Drug Hypersensitivity Reactions: Pathomechanism and Clinical Symptoms

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KEYWORDS

• Hapten • P-i concept • Gell and Coombs classification
• Specific IgE • Type IV reactions • Exanthema
• Multiple drug hypersensitivity • Flare-up reactions

The immune system has developed to combat infections, which it achieves by a sophisticated interplay between the innate and adaptive immune systems. People are exposed to many infectious agents, but also encounter many (new) chemicals, mostly in very small amounts. Some chemicals, such as drugs, are given consistently and in comparatively high doses. These chemicals can interfere with the immune system in various ways and may lead to somewhat neglected, phenotypically unusual consequences, which are a potential cause of allergic diseases.

Drug-induced adverse reactions are often classified as type A and type B reactions: Type A represent predictable side effects due to a pharmacologic action of the drug, whereas type B reactions are assumed not to be predictable. They comprise so-called idiosyncratic reactions due to some individual predisposition (eg, an enzyme defect), and hypersensitivity reactions.[1] About 1 in 6 adverse drug reactions represents drug hypersensitivity, and are allergic or non–immune-mediated (pseudoallergic) reactions. The latter are common causes of side effects to nonsteroidal antiinflammatory drugs (NSAIDs) (see the article by Mario Sánchez-Borges elsewhere in this issue for further exploration of this topic). It is rare for drugs to cause autoimmunity or immunodeficiency. Such abnormal immune reactions to a drug are a substantial cause of

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morbidity, and even mortality, and deserve special attention by the medical community because they represent iatrogenic diseases.

The clinical symptoms and diseases of drug hypersensitivity reactions are heterogeneous and can imitate many different diseases, which often delays a correct diagnosis. Some side effects are mild, but others are severe and even fatal.[2,3] Many allergic reactions affect the skin and can cause a variety of different exanthems. Most common is a maculopapular rash, which is observed in about 2% to 3% of hospitalized patients.[4,5] However, drug hypersensitivity reactions can also affect various internal organs, causing hepatitis, nephritis, carditis, pneumonitis, and so forth.

Any drug is assumed to be able to elicit hypersensitivity reactions. However, the frequency differs widely. Antibiotics and antiepileptics are the most prevalent causes. The risk of sensitization and the severity of clinical symptoms depend on the state of immune activation of the individual, the dose, the duration of treatment, sex (more frequent in women), and the immunogenetic predisposition (in particular human leukocyte antigen B [HLA-B] alleles), whereas a pharmacogenetic predisposition has rarely been detected.

Epicutaneous application of a drug clearly increases the chance of sensitization compared with oral or parental treatments. It may be due to the high density of dendritic cells (DCs) in the skin. Atopy (defined as the genetic predisposition to mount an immunoglobin E [IgE] response to inhaled or ingested innocuous proteins) is normally not associated with a higher risk of drug hypersensitivity. However, an atopic predisposition may prolong the persistence of drug-specific IgE in the serum,[6] and an ongoing IgE-mediated allergic inflammation such as asthma may aggravate the symptoms of an IgE-mediated drug hypersensitivity reaction.

HOW DO SMALL MOLECULES STIMULATE THE IMMUNE SYSTEM?

Hapten and Prohapten Concepts

Small chemical compounds, usually less than 1000 Da, are not immunogenic per se. These compounds are normally degraded, metabolized, and eliminated without stimulating an immune response. However, if the chemical is reactive and able to bind covalently to proteins, DNA, and so forth, a new antigenic determinant arises that can produce a new immune response. This modification can, theoretically, affect any kind of autologous protein, such as soluble extracellular proteins (eg, albumin), membrane proteins (eg, an integrin), and intracellular proteins (eg, enzymes). It can even bind directly to the peptide embedded in the major histocompatibility complex (MHC) molecule itself. The hapten modification may also affect essential proteins or the DNA, which may result in a dose-dependent toxicity (Fig. 1A).

