hypersensitivity. It may be possible to treat through mild T-cell-mediated reactions, but it is currently not possible to desensitize these individuals.

## INTRODUCTION

This review concentrates on the essential practical elements currently needed to understand and manage immune-related adverse drug reactions and immunologically mediated drug hypersensitivity, with an emphasis on biologics used for the treatment of immune-mediated hypersensitivity conditions. This includes how to proceed when a suspected immune-related adverse drug reaction and immunologically mediated

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drug hypersensitivity is already noted in the medical record, how to treat immune-related adverse drug reactions or immunologically mediated drug hypersensitivity during therapy, and how to potentially prevent immune-related adverse drug reactions and immunologically mediated drug hypersensitivity from occurring when using biologicals or other therapeutic or diagnostic agents.

## DEFINITIONS

The general term that best describes an inability to safely administer or re-administer a specific drug because of fear, preference, genetic, clinical, or metabolic considerations, or a previous adverse reaction associated with, attributed to, or caused by specific drug is intolerance.<sup>1</sup> Most reported drug intolerances, commonly mislabeled as an “allergy” in the electronic health record (EHR) are just expected side effects.<sup>2</sup> It is important not to expose susceptible individuals to specific drugs when a contraindicating physiologic or genetic condition is present, such as certain HLA haplotypes, enzyme abnormalities, or co-usage of another medication that effects enzyme function or metabolism. Only a small fraction of what are typically reported in the EHR as drug “allergy” have anything to do with the immune system.<sup>3</sup> Only a subgroup of these are because of antigen-specific hypersensitivity, and only a very small group are from clinically significant immunoglobulin (Ig)E-mediated allergy.<sup>4</sup> It is also possible to have immune-related adverse drug reactions from medications interacting with immune system cells or proteins through antigen nonspecific mechanisms resulting in generalized pathologic immune activation or suppression.

Immunologically mediated drug hypersensitivity refers to the limited subset of adverse drug reactions that are mediated through antigen-specific immunoglobulins or antigen-specific T lymphocytes.<sup>5</sup> Antigen-specific immunoglobulins, including IgG, which may or may not be able to activate the complement system, and IgE, which when bound to mast cells can be cross-linked by polyvalent antigen exposure and induce urticaria or anaphylaxis through acute mast cell activation and mediator release. Antigen-specific T cells can be activated by peptide fragments via the T-cell antigen receptor (TCR), which is composed of a ligand-binding subunit, the  $\alpha$  and  $\beta$  chains, and a signaling subunit, namely the CD3 $\epsilon$ ,  $\gamma$ , and  $\delta$  chains and the TCR $\zeta$  chain.<sup>6</sup> T cells can also be activated by the noncovalent pharmacologic interaction of small molecules with distinct HLA molecules or TCRs, the p-i concept.<sup>7</sup> P-i reactions differ from other off-target adverse drug reactions, as the reaction is not due to the effect on the drug-modified cells themselves, but is the consequence of reactive T cells.

The word “allergy” needs to be reserved to describe clinically significant antigen-specific IgE-mediated acute-onset hypersensitivity that can be desensitized.<sup>1,5</sup> A person with a positive skin test result or serum IgE test result does not have a drug allergy unless the person also experiences clinically significant acute-onset hives or more serious IgE-mediated systemic symptoms, such as hypotension or shortness of breath: anaphylaxis, with a full-dose reexposure. If a person has acute-onset mild hives, or even a benign maculopapular rash, associated with oral exposure to an antibiotic and needs that specific antibiotic for a several-day course, it is often OK to continue the course uninterrupted and treat through the benign reaction.<sup>5</sup> This is functionally the same as having hives during a desensitization and continuing to treat through to a therapeutic dose. It is critical not to stop a medication suspected of inducing IgE, wait more than 5 half-lives, and then restart the same medication at a therapeutic dose, because of an elevated risk of inducing anaphylaxis. With most small molecules that need to haptenate serum proteins to trigger immune reactions, anaphylaxis is extremely rare. With intact antigens, such as therapeutic proteins,

such as biologicals, anaphylaxis is much more common. Anaphylaxis is still often over-coded in EHRs.<sup>8</sup> When evaluating the incidence of medication-associated anaphylaxis through EHR coding, it is essential to audit the actual event, and not just tabulate the codes.

