

Allergic reactions to small-molecule drugs: Will we move from reaction to prediction?

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Purpose. This primer provides background and an update on immune mechanisms which allow small-molecule drugs to trigger drug allergy.

Summary. For many years, understanding of drug allergy was limited. The hapten model of drug allergy applies only to a subset of drugs known to cause allergic reactions. More recently, the understanding of immune reactions has expanded to include pharmacologic interactions with the molecules involved in immune identity and surveillance. These insights are presented and discussed here.

Conclusion. Greater understanding of allergic reactions to drugs offers the promise to move from a position of reacting to immune reactions to a more proactive model. This may translate to new opportunities to characterize risk in drug development, confirm the nature of reactions in clinical settings, enhance the targeting of alerts, and ultimately to allow patient-specific prediction.

Keywords: delayed hypersensitivity, drug allergy, drug eruptions, drug hypersensitivity, hypersensitivity, immediate hypersensitivity, Stevens–Johnson syndrome

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Adverse drug reactions may interfere with achieving optimal drug therapy outcomes. Many of these reactions are dose-related (Type A), and the risk may be modified by careful individualization of dose. However, many adverse reactions are far less predictable (Type B), and not related to clearly modifiable risk factors. Since they are unpredictable, they cannot be readily avoided, except to avoid second exposures after an initial observation. These types of reactions account for 6% to 10% of reported adverse reactions.¹ When they are caused by immunologic events, these are often broadly termed drug allergy. Recently established insights into drug allergy offer the promise of an enhanced ability to predict and avoid these significant events.

A clear understanding of established drug allergy mechanisms, as well as an awareness of emerging data, are essential to pharmacists within health care systems. Pharmacists are often

called upon to address patient-specific questions on drug allergy and cross-reactivity. In addition, pharmacists may lead efforts to improve clinical documentation and allergy alerting. In particular, as pharmacists have become engaged in decisions to improve alerts in electronic health record (EHR) systems, they can make essential contributions to clinical decisions and system configuration.²

Mechanistic insights are essential to the accurate prediction of allergy and cross-reactivity. It is important to minimize the lag between scientific understanding and implementation of this knowledge in clinical practice. The purpose of this article is to provide a review of foundational science related to immune surveillance, and present new details concerning how small-molecule drugs disrupt these processes to trigger immune reactions. The interested reader should consider

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the excellent review by Chen et al.³ for a more detailed mechanistic discussion on small-molecule drug allergies.

Foundational immunologic background

Understanding how small molecules can become allergens requires a solid understanding of how the immune system is equipped to differentiate “self” from “nonself.” To identify the presence of an invading organism, the human immune system has the capability to differentiate proteins which originate from “self” from those which originate from a “nonself” source. In order to generate specific (adaptive) immune responses, the recognition of “nonself” protein is key. Recognition permits the initiation of powerful protective processes which either produce specific antibodies or activate cell-mediated cytotoxicity.^{3,4}

Much of the immune system response is not triggered by intact “nonself” proteins. Instead, the presence of foreign protein is detected through a process in which short peptide fragments (9–14 amino acids) derived from these proteins are “presented”—displayed in the context of specialized cell-surface molecules—to the host immune cells responsible for surveillance.⁴ When a novel protein is