A certain toxic effect may also be important for inducing an immune response: the toxicity is sensed by the innate immune system as a danger, and DCs react to so-called danger signals by upregulating costimulatory molecules and cytokines. These danger signals can be generated by a toxic effect on cells, which are then sensed by DCs; or it may occur by activating DCs themselves.

Simultaneously, this drug-protein complex generates new antigenic determinants, which may be recognized by antigen-specific receptors of the immune system. This combined stimulation of innate (DCs and other cells) and adaptive immunity (T and B cells) results in a new, antigen-specific immune response, which is based on T cells and antibody production, both specific to the drug-protein complex (ie, hapten-carrier complex). The ensuing immune response is variable, because it uses against the drug

noncovalent interactions between the drug molecule and the antigen presentation groove. It is tempting to speculate that the interaction of abacavir with empty MHC class I molecules may stabilize these MHC molecules, because MHC molecules without peptides are unstable.

This and other strong MHC class I–associated drug hypersensitivity reactions were among the first examples of personalized medicine; nowadays HLA-B*5701 typing is regularly done before abacavir is prescribed, which has almost eliminated severe abacavir-related drug hypersensitivity reactions. Similarly, among Han Chinese, HLA-B*1502 typing greatly reduces the incidence of Stevens-Johnson syndrome (SJS)/toxic epidermal necrolysis (TEN) in carbamazepin-treated patients.

Based on these findings, 2 types of p-i mechanism may occur. In the case of MHC class I restricted drug hypersensitivity reactions, the drug may first bind to the MHC class I molecules, and subsequently elicit a strong (CD8+ T cell) immune response. Whether this drug binding affects empty MHC I molecules, or whether the MHC-embedded peptide could influence the interaction, is still not clear. Nevertheless, the direct binding of the drug to the MHC molecule itself (and not to the peptide) could explain the extremely strong association with the MHC class I molecule (see Fig. 1C), and that eluting peptides from the MHC molecule failed to identify (covalently) drug-peptide complexes.[26]

Alternatively, a more polymorphic CD4+ T-cell response would occur if the drug interacts primarily with the TCR. Full stimulation of these CD4 cells would still require an interaction with the MHC class II molecules; however, probably just by binding to common determinants of the MHC structure, as various MHC class II molecules do, seems to be sufficient to provide T-cell stimulation. Therefore, in CD4 cell reactions, no MHC-associations have been found for these clinically mostly mild reactions (mainly maculopapular exanthems, rarely drug rash with eosinophilia and systemic symptoms [DRESS]). Some clinical features of the p-i concept are as follows:

- Positive skin test reactions to inert drugs, although no cutaneous metabolism of this peculiar drug is known
- Immune reactivity at the first encounter, without time of sensitization.[7] In this case, the drug may already interact with many T cells.
- Generalized reaction to a drug without local danger signs
- Fulminant course of a T-cell–mediated hypersensitivity (as with superantigen stimulations)[7,27]
- Flare-up reactions to a novel drug (?)
- It reflects an abnormal T-cell stimulation with massive/fatal self-destruction as seen in SJS/TEN and DRESS/drug-induced hypersensitivity syndrome (DiHS) (?)

The p-i concept represents a new way to explain drug-induced hypersensitivity reactions. It suggests that certain drug hypersensitivities are also pharmacologic reactions, because the drug interacts not only with the target for which it is designed but also with some immune receptors. The enormous diversity of immune receptors facilitates this possibility of additional drug interactions outside the original scope. The dogma that small chemicals are not full antigens is still valid and must not be rejected, but drugs are able to interfere with the human immune system in additional ways. Related to this finding of pharmacologic stimulation of the immune system by drugs is the development that some of the so-called unpredictable type B drug reactions become the most predictable drug reactions and a paradigm for personalized medicine. It seems that the belief that type B reactions are bizarre reactions is becoming outdated.