Using the word “allergy” to describe delayed-onset T-cell-mediated hypersensitivity may result in therapeutic mis-adventures, such as performing puncture or intradermal skin testing and reading the results 15 minute later or even worse, attempting a desensitization.<sup>5</sup> It may be possible to treat through mild T-cell-mediated reactions, but it is not possible to alter clinically significant T-cell-mediated reactions by administering doubling doses of a medication, unlike mast cell-mediated reactions triggered by antigen-specific IgE. Serious cutaneous and systemic adverse drug reactions (SCARs) are fortunately extremely rare, even with biologicals. Stevens-Johnson syndrome (SJS) is often overdiagnosed.<sup>9</sup> Suspected SCARs should always be biopsied, and laboratory testing for eosinophilia and liver enzymes should be obtained.<sup>2</sup>

The elements of the immune system, including cells and serum proteins, function as biologic amplifiers. They can act through antigen-specific reactions, antibody and T-cell receptors, and also through direct effects of drugs interacting with a variety of surface and intracellular receptors on lymphocytes, mast cells, basophils, eosinophils, neutrophils, and platelets, and the proteins that make up the classic and alternative complement pathways.

Pichler<sup>10</sup> in 2006 reviewed adverse side effects associated with the use of protein biological agents. He grouped these adverse side effects into 5 groups: type  $\alpha$ , cytokine release syndrome; type  $\beta$ , immune-mediated reactions against the agent; type  $\gamma$ , immune or cytokine imbalance; type  $\delta$ , cross-reactivity; and type  $\epsilon$ , non-immunologically associated side effects.<sup>10</sup> Please see [Table 1](#).

## BACKGROUND

Most of what is labeled as drug allergy in the medical record, when referring to nonprotein small molecules, has nothing to do with IgE-mediated allergy or even

**Table 1**  
**Pichler's grouping of adverse side-effects of biologic agents**

|                 | Categories                                  | Mechanisms                                                                                                                                                                 |
|-----------------|---------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Type $\alpha$   | Cytokine release syndrome<br>Cytokine storm | a. Capillary leak<br>b. Endothelial damage<br>c. Disseminated intravascular coagulation                                                                                    |
| Type $\beta$    | Immune-mediated                             | a. Immunoglobulin (Ig)E-mediated allergy<br>b. T-cell-mediated hypersensitivity                                                                                            |
| Type $\gamma$   | Immune or cytotoxic imbalance               | a. Impaired immune function, immunodeficiency, resulting in infections<br>b. Autoimmunity<br>c. Induce IgE-mediated allergy to another antigen                             |
| Type $\delta$   | Cross-reactivity                            | Exogenously produced antitumor monoclonal antibodies binding to antigens on normal cells causing their death or dysfunction                                                |
| Type $\epsilon$ | Nonimmunologic side effects                 | Binding to the intended target of the biologic agent in nontargeted cells, such as in nervous system, endocrine tissue, or the heart, resulting in unintended side effects |

Data from Pichler WJ. Adverse side-effects to biological agents. *Allergy* 2006;61:912-20.

immunologically mediated drug hypersensitivity. IgE-mediated immune responses are primarily possible against small molecules that are able to covalently bind to serum proteins. The classic examples are penicillins and other beta-lactams that are able to bind to serine, their target in bacterial penicillin binding proteins, and also present on human serum albumin and on other serum proteins. Molecules that are not covalently serum protein bound, such as macrolide antibiotics, are very much less likely to induce IgE-mediated allergy. The rate of immunologically mediated adverse reactions can vary widely with the same drug depending on how it is stored and the route of administration. A classic example are the penicillins, which are unstable in aqueous phase.<sup>11</sup> Aged penicillins in aqueous solutions administered parenterally induce much higher rates of antibody-mediated hypersensitivity than the same molecules administered as a pill orally. Many biological therapeutics used to treat immune-mediated hypersensitivity conditions are proteins capable of directly triggering the production of antigen-specific immunoglobulins, including IgE.