KEY POINTS

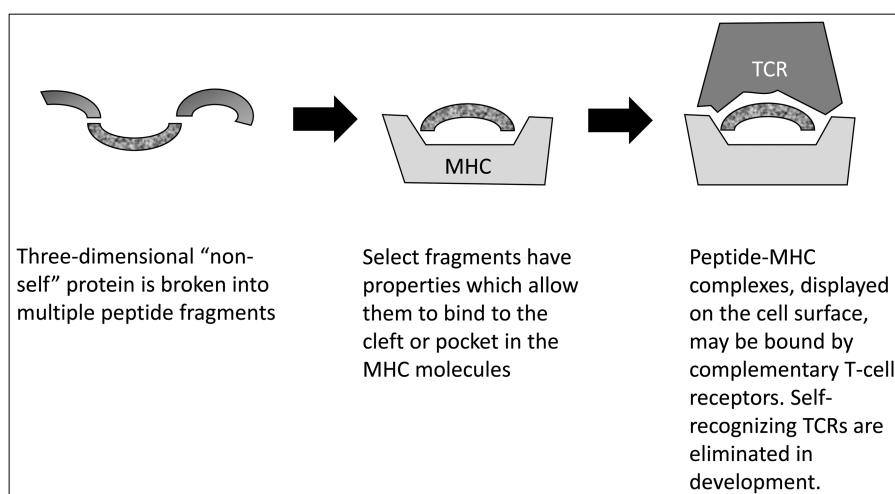
- Small-molecule drugs trigger allergic reactions by altering normal host proteins or through direct interactions with immune receptors.
- The specific location of binding has been determined for only a small number of drugs, but molecular techniques have demonstrated patterns of binding which may allow enhanced prediction in the future.
- Pharmacists can act as critical intermediaries between general, automated allergy “alerts,” ensuring accurate representation of allergy histories in the EHR, and promoting decisions based on the most current evidence.

introduced to a cell and broken down by intracellular proteasomes, a new set of peptide fragments is produced, some of which fulfill requirements to bind to the individual’s specific major histocompatibility complex (MHC) molecules (Figure 1).⁴

MHC proteins, also termed human leukocyte antigens (HLA), are essential to the presentation of these protein fragments to immune cells. MHC class I molecules are carried by all cells, while class II molecules are generally limited to specialized cells that direct a variety of immune responses. Both types of MHC molecules hold protein fragments in a 3-dimensional context, which allows immune cells to trigger, amplify, or suppress a response.⁴ Individuals are equipped with several genes encoding MHC class I or class II molecules (they are polygenetic). Each class has sub-types, such as the A, B, and C variants of MHC Class I molecules. Even within a specific MHC type, there is substantial variability corresponding to the areas of DNA which encode the peptide binding site (each gene is polymorphic). These characteristics (polygenic, polymorphic), ensure significant genetic variation among these genes to establish a general immunologic identity to an individual, a fact which has led to the matching of organ donors to recipients through an analysis which includes their MHC (HLA) profiles.

Binding to the MHC molecules is restricted to protein fragments which can be effectively held in place by non-covalent (such as hydrophilic [polar])

Figure 1. Representation of the “loading” of peptide. A protein is broken into fragments. Fragments of suitable length and binding characteristics bind to the MHC molecule. The resulting complex presents a 3-dimensional identity to the circulating immune surveillance cells. MHC = major histocompatibility complex; TCR = T-cell receptors.



interactions within the binding cleft or pocket.⁴ The fragments which successfully occupy the binding site are displayed to the external environment, which means they are accessible to “surveillance” by immune cells. The receptors on circulating immune cells (primarily T cells of varying subtypes) may interact with the displayed molecular complex—bound fragment in association with the broader MHC molecule.^{3,4} A “docking” event occurs when 3 components—histocompatibility molecule, bound fragment, and immune receptor—demonstrate sufficient affinity through their non-covalent molecular forces of attraction to engage with each other.

During development, a wide diversity of potential T-cell receptors (TCRs) are generated by complex gene rearrangements (which parallel the processes used to create antibody diversity).⁵ However, when the end result of gene rearrangement produces TCRs capable of binding to MHC molecules with self-peptides, the cell lines are usually eliminated. This ensures that remaining cells carry TCRs which are generally capable of binding only when novel or “foreign” peptides are loaded.

Recognition by receptors on immune effector cells is essential to confirm the “nonself” nature of a protein. Peptide from a “nonself” source, such as proteins derived from an infectious agent, are displayed by the MHC and can interact with the host’s immune cell receptors. This recognition is essential to trigger an adaptive immune response.^{3,4}

Small-molecule drug immunogenicity

As discussed above, the immune system is engaged in constant surveillance and ready to react to “nonself” proteins. Most drugs are small molecules and not protein in composition. Yet many of these small molecules are obviously capable of triggering an immunologic reaction.³ Clearly, some mechanism must exist for the drug molecules to disrupt normal protein-based surveillance. Understanding how small molecules become associated with the molecules

which are responsible for the identity of the host, and recognition of disruptions in identity are key to understand efforts to predict drug allergy. In our current understanding there are several ways in which drugs may alter normal recognition mechanisms to provoke an immune reaction. These include hapten formation as well as direct interaction with immune receptors.