CLASSIFICATION OF DRUG HYPERSENSITIVITY REACTIONS

Coombs and Gell[28] classified drug hypersensitivity, as well as other immune reactions, into 4 categories termed type I-IV reactions: This classification relies on the formation of IgE antibodies that bind to high-affinity IgE receptors on mast cells and basophilic leukocytes, on complement-fixing antibodies, and in T-cell reactions. Because recent immunologic data reveal that T cells orchestrate different forms of inflammation, which may result in different symptoms, the classification of Coombs and Gell[28] has been refined[7] into IVa, IVb, IVc, and IVd reactions, to better accommodate this heterogeneity of T-cell functions.

The extended Coombs and Gell[28] classification is a simplification of complex events occurring in vivo. The immune system combines different approaches to defend against a real or presumed pathogen, even if the pathogen is not dangerous, as in allergy. Nevertheless, a certain type of immune reaction may dominate the clinical situation: for example, in anaphylaxis to β-lactam antibiotics, there may not only be drug-specific IgE but also a T-cell reaction to the drug. However, the formation of drug-specific IgE is the relevant clinical event. In patients with an exanthem and hepatitis, an eosinophilic infiltrate may be found in the skin biopsy, but the liver cell destruction by cytotoxic T cells may be the more dangerous event. For the diagnosis of a drug allergy, the skin event may be sufficient.

Type I (IgE-mediated) Allergies

The IgE system reacts to small amounts of antigen. It achieves this sensitivity by the ubiquitous presence of mast cells armed with high-affinity fragment crystallizable IgE receptors (Fc-IgE RI), to which allergen- or drug-specific IgE is bound. On cross-linking the Fc-IgE RI, various mediators (histamine, tryptase, leukotriens, prostaglandins, TNFα, and so forth) are released, which cause the immediate symptoms and may start and facilitate late-appearing allergic inflammations.

IgE-mediated reactions to drugs are believed usually to depend on the prior development of an immune response to a hapten/carrier complex: B cells, able to interact via their surface Ig receptors with the hapten-carrier complex, mature into IgE-secreting plasma cells. This maturation is helped by hapten-carrier complex–specific T cells, which interact with B cells (ie, via CD40-CD40L interaction) and which release IL-4/IL-13, which are switch factors for IgE synthesis. This sensitization phase is normally asymptomatic. On renewed contact with the drug, a hapten-carrier complex is formed again, which then cross-links preformed drug-specific IgE on mast cells and causes mast cell degranulation and immediate allergic symptoms (Fig. 2).

Peculiar features of IgE-mediated reactions to drugs

IgE-mediated reactions to drugs have some features that need to be considered to better understand these reactions:

1. Very small amounts of a drug seem to be sufficient to allow interaction and cross-linking of receptor-bound IgE molecules. Even intradermal (ID) skin tests with drugs may elicit systemic reactions, and fatal reactions to ID testing have been described.[29] What is the difference to protein-specific reactions? Why are drug-induced anaphylactic reactions often so severe?

The drug itself is normally too small to cross-link 2 adjacent IgE molecules, and it needs to bind covalently to proteins to cross-link specific IgE bound to Fc-IgE receptors (see Fig. 2). If a protein does not consist of repetitive determinants, it needs at least 2 distinct IgE-binding sites (epitopes) that can bind and cross-link 2 distinct

IgE molecules. If the protein contains only 1 epitope, no cross-linking can occur, because the IgE molecules can only bind to a single epitope, making cross–linking impossible.[30]

The situation is different for haptens. A hapten may modify a protein at various positions. Consequently, different new epitopes arise (see Fig. 2, position A, B, and so forth). If these new epitopes are spacially distinct enough to allow binding of distinct IgE molecules, at least 2 or more IgE could bind. Even IgE with the same hapten specificity could bind, and cross-linking Fc-IgE receptors would no longer depend on the proximity of at least 2 distinct IgE molecules. Consequently, hapten formation is the main facilitator of IgE cross-linking, as a single hapten-modified protein can cross-link IgE molecules with the same (or different) specificity. This enhanced cross-linking ability may result in rapid and fulminant mast cell degranulations, and may explain the severity of drug-induced anaphylaxis (see schematic representation in Fig. 2).