The key elements of an IgE-mediated drug allergy are as follows.<sup>5</sup> Previous exposure is needed to sensitize. Although cross-reactivity is often considered or hypothesized as possible, it is rarely confirmed. The reaction typically starts to occur within minutes of the first dose of the exposure.<sup>12</sup> Shorter times to the start of the reaction are noted after parenteral exposures compared with oral exposures. The reactions can vary from benign hives to life-threatening anaphylaxis. There is a threshold dose needed to trigger a reaction, and this may be as low as 1/2000th of a typical therapeutic dose. Individuals with confirmed IgE-mediated drug allergy who need the drug can be desensitized by administration of doubling doses, starting at approximately 1/2000th of the needed therapeutic dose.<sup>5</sup> True IgE-mediated hypersensitivity can wane with time. A positive skin test or in vitro-specific IgE antibody test result does not define a clinically significant allergy, one must also have clinically significant IgE-mediated symptoms, hives or anaphylaxis, with reexposure. False positive skin test results are common, and more common the smaller the wheal size used to define a positive test result. In general, at least 5 to 7 mm of wheal with flare greater than wheal is the minimum threshold that should be used to diagnose a clinically significant IgE-mediated drug allergy when skin testing, using a reagent concentration that does not induce this size of a wheal in a large group of individuals who tolerate the medication.

Timing is everything in the history. Blumenthal has noted that 2 significant risk factors for a confirmed IgE-mediated allergy are a history of anaphylaxis as the index event and onset of symptoms in less than 1 hour.<sup>12</sup> The key question in evaluating a reported drug intolerance is how long after the first dose of the last course did the adverse reaction start to appear. The international consensus for immediate-onset hypersensitivity is less than 6 hours, but with parenteral medications it is almost always within 30 minutes, and with oral medications causing clinically significant IgE-mediated allergy, within 1 hour.<sup>2</sup>

## HISTORY

There are 2 highly feared immunologically mediated adverse reactions: IgE-mediated anaphylaxis and T-cell-mediated serious systemic reactions or SCARs.<sup>5,13</sup>

Anaphylaxis is defined as a multisystem affected syndrome caused by mast cell degranulation. It can be caused by an IgE-mediated mechanism, but also by direct mast cell activation without any IgE involvement. The alternative mechanisms include antigen-specific IgG activating complement, specifically C5a, and direct binding of a small molecule, such as a fluoroquinolone antibiotic, to mast cell receptors, most

significantly MRGPRX2, or via the cyclooxygenase (COX) pathway, as is seen with nonsteroidal anti-inflammatory drug (NSAID) hypersensitivity.<sup>14,15</sup>

SCARs include drug eruption and systemic symptoms (DRESS), SJS, and toxic epidermal necrolysis (TEN). SJS can also occur after infections, independent of any specific drug administration. SJS and even SJS/TEN overlap is often overdiagnosed or misdiagnosed. It is essential to obtain a skin biopsy, liver enzyme measurements, and a peripheral blood eosinophil count when DRESS/SJS/TEN is suspected to confirm the correct diagnosis.<sup>13</sup> With SJS/TEN it is also important to carefully quantify the percentage of body surface area affected to determine the mortality risk. TEN is defined as at least 30% body surface area skin loss, typically requires management in a burn unit, and has a high death rate, often greater than 30%. SJS syndrome can be managed with careful nursing care in a general medical unit, as noted by work done in South Africa in patients positive for human immunodeficiency virus who required rechallenges with anti-tuberculosis (TB) drugs for multiple drug-resistant TB.<sup>13</sup> SCARs are more common in children with complex chronic conditions, and up to 16.7% of children hospitalized with SJS or TEN have at least 1 currently active underlying chronic complex conditions. The most commonly associated chronic complex conditions are metabolic, cardiac, or neurologic. The least commonly associated chronic complex conditions are malignancy, respiratory, or renal.

With DRESS syndrome it is important to be aware that severe systemic delayed-onset life-threatening eosinophilic inflammation of the heart is possible, even without any further drug exposure. Bourgeois and coworkers<sup>16</sup> in 2010 reviewed DRESS-associated myocarditis and noted that it can occur with initial DRESS symptoms onset or with a delay of up to 4 months. The severe version, acute necrotizing eosinophilic myocarditis, has a mortality rate of up to 50% and median survival of only 3 to 4 days. Ventricular assist devices can be life-saving and allow cardiac recovery while the eosinophilic inflammation is treated.