Hapten formation

The formation of haptens—covalent binding of reactive small molecules to host proteins—is the most familiar mechanism to many pharmacists. The hapten model of drug allergy was identified as a predominant mechanism of penicillin allergy decades ago. The triggering of antibody-mediated reactions, with anaphylaxis as the prototype, has been mechanistically related to the covalent attachment of the drug molecule to a native protein.³ The formation of these structurally altered proteins is an established mechanism by which “self” appears to become “nonself.” This alteration initiates production and expansion of specific antibodies. On repeat exposure, the antibody response is robust, resulting in specific binding to these altered proteins and further augmentation of immune responses including events such as the degranulation of mast cells and/or complement activation. Because haptenization produces a stable alteration of a normal protein, it is relatively easy to understand how this kind of stable structural modification may be recognized in its 3-dimensional representation as well as in subunit analysis (after the protein is broken down to peptides) as a “foreign” molecule.

Even in the case of hapten formation, it is important to inform prediction with the best understanding of the influence of molecular structure on allergy mechanisms. Past efforts to correlate risk of cross reaction to one component of the chemical structure, led to over-statement of risks. In the case of penicillins and cephalosporins, it was postulated that the structural presence of a beta-lactam ring was essential to

this reaction. While the opened beta-lactam formed the place of attachment to the protein, it was the side chains of these compounds that were primarily exposed to antibody recognition and targeting. New generations of molecules shifted toward increasingly dissimilar side chains, correlating with less (or no) cross-reactivity between some beta-lactam containing drugs.⁶⁻⁸ This emphasizes the need to evaluate how the structure is related to the process of immune activation. By establishing their knowledge of the role specific structures play in determining cross-reactivity, pharmacists can be important partners when prescribers are evaluating risk based on chemical similarities.

The p-i concept

Many therapeutic agents are low molecular weight, non-reactive small molecules. They cannot form covalent bonds with proteins and therefore do not meet the criteria to become haptens. The fact that many of these compounds trigger cytotoxic reactions (which implicate T cells and not antibody-producing B cells as effector cells), served as an important clue to investigators seeking to explain these observations. In the classic Gell and Coombs classification, these reactions fall into the type IV category (delayed hypersensitivity) and correspond to T cell-mediated cytotoxicity. A modification of this classification scheme has been elaborated to incorporate some of the complexity and specific effector mechanisms of delayed-type reactions.⁹

Over a decade ago, Dr. Werner Pichler and colleagues proposed the potential, and identified the implications, of pharmacologic interactions between drugs and immune receptors. This was termed the p-i concept.¹⁰ Many drugs exert their effects through non-covalent interactions with cell surface receptors, either to augment or suppress the normal function of these receptors. These receptors serve as targets of therapy but originated as binding sites for endogenous chemicals. The immune system relies on intricate communications between cells to develop and regulate immune

responses. Small-molecule therapeutic agents can be quite effective at localizing to cell surface receptors on the basis of their physicochemical properties. It is not surprising, then, for drug molecules to bind to cell surface proteins which are essential to the interplay between antigen presentation and immune cell activation. Exploring these interactions with immune receptors offered a new opportunity to understand how allergic reactions can be initiated by the presence of a small molecule.

Progress in drug allergy—localizing the drug molecules

Within the framework of the p-i concept, exploration of drug allergy mechanisms has continued to advance. Deeper understanding of the genetics of immune reactions, coupled with the application of sophisticated technologies for investigation, have progressed to allow a more comprehensive view of drug allergy.