2. A second feature of drug-induced anaphylaxis is that 50% or more of patients with immediate reactions to various drugs deny any prior contact with the drug; 4/5 of the patients with lethal anaphylaxis had no prior contact with the drug.[31] This was previously interpreted as sign of a non–immune-mediated anaphylaxis (pseudoallergy), because prior contact with the drug was believed to be essential for specific IgE formation. However, IgE specific to neuromuscular blocking agents (NMBAs) could be detected in perioperative anaphylaxis by skin tests and by serology even at the first encounter with these

anaphylaxis was found to be sixfold more frequent in Norway than in Sweden.[34] Pholcodein was licensed in Norway, but not in Sweden. Pholcodein use stimulated the production of pholcodein- and morphin-specifc IgE molecules, which also reacted with tertiary and quaternary ammonium groups contained in NMBA.[35] Thus, in Norway many people were silently sensitized to a cross-reactive compound contained in an antitussive.[34] Their reactions were clearly IgE mediated and pholcodein/NMBA/quarternary ammonium specific, but not elicited by NMBA.

3. Anaphylactic reactions were often considered to be dose independent, as sometimes very small amounts can cause severe reactions. However, all drug-induced reactions are dose dependent. However, the reaction due to IgE is often caused by minute amounts. Further diminishing the dose, as is done in desensitization procedures, shows that even these reactions are dose dependent.[36]

Clinical features of IgE-mediated reactions

IgE-mediated reactions can cause mild to severe, even lethal, diseases: in sensitized individuals, the reaction can start within seconds after contact with the parentally applied drug, and minutes after oral drug uptake. Symptoms may start with palmar, plantar, genital, and axillar itch, and facial and thoracal redness. These symptoms should be considered an alarm sign, as they often herald a severe, anaphylactic reaction, developing rapidly within minutes (Fig. 3). The symptoms rapidly generalize and, within approximately 10 to 20 minutes, a generalized urticaria may develop. The patient becomes restless and anxious. Laryngeal swelling may be suspected if he/she has difficulty speaking or swallowing, because the tongue is swollen. He or she may also complain about chest tightness and dyspnea; signs of acute bronchospasm. Periorbital and perioral swellings often occur later. More severe and complex reactions are called anaphylaxis,[37] and, in most cases with anaphylaxis, some circulatory events with decrease of blood pressure and (transient) unconsciousness are observed, together with a generalized redness, itch, or urticaria.

Anaphylactic shock occurs often within 10 to 15 minutes, and asphyxia due to laryngeal edema often occurs between 15 and 60 minutes. Asphyxia may account for 60% of anaphylaxis-related deaths.[38] Some patients develop gastrointestinal symptoms (nausea, cramps, vomiting, and fecal incontinence). The reduction in blood pressure may be due to a shift of intravascular volume into the extravascular space or to the development of a cardiac arrhythmia, which is more serious. The full syndrome is anaphylactic shock, which is lethal in approximately 1% to 2% of all anaphylaxis cases. The more rapidly it appears, the more serious it is likely to be. Risk factors for a severe course are high-dose, preexisting (undertreated) asthma, and older age, because myocardial infarction, cerebral hypoxia, and brain damage can lead to death days after the acute event. Patients with recurrent anaphylactic reactions to various triggers (eg, food, drugs, hymenoptera stings) may have mastocytosis.

Although most patients show the involvement of different organs, in perioperative anaphylaxis the symptoms may initially affect only 1 organ system (eg, the cardiovascular system with arrhythmia); skin symptoms may not be visible but can appear later. Anaphylaxis is a severe event, and survivors often have some cognitive or intellectual impairment. Table 1 summarizes the main drugs causing anaphylaxis.