Immune-related adverse events (irAEs) associated with the use of immune checkpoint inhibitors (ICIs), programmed death inhibitors (PDLs), and cytotoxic T-cell-associated protein-4 inhibitors are being increasingly recognized.<sup>17</sup> The primary systemic targets are liver, endocrine, and renal.<sup>18</sup> Autoantibody production can also occur. Women typically report more immune-related adverse events. Chronic inflammatory arthritis can occur in 3% to 6% of people treated with ICIs.<sup>19</sup> Combining tumor necrosis factor (TNF) or interleukin (IL)-6 inhibitors with ICIs may both increase the effectiveness of the ICI therapy and reduce irAEs.<sup>19</sup>

## EPIDEMIOLOGY

Female individuals report more drug intolerances than male individuals.<sup>20</sup> Drug “allergy” is baggage that accumulates with increasing age and higher levels of drug exposures. Drug “allergy” prevalence is particularly high in individuals with cystic fibrosis and cancer.<sup>8</sup> Individuals who have reported any drug “allergy” will report higher rates of new drug “allergy” with all drug exposures. Multiple drug intolerance syndrome, defined as  $\geq 3$  unrelated drug “allergy” reports is more common in female individuals and with increasing age.<sup>20</sup> Such individuals are not at any increased risk to be confirmed to have any specific drug-associated immunologically mediated hypersensitivity compared with individuals with only 1 specific reported drug intolerance. Even though women are more likely to report a penicillin “allergy,” they are no more likely than men to be confirmed on testing.<sup>21</sup>

The rate of “allergy” reported to protein biological therapeutic agents is fairly high, often greater than 5%, compared with the rates of new “allergy” reported after NSAID,

opiate, or antihypertension medication usage, typically less than 2% per course.<sup>20</sup> With most antibiotics, a new “allergy” is reported after approximately 0.5% to 4% of all exposures. Sulfonamide antibiotics routinely have the highest “allergy” rates and macrolide and tetracycline antibiotics are typically the lowest. Only a small fraction, typically approximately 10% for sulfonamides and approximately 3% for penicillins will be confirmed by rechallenge to have clinically significant immune-mediated hypersensitivity.<sup>21,22</sup> Individuals with a penicillin “allergy” who are subsequently de-labeled after tolerating an oral challenge with a therapeutic dose are still approximately 2 to 3 times more likely to report a new “allergy” with each future therapeutic course compared with random patients with no reported drug intolerances.<sup>23</sup> But again, typically fewer than 3% will be confirmed to have developed a new immunologically mediated hypersensitivity if reevaluated.<sup>24</sup>

With angiotensin-converting enzyme inhibitors, the nonimmunologically mediated side effects of coughing and angioedema steadily increase with increased duration of use.<sup>25</sup>

With opiates, the rates of “allergy” reported are typically reflections of patient preference and the common side effect of direct mast cell activation and itching can be controlled by the co-use of non-sedating antihistamines. Constipation, respiratory depression, and central nervous system side effects are expected with all opiate use and are not necessarily contraindication to reuse.<sup>20</sup>

With adenovirus vectors used for gene transfer, the rate of humoral and cell-mediated immune reactions approach 100% with reexposure. These materials essentially function as adenovirus vaccines.<sup>26</sup>

## MAST CELL ACTIVATION

There are multiple surface receptors on mast cells that can induce activation and mediator release including toll-like receptors, protease-activated receptors, and Mas-related G-protein coupled receptor member X2 (MRGPRX2).<sup>14,27</sup> Cofactors, such as temperature changes, NSAIDs, exercise, sleep deprivation, beta-blockers, angiotensin-converting enzyme inhibitors, and iodinated contrast media can exacerbate clinical symptoms and worsen anaphylaxis, independent of the triggering event.<sup>28</sup>

Direct mast cell activation through the MRGPRX2, protein kinase A, and PI3 kinase pathways is also rapid. Many unrelated drugs can activate the MRGPRX2 pathway, including neuromuscular blocking agents, quinolones, icatibant, polymyxin B, and phenothiazine. Certain opiates, notably codeine and morphine, directly activate mast cells via the protein kinase A and PI3 kinase pathways.<sup>29</sup>