As discussed above, the MHC class I molecules confer an identity to cells of an organism. These were first recognized clinically as a “tissue type” which dramatically impacted tolerance of transplanted organs. In the case of abacavir, the presence of a specific MHC class I molecule (identified by the presence of a genetic marker denoted as HLA-B*5701) was noted to have a strong association with development of severe dermatologic reactions. Testing of HLA subtypes may predict those patients at

highest risk, with a negative predictive value of nearly 100% and a positive predictive value estimated to be approximately 50%.¹¹ Testing has become a standard clinical practice to effectively limit reactions to this drug. This fundamental paradigm shift, moving from a position where health care providers react to adverse patient outcomes to a proactive position of prediction and avoidance, was anticipated to progress rapidly.

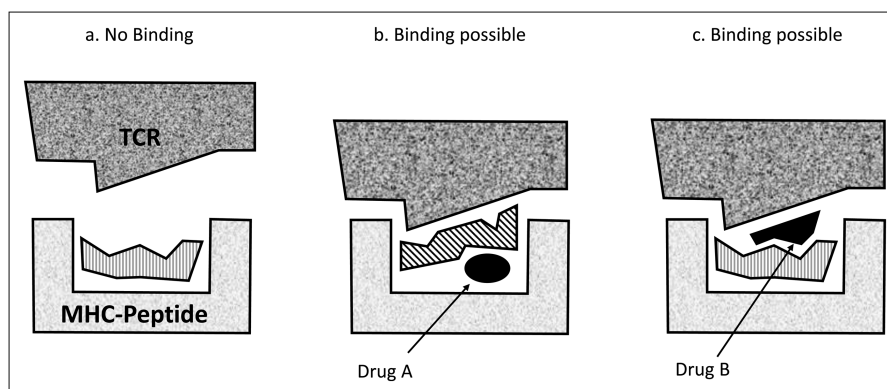
Abacavir, unfortunately, turned out to be an unusually clear-cut case in immunological terms. Although HLA/MHC associations have been established with other drugs, the number of drugs with established relationships to specific MHC variants remains limited.¹² With many drugs, a less direct relationship to a genetic marker is likely, and the expectation that most drugs will demonstrate the potential for a direct HLA-based prediction of allergenicity has diminished.

However, this does not mean that investigations related to small-molecule interactions with immune receptors have been a failure. Recalling that immune receptor is composed of the MHC molecule plus an associated peptide, it is now clear that small molecules can disrupt immune recognition and trigger reactions by altering peptide presentation in several ways. A recent study provided illustrations of several different types of small-molecule interactions with

immune molecules.¹³ The study joined molecular modeling techniques and data from x-ray crystallography to characterize the 3-dimensional “fit” between all components: MHC Class I molecules, peptide, and TCRs, as well as individual drug molecules (specifically, abacavir and carbamazepine). In addition, a mathematical analysis was conducted to evaluate the binding forces between the molecular structure of the drug and the involved molecules.

In 3-dimensional modeling, abacavir binds within the cleft of the MHC molecule itself (Figure 2). This binding alters the shape and affinity of the cleft, creating a novel environment for “self” peptide fragments to bind to the remaining exposed residues from the MHC molecule as well as the drug molecule. The peptide which would normally occupy the site is replaced by another, resulting in a new molecular presentation.^{14,15} In this new conformation, the MHC molecule-new peptide complex appears to be a “nonself” marker, since this particular peptide and conformation were not present when TCRs with self-binding properties were being eliminated from the repertoire. As a result, this MHC-peptide complex which has been constructed in the presence of abacavir can be bound by a TCR and trigger an immunologic reaction. Since a particular subtype and variant of the MHC I (HLA-B*5701) molecule provides the primary site for abacavir binding, these

Figure 2. Drug alteration of MHC-peptide: (a) MHC-peptide with normal peptide fragment. (b) MHC-peptide demonstrating intercalation of a drug between a peptide and the MHC molecule. Drug distorting the peptide binding site allows a different peptide to bind. Interaction with TCR possible. (c) Intercalation between peptide bound to MHC and TCR. The drug binds peptide and participates in binding to the TCR. MHC = major histocompatibility complex; TCR = T-cell receptor.



reactions are limited to patients with this genetic marker.