Most IgE-mediated reactions to drugs are less severe, and often only an urticaria, angioedema, or a local wheal may develop. However, any IgE-mediated drug allergy can be potentially life threatening, because the mild symptoms might be due to a low dose, and each treatment might boost the drug-specific IgE response.

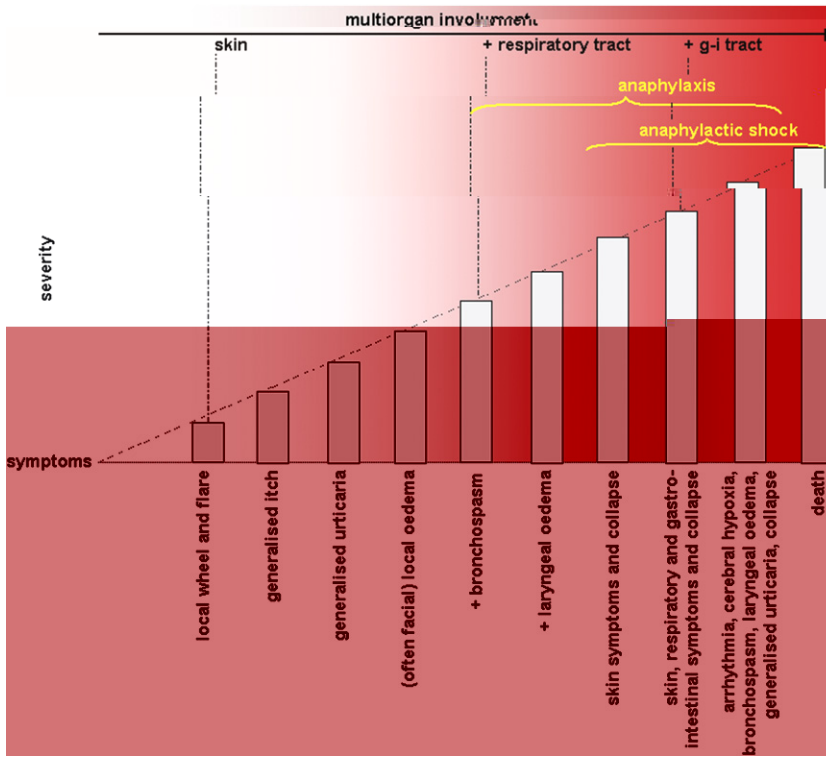


Fig. 3. Anaphylaxis. Anaphylaxis is a complex and severe allergic reaction affecting multiple organs. It can be seen as the sum of different, severe allergic manifestations in various organs. Symptoms resemble mild to moderate allergic reactions (urticaria, angioedema, bronchospasm). In many, but not all, cases, the cardiovascular system is involved, as a result of relative hypovolemia, due to a shift of intravascular volume to extravascular space (less dangerous), or due to arrhythmia. The most severe form is anaphylactic shock, which can result in death in 1% to 2% of affected persons (see text). (*From* Pichler WJ. Drug hypersensitivity: classification and relationship to T-cell activation. In: Pichler WJ, editor. Drug hypersensitivity. Basel (Switzerland): Karger; 2007. p. 168–89; with permission.)

PSEUDOALLERGY (NON–IMMUNE-MEDIATED HYPERSENSITIVITY)

So-called pseudoallergic reactions (non–immune-mediated hypersensitivities) to drugs, which are as frequent as true IgE-mediated reactions, are a pathogenetically poorly defined problem.

Most of these reactions resemble the clinical features of milder forms of immediate, IgE-mediated reactions (erythema, urticaria), but some reactions cause anaphylaxis and can be lethal. Detection of specific immune mechanism is negative. NSAID-induced pseudoallergic reactions seem to arise less rapidly (often >15 minutes after intake) than true IgE-mediated allergies, and they may require higher drug doses than true IgE-mediated reactions. Increased tryptase levels in the acute stage underline the role of mast cell degranulation in some of these reactions (see Table 1).