The clinical symptoms associated with direct mast cell activation with NSAIDs typically take approximately 104 minutes to be apparent.<sup>30</sup> NSAIDs induce mast cells to release cycLTs and PGD<sub>2</sub> and platelets to release PGD<sub>2</sub>. Boyce<sup>15</sup> reviewed the idiosyncratic activation of mast cells by nonselective COX inhibitors in 2019. He concluded that this intolerance is due to a complex multifactorial process that leads to dysregulation of mast cell function with an aberrant dependency on COX-1-derived prostaglandin E<sub>2</sub> to maintain homeostasis. Complement-derived anaphylatoxins, including C3a, C4a, and most importantly C5a, can also activate mast cells. C5a can also activate neutrophils. Iron nanoparticles can directly activate complement and intracellular Toll-like receptors 3, 7, and 9 and IL-1 $\beta$ .<sup>27</sup>

## SMALL MOLECULES

Small molecules, in general, must be able to bind to autologous proteins to induce antigen-specific antibody production. Supposedly inert ingredients such as

polyethoxylated castor oil derivatives including Kolliphor EL are present in a number of parenteral anticancer chemotherapeutics, vitamin K, and cyclosporin preparations. These materials can activate the complement system and directly activate mast cells.<sup>31</sup>

## HUMAN AND HUMANIZED PROTEINS

The widely used anti-B-cell monoclonal rituximab is associated with high rates of adverse reactions, up to 77%, with initial exposure.<sup>32</sup> Most are only grade 1 or 2, but those with grade 3 or 4 reactions warrant a workup for immune-mediated hypersensitivity. Replacement recombinant proteins in individuals unable to make the protein commonly induce strong IgG immune responses that can also activate complement and induce anaphylaxis.<sup>33</sup> IgE immune responses are also possible, but rarer.<sup>33</sup> With humanized monoclonal antibodies the rates of clinically significant IgG-mediated or IgE-mediated hypersensitivity is typically less than 5% with prolonged recurrent exposures.<sup>34</sup> With replacement proteins in individuals with a genetic inability to produce the protein, the rates are much higher, and approach 100% with recurrent exposures.<sup>35</sup> Antibodies are typically directed against protein epitopes on biologicals, but antibodies against carbohydrates, the classic case being alpha-gal, are also possible with therapeutic proteins.<sup>36</sup>

## XENOGENEIC PROTEINS

The most common xenogeneic protein that individuals are exposed to during health care include latex, bovine serum albumin, and mouse monoclonal antibodies.<sup>37,38</sup> All are able to induce robust IgG immune responses with parenteral or mucosal exposures, and occasionally IgE responses resulting in anaphylaxis. With repeat exposures to xenogeneic proteins such as bovine serum albumin or mouse monoclonal antibodies, the rates of immunologically mediated adverse reactions are high and can also approach 100%.<sup>38</sup>

## CONFIRMING IMMUNOLOGICALLY MEDIATED HYPERSENSITIVITY

In general, intradermal skin testing for injectable therapeutic proteins can be safely performed with the materials diluted to 1 µg/mL, using at least 7-mm wheel with flare > wheel as the criterion for a positive test result.<sup>39</sup> Small molecules used for diagnostic skin testing must be able to haptenate serum proteins and not be direct mast cell activators through non-IgE-mediated pathways.

For suspected T-cell-mediated hypersensitivity, a single challenge with a therapeutic dose followed by approximately 1 week of observation is adequate in most settings to confirm current tolerance.<sup>5</sup>

Before all challenges, it is essential to obtain informed consent from the patient.<sup>5</sup> The patient must be willing to experience a reaction at least as severe as the index reaction, and the physicians doing the testing must have the ability to treat any potential challenge reactions and follow the patient long enough based on the time to the onset of the index reaction and the suspected mechanism of the feared reaction.<sup>5</sup>

Stevenson and coworkers<sup>40</sup> reported in 2019 on a risk stratification strategy guiding penicillin allergy delabeling evaluations. They determined that any patient with a benign penicillin-associated rash more than 1 year ago could safely undergo a direct oral challenge with a therapeutic amoxicillin dose. We had previously come to the same conclusion.<sup>21</sup>

Krantz and coworkers<sup>22</sup> reported in 2019 on 204 individuals rechallenged with trimethoprim-sulfamethoxazole and noted only 13 (6.4%) were challenge positive. Younger age and short time since index reactions were associated with positive challenge reactions. We have noted that despite having a negative challenge, subsequent therapeutic exposure can still result in a 5% to 10% rate of recurrent reactions, although sometimes after tolerating several therapeutic courses. The key take-home message is that reactions are possible after all drug exposures, even after negative hypersensitivity testing.