In a second part of the study, the binding characteristics of carbamazepine were examined. In this structural analysis, it is clear that the binding location of carbamazepine does not correspond to the area within the MHC peptide binding cleft. Instead, binding has been demonstrated to occur at the surface of the peptide-MHC complex. The molecular binding analysis revealed that binding of drug to the peptide-MHC complex is significant, but the calculated forces of attraction were highest between the drug and the TCR isolated from the patient. The drug molecule appears to be “sandwiched” between the MHC-peptide and the TCR. The association of drug at this interface may trigger a reaction to cells bearing this complex (Figure 2).

These studies illustrate how different components of normal presentation and immune surveillance can be altered by pharmacologic interactions. Triggering cytotoxic reactions requires a convergence of factors where the small molecule intercalates into this intricate system and changes either the identity of, or the ability to correctly identify, the host's cells.

Characterization of the specific location of small (drug) molecule binding may correlate to a specific MHC gene variant. Correlation to genes encoding the MHC molecules will likely be strongest when drug binding is directly to the MHC isotype, as opposed to binding at the MHC-peptide interface. The location for optimal affinity of a small-molecule drug will also depend on the variability of peptides loaded to the MHC and the subtle differences in conformation when the peptides of interest are displayed by the MHC isotypes.

Of course, a final element underscoring the complexities of a drug's influence on MHC-peptide-TCR interactions is the recognition by the TCR itself. Potential TCR variation, in terms of alpha/beta TCRs, has been estimated to be as high as 1×10^6 possibilities.⁵ The extreme variability introduced by TCR gene rearrangements may create another variable

in determining whether the patient successfully produces a TCR capable of binding the drug at the MHC-peptide interface.

The future of drug allergy: Understanding may lead to prediction

The literature related to small-molecule drug allergy includes many observations where a reaction was initially recorded and extrapolated within a limited mechanistic framework. For example, there was a long-standing practice of assuming that all medications with a sulfonamide structure, such as loop diuretics and sulfonylureas, would share the risk of a reaction first observed with a sulfonamide antibiotic. This confusion persisted for many years before the shared immunologic risk was more correctly associated with the arylamine-containing (antibiotic) sulfonamides.^{16,17}

The overall strategy with respect to allergy has been reactive. A more detailed understanding of the mechanisms of drug allergy may lead to an enhanced ability to predict both initial reactions and potential cross reaction. Screening in drug development, confirmation of a presumed immune reaction, and future prediction are all potential benefits associated with a more complete understanding of drug allergy mechanisms.

Role of the pharmaceutical industry

Drug development can be significantly influenced by adverse reactions. Identifying risk early in development is valuable. Characterization of any potential association with MHC genotype and/or potential peptide binding for new medications would provide valuable information to allow prospective identification of patients at risk, allowing the drug to be introduced with an enhanced safety profile by excluding patients at highest risk or recommending prospective individualized testing to exclude these patients. In the short term, assessment of observed cytotoxic immune reactions may include a structural analysis of binding similar to

the methods employed by Zhou et al.¹³ to determine the localization of binding.

An extension of these insights may be an improved ability to screen drugs in development for allergic reaction potential and some characterization of the risk of allergy prior to release.^{18,19} One strategy suggested in screening candidate drugs for potential allergy has been the creation of MHC “libraries” to represent common genetic variations in a population.²⁰

Due to the high degree of variability in MHC genetics, population libraries of several thousand patient-derived samples might identify whether the potential is higher or lower based on an inheritable component. In order to screen for drugs binding at the peptide-TCR interface a wide sample of MHC molecules with a variety of peptides loaded in each would be necessary.

The type of high-volume analysis required in these instances may be more reasonably accomplished in computer simulations. This was exemplified in a study by Van Den Driesche²¹ in which computer-assisted design to analyze molecular docking was employed. This method was used to evaluate and analyze HLA-drug binding potential over thousands of variants. In the future, these types of high-volume explorations may be extended to include characterization of binding at the interface as well as to a wide sample of TCRs.