Pseudoallergic reactions can be elicited by many drugs, but some drugs seem to elicit them more often (see Table 1). Some drugs might elicit either pseudoallergic, or presumably true allergic reactions, because positive prick skin tests can be

detected (contrast media, NMBAs). In vitro, these drugs do not spontaneously release mediators from basophils.

Some people seem to show a higher tendency to react in this way (urticaria),

Hemolytic anemia has been attributed to penicillin and its derivatives, cephalosporins, levodopa, methyldopa, quinidine, and some antiinflammatory drugs. Cephalosporins are currently the main cause. The clinical symptoms of hemolytic anemia are insidious and may be restricted to symptoms of anemia and jaundice with dark urine. Occasionally a positive direct and (if the drug is present during the test) indirect Coombs test can be found.

Thrombocytopenia is a common side effect of drug treatment, in particular following quinine, quinidine, and sulfonamide antibiotics. It is a common complication of treatments with certain biologicals (mainly monoclonal antibodies). Drug-induced immune thrombocytopenia usually develops after 5 to 8 days of exposure to the sensitizing medication, or after a single exposure in patients previously exposed to the same drug. Patients with this condition often present with widespread petechial hemorrhages in the skin and buccal mucosa, sometimes accompanied by urinary tract or gastrointestinal bleeding. Intracranial hemorrhage is rare. After discontinuation of the provoking medication, platelet counts usually return to normal within 3 to 5 days. (See the article by Trautmann and Seitz elsewhere in this issue for further exploration of this topic).

Formation of immune complexes is a common event in a normal immune response and does normally not cause symptoms. It is not clear why, under certain circumstances, an immune complex disease develops: Very high immune complex levels; a relative deficiency of some complement components, and thus lower capacity to eliminate immune complexes; or an aberrant Fc-IgG-R function might be considered.[40] Thus, reduced removal of immune complexes may lead to inappropriate deposition of immune complexes and recruitment of inflammatory cells, in particular polymorphonuclear cells (PMNs), because of immune complex binding to Fc-IgG-R on PMNs. In addition, anaphylatoxins C3a and C5a, generated as a result of local complement activation, may attract PMNs.

A type III reaction may result in a small vessel as vasculitis or serum sickness: In serum sickness, antibodies are generated within 4 to 10 days. Complement (C1q)-containing immune complexes are deposited in the postcapillary venules and attract neutrophilic leukocytes by interacting with their Fc-IgG-RIII,[41] which thereby release proteolytic enzymes that can mediate tissue damage.

Nonprotein and protein drugs (biologicals) are responsible for serum sickness. Hypersensitivity vasculitis reportedly has an incidence of 10 to 30 cases per million people per year. Most reports concern cefaclor, followed by trimethoprim-SMX, cephalexin, amoxicillin, NSAID, and diuretics. Biologicals such as rituximab, infliximab, and natalizumab have increasingly been associated with serum sickness[42] (see the article by Hausmann and colleagues elsewhere in this issue for further exploration of this topic). Vasculitis may be localized, mainly to the skin, as palpable purpura; purplish red spots, usually found on the legs. In children, it is often referred to as Henoch-Schönlein purpura, sometimes appearing in combination with an arthritis. The prognosis is good when no internal involvement is present. Histology can reveal IgA-containing immune complexes, and the histology of kidney lesions is identical to IgA nephropathy, a main cause of chronic renal failure (Fig. 4).

T-CELL–MEDIATED, DELAYED DRUG HYPERSENSITIVITY REACTIONS

Subclassification of Type IV Reactions

The detailed analysis of T-cell subsets and functions in the last 30 years has revealed that T cells play a major role in most immune reactions: as helper T cells, which regulate B-cell maturation to antibody-producing cells; as drug-specific T