### **MANAGING PATIENTS WITH HISTORICAL REACTIONS WITHOUT TESTING OR RECHALLENGE**

Not all suspected immune-related or immune-mediated reactions require testing or diagnostic rechallenges. Radiocontrast hypersensitivity reactions are relatively rare with the non-ionic iso-osmolar radiocontrasts commonly used now, compared with hypertonic hyperosmolar media used historically.<sup>41</sup> Both delayed-onset apparent T-cell-mediated hypersensitivity, 2 to 5 days after exposure, and acute-onset direct mast cell activation, within minutes of exposure, can occur with non-ionic iso-osmolar radiocontrasts. Pretreatment with corticosteroids and antihistamines has not been shown to reduce recurrent acute-onset or delayed-onset reaction rates when the same material is administered in the future.<sup>41</sup> Most patients can be safely managed by just selecting an alternative non-ionic iso-osmolar radiocontrast.<sup>41</sup>

Slowing the infusion rate and pretreatment with NSAIDs and antihistamines will often reduce infusion-associated reactions with protein biologic therapeutics.<sup>42</sup>

### **DESENSITIZATIONS**

Desensitization can be reliably accomplished only when IgE-mediated allergy has been confirmed and in a few other situations in which mast cell activation occurs via a non-IgE-mediated mechanism.<sup>42</sup> It is not possible to desensitize individuals with T-cell-mediated hypersensitivity, although it may be possible to treat through mild reactions.<sup>5</sup> The key to a successful desensitization is administering doubling doses of the material every 15 to 30 minutes, starting at below the threshold dose needed to initiate anaphylaxis, typically approximately 1/2000th of the therapeutic dose, and continuing up to the therapeutic dose. Castells and coworkers<sup>42</sup> have published a 3-bag protocol that works for both therapeutic proteins and small molecules. For medications that require sustained exposures, it is essential to maintain continuous exposure, or anaphylaxis may occur with repeat exposure. If an individual requires a medication acutely that requires a sustained exposure and had a positive diagnostic challenge reaction to a therapeutic dose, once the challenge reaction is treated and the patient is stabilized, it is appropriate to just continue the therapeutic dosing, maintaining constant exposure.

### **BLOCKING NEW IMMUNE REACTIONS**

The use of replacement recombinant proteins for a variety of genetic diseases and adenovirus vectors in gene therapy has led to the need to be able to block new antibody production and new T-cell-mediated immune responses. Adenovirus vectors used for gene transfer therapies commonly induce a strong protective immune response, precluding reuse of the same vector.<sup>26</sup> It is important to test subjects before exposure to ensure they do not have a natural immunity to the vector.<sup>26</sup>

Currently the strategies used to prevent immune responses to biologic therapies are the same as those used for treating autoimmune diseases or with organ transplantation. These methods include suppression of autoantibody production with steroids or other immunosuppressive drugs, such as azathioprine, methotrexate, or by knocking out B cells that produce antibodies, such as the anti-CD20 antibody rituximab, and/or immunomodulation that targets T-cell function, such as cyclosporine or mycophenolate.<sup>43</sup>

The first report using engineered T cells against an autoreactive B-cell receptor/autoreactive B cells was in a preclinical model of pemphigus vulgaris in 2006.<sup>44</sup> In theory, one could specifically target autoreactive B cells and thus deplete circulating autoantibodies, although the approach has not proceeded into clinical trials to date.

B-cell depletion with rituximab has been widely used for some 20 years now to manage autoimmune conditions and B-cell malignancies. There is a certain degree of specificity in that autoantibodies appear to decline more than the bulk of protective antibodies, probably owing to being produced by short-lived plasma cells. However, from the start, the desire has been to remove autoantibodies specifically without impact on normal B-cell function. This turns out to be a very difficult task for antibodies like rheumatoid factors but may be easier for antibodies to local antigens like acetylcholine receptor. A recent review by Chang and colleagues<sup>45</sup> suggests that specific autoantibody deletion strategies may at last be feasible, thus potentially leading to a method to block antibody production against large-molecule biologic therapies.