Role of clinical research and specialty practice

Translating preclinical observations and extending new insights into practice may be an important area of practice development for pharmacists. In the clinical setting, it can be difficult to attribute a set of symptoms to a specific medication. A rapid, correct attribution of an immune-based reaction can influence treatment decisions. Clinical testing to identify and confirm a severe drug reaction related to immune mechanisms may translate to better patient outcomes. As an example, an assay for granzyme release may allow a more precise confirmation of Stevens–Johnson syndrome.²² This and other tests are currently used

in research settings but moving steadily closer to acceptance in practice.²³ In patients experiencing a reaction where a genetic marker has been associated with higher risk for a specific drug, testing could lend support to the drug's involvement. Likewise, confirmation of the drug binding to the molecules involved in immune activation could confirm involvement and contribute to the knowledge of drug localization.

Of course, the most valuable development would be reliable prediction of an individual patient's risk of experiencing an adverse reaction to a specific medication. Abacavir offers a proof of concept that if the components of a reaction are sufficiently understood, individual testing may be successful in avoiding the reaction. However, as noted above, HLA typing represents a relatively narrow area of exploration.

Patient-specific binding assays may be developed to confirm, and potentially predict, patients who have the requisite MHC and/or peptide characteristics to permit drug binding to this complex. Markers identified in preclinical studies may prompt more specific investigation to confirm this association with risk, and the likelihood of cross-reaction with other similar agents. To confirm activation is possible, testing for drug allergy would likely need to occur in a situation where the full set of potential participants are represented. A patient-specific exploration of potential reactivity would parallel testing of transplant compatibility, evaluating immunologic triggering when all components are present—the drug, the full complement of MHC molecules, and the patient's specific armament of TCRs. In the same way that testing can identify incompatibilities between host and recipient transplants by identifying *in vitro* immune activation, tests which identify lymphocyte activation may reveal a potential for the drug to trigger allergy. Lymphocyte stimulation has been explored as a confirmatory test in patients who experience presumed allergic reactions.^{3,20} Such an approach has been reported, using a lymphocyte stimulation assay to identify mesylamine allergy.²⁴

Whether it is cost-effective to screen patients in this way will likely depend on the frequency of the reaction and the severity. However, once an individual has experienced a reaction, it may shift the burden to screen other medications which may carry a risk of cross-reaction.

Role of the pharmacy clinician: Design and assessment alerts

Individual clinicians are often asked to address questions of allergy and cross-reactivity. Pharmacists represent a critical conduit for new information on drug allergy to be integrated into clinical decision-making. Awareness of risk data generated by preclinical studies, assurance of appropriate testing, and the application of research findings to individual cases will provide challenges to pharmacists for many years into the future.

As knowledge develops, it is important for pharmacists to take the lead in the assessment of drug allergy, using the most current information available. Electronic records and triggers act as a broad net to identify potential risk, but they are limited in specificity. Pharmacists who excel in their understanding of allergic mechanisms, who can integrate medicinal chemistry and immunology with clinical awareness, may play an increasing role in health systems. Dougherty and Bonfiglio²⁵ advocated for more active integration of pharmacists as an approach to limit alerts displayed to prescribers. In this model, the potential to establish a mechanism for pharmacists to investigate issues without immediate disruption of the prescribing process may simultaneously decrease the noise of alerting while allowing pharmacists to investigate and, when justified, either correct the allergy data recorded in the health record or apply current understanding of cross-reactivity to determine the need to advise the prescriber.