Immunosuppressants are widely used in transplantation immunology, such as cyclosporine, tacrolimus, pimecrolimus, mycophenolate mofetil, cyclophosphamide, and/or azathioprine, and a variety of monoclonal antibodies including baskilizimab.<sup>43</sup> Combination therapy with rituximab, methotrexate, and intravenous gamma globulin (IVIg) has been used to blunt the generation of new antigen-specific immune responses to acid alfa glucosidase when giving enzyme replacement therapy in Pompe disease.<sup>33</sup> It is typically started concurrently with enzyme replacement therapy. Organ transplantation preconditioning protocols using IVIg replacement after plasmapheresis, with or without rituximab and thymoglobulin induction therapy, combined with tacrolimus, mycophenolate mofetil, and/or prednisone have also been considered to blunt the development of new immune responses against adenovirus gene transfer vectors.

## **PATHOLOGIC IMMUNE ACTIVATION**

Therapeutic materials that interfere with normal immune regulation, most notably muromanab-CD3, alemtuzumab, and rituximab, have been implicated in triggering cytokine storm.<sup>46</sup> The primary symptoms of cytokine storm include fever, edema, erythema, fatigue, and nausea. Capillary leak can occur with endothelial damage leading to acute respiratory distress syndrome, cardiovascular shock, disseminated intravascular coagulation, and renal failure. The primary cytokines implicated include TNF $\alpha$ , interferon- $\alpha$ , IL-1 $\beta$ , and IL-2, IL-4, IL-6, IL-8, IL-10, and IL-12. Cytokine storm management typically relies on blunting the effect of the preceding mediators through the use of angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, gemfibrozil, NSAIDs, corticosteroids, IVIg, hemofiltration, anti-IL-6 (tocilizumab), and blocking C5a activity with anti-vitamin D binding protein antibodies.<sup>47,48</sup>

## **PATHOLOGIC IMMUNE SUPPRESSION**

Both B cell and T cells can be adversely affected by therapeutic material used to treat allergic conditions. Hypogammaglobulinemia, sometimes irreversible, can occur after

the use of anti-B-cell monoclonal antibodies, including rituximab and belimumab. Tyrosine kinase inhibitors, imatinib and dasatinib, along with commonly used immunosuppressives, including corticosteroids and azathioprine, can cause hypogammaglobulinemia.<sup>49</sup>

## SUMMARY

Biologic therapeutics and other agents used to treat immune-mediated hypersensitivity conditions can result in immune-related adverse drug reactions and immunologically mediated hypersensitivity. Time to onset and the nature of the reactions are the keys to determining potential mechanisms. Diagnostic testing and rechallenge may be useful, and in the specific setting of IgE-mediated allergy, desensitization is possible. It remains extremely difficult to stop antigen-specific antibody or T-cell-mediated responses once they have occurred without inducing generalized immune suppression.

## CLINICAL CARE POINTS

- The immune system can be involved in adverse reactions associated with therapeutic agents used to treat immune-mediated hypersensitivity conditions.
- Immune-mediated hypersensitivity can occur when medications are able to haptenate autologous proteins, which then activate B cells to produce antibodies, directly or indirectly activate T cells, trigger the complement system, and/or directly activate mast cells.
- Therapeutic agents can also trigger the immune system, resulting in generalized activation or suppression, leading to adverse reactions.
- Some humans can make immunoglobulin (IgE) against just about every humanized monoclonal antibody or therapeutic protein with a molecular weight on greater than 5000 kD. The rate is much higher with nonhumanized therapeutic proteins.
- You can only reliably desensitize individuals with clinically significant IgE-mediated allergy. You cannot desensitize individuals with clinically significant T-cell-mediated hypersensitivity.
- Skin testing to identify clinically significant IgE-mediated allergy is possible with all therapeutic proteins, but with only a very limited set of smaller molecules that can haptenate autologous proteins and do not directly activate cutaneous mast cells.

## DISCLOSURE

E. Macy has received research grants to study drug allergy from ALK. He has served on data and safety monitoring boards for BioMarin and Audentes. He has performed consulting for Kalobios and Audentes. He is a member of the Ask an Expert Panel of the American Academy of Allergy, Asthma, and Immunology.

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