Currently, automated alerts in the EHR are a key part of strategies to avoid re-exposure following a prior immune reaction. However, skepticism due to a lack of alert sensitivity and specificity is common. A longitudinal survey of allergy

overrides noted a rise in the number of allergy alerts overridden between 2004 and 2013, the frequency of overrides increased from 83% to 88%.²⁶ The lack of precision and value to these alerts is particularly clear when it is noted that over 50% of the alerts were triggered in cases where the patient had safely received the medication before.²⁶

As a simple step forward, clinical documentation must be accurate. In a recent study in which extensive overrides of allergy alerts were described, 94% of the overrides were considered appropriate.²⁷ In this study, the most common descriptions of drug allergy were characterized as “unknown,” “rash,” or “GI upset.” The first term is unhelpful, the second is non-specific, and the third generally represents an intolerance rather than a drug allergy. Once included in the medical record, these data tend to persist, triggering many generalized alerts over time. Pharmacists can investigate recorded data for accuracy and fidelity to the intent of true allergy screening by correcting these records.

In the past, it has taken a long time for drug allergy data to adjust to newer insights. In some cases, long-asserted cross-reactivity predicated on structural similarity and/or correlative case reports has been disproven by more rigorous investigation. As noted above, this was particularly evident with sulfonamide-containing drug classes.¹⁶ Advances were integrated only after countless alerts were introduced into clinical decision-making. Pharmacist assessment of alerts could limit the disruption to prescribers and ensure that current understanding is applied, if a workflow were established to facilitate this activity.²⁵ Until the commercial source reflects this knowledge, pharmacists may advocate with commercial providers, or even customize commercially supplied data to limit nuisance alerts.²

In addition, screening models must become more patient specific. Current commercial models cannot accommodate the individualized nature of risk, such as MHC profile. In addition, current systems do not incorporate clinical actions such as desensitization. These

deficiencies can begin to be addressed proactively, so that emerging data may be readily incorporated, rather than waiting for system design to occur after these data are available.

Summary

The understanding of drug allergy continues to progress. Triggering of an immunologic reaction to a drug could occur by alteration of the native protein, the MHC molecule's binding properties, the surface of the MHC-peptide exposed to immune surveillance, or the TCR surface.³

As distinct mechanisms have been elucidated, the potential to predict these rare reactions has been expanded. The potential to predict these rare but significant adverse effects could be a step forward in ensuring the best possible outcomes from pharmacotherapy. Pharmacists have a unique role within the health care team, encompassing medicinal chemistry, immunology, along with clinical knowledge and skills. For this reason, pharmacists may be at the forefront of investigation, education, and implementation of this knowledge.

Conclusion

Greater understanding of allergic reactions to drugs offers the promise to move from a position of reacting to immune reactions to a more proactive model. This may translate to new opportunities: to characterize risk in drug development, confirm the nature of reactions in clinical settings, enhance the targeting of alerts, and ultimately allow patient-specific prediction.

Disclosures

The authors have declared no potential conflicts of interest

References

- Adkinson NF Jr, Essayan D, Gruchalla R et al.; Health and Environmental Sciences Institute Task Force. Task force report: future research needs for the prevention and management of immune-mediated drug hypersensitivity reactions. *J Allergy Clin Immunol*. 2002; 109:S461-78.
- Brodowy B, Nguyen D. Optimization of clinical decision support through minimization of excessive drug allergy alerts. *Am J Health-Syst Pharm*. 2016; 73:526-8.
- Chen CB, Abe R, Pan RY et al. An updated review of the molecular mechanisms in drug hypersensitivity. *J Immunol Res*. 2018; 2018:6431694.
- Blum JS, Wearsch PA, Cresswell P. Pathways of antigen processing. *Ann Rev Immunol*. 2013; 31:443-73.
- Arstila TP, Casrouge A, Baron V et al. A direct estimate of the human alphabeta T cell receptor diversity. *Science*. 1999; 286:958-61.
- Pichichero ME. Use of selected cephalosporins in penicillin-allergic patients: a paradigm shift. *Diagn Microbiol Infect Dis*. 2007; 57(3 suppl):S13-18.
- Moreno E, Macías E, Dávila I et al. Hypersensitivity reactions to cephalosporins. *Expert Opin Drug Saf*. 2008; 7:295-304.
- Romano A, Gaeta F, Valluzzi RL et al. IgE-mediated hypersensitivity to cephalosporins: cross-reactivity and tolerability of penicillins, monobactams, and carbapenems. *J Allergy Clin Immunol*. 2010; 126:994-9.
- Pichler WJ. Delayed drug hypersensitivity reactions. *Ann Intern Med*. 2003; 139:683-93.
- Pichler WJ. Pharmacological interaction of drugs with antigen-specific immune receptors: the p-i concept. *Curr Opin Allergy Clin Immunol*. 2002; 2:301-5.
- Mallal S, Phillips E, Carosi G et al.; PREDICT-1 Study Team. HLA-B*5701 screening for hypersensitivity to abacavir. *N Engl J Med*. 2008; 358:568-79.
- Pompeu YA, Stewart JD, Mallal S et al. The structural basis of HLA-associated drug hypersensitivity syndromes. *Immunol Rev*. 2012; 250:158-66.
- Zhou P, Zhang S, Wang Y et al. Structural modeling of HLA-B*1502/peptide/carbamazepine/T-cell receptor complex architecture: implication for the molecular mechanism of carbamazepine-induced Stevens-Johnson syndrome/toxic epidermal necrolysis. *J Biomol Struct Dyn*. 2016; 34:1806-17.
- Illing PT, Vivian JP, Dudek NL et al. Immune self-reactivity triggered by drug-modified HLA-peptide repertoire. *Nature*. 2012; 486:554-8.
- Norcross MA, Luo S, Lu L et al. Abacavir induces loading of novel self-peptides into HLA-B*57:01: an autoimmune model for HLA-associated drug hypersensitivity. *AIDS*. 2012; 26:F21-9.
- Brackett CC, Singh H, Block JH. Likelihood and mechanisms of cross-allergenicity between sulfonamide antibiotics and other drugs containing a sulfonamide functional group. *Pharmacotherapy*. 2004; 24:856-70.
- Lehmann DF. The metabolic rationale for a lack of cross-reactivity between sulfonamide antimicrobials and other sulfonamide-containing drugs. *Drug Metab Lett*. 2012; 6:129-33.
- You Q, Cheng L, Li D et al. Development of a screening assay to evaluate the potential of drugs to cause immune-mediated hypersensitivity reactions. *J Immunotoxicol*. 2014; 11:110-5.
- Corsini E, Casula M, Tragni E et al. Tools to investigate and avoid drug-hypersensitivity in drug development. *Expert Opin Drug Discov*. 2018; 13:425-33.
- Faulkner L, Gibson A, Sullivan A et al. Detection of primary T cell responses to drugs and chemicals in HLA-typed volunteers: implications for the prediction of drug immunogenicity. *Toxicol Sci*. 2016; 154:416-29.
- Van Den Driessche G, Fourches D. Adverse drug reactions triggered by the common HLA-B*57:01 variant: a molecular docking study. *J Cheminform*. 2017; 9:13.
- Lin YC, Sheu JN, Chung WH et al. Vancomycin-induced Stevens-Johnson syndrome in a boy under 2 years old: an early diagnosis by granulysin rapid test. *Front Pediatr*. 2018; 6:26.
- Porebski G. In vitro assays in severe cutaneous adverse drug reactions: are they still research tools or diagnostic tests already? *Int J Mol Sci*. 2017; 18:1737.
- Saito D, Hayashida M, Sato T et al. Evaluation of the drug-induced lymphocyte stimulation test for diagnosing mesalazine allergy. *Intest Res*. 2018; 16:273-81.
- Dougherty JA, Bonfiglio M. The future CPOE workflow: augmenting clinical decision support with pharmacist expertise. *Hosp Pharm*. Epub ahead of print. (DOI: 10.1177/0018578718791556).
- Topaz M, Seger DL, Slight SP et al. Rising drug allergy alert overrides in electronic health records: an observational retrospective study of a decade of experience. *J Am Med Inform Assoc*. 2016; 23:601-8.
- Wong A, Amato MG, Seger DL et al. Evaluation of medication-related clinical decision support alert overrides in the intensive care unit. *J Crit Care*. 2017; 39:156-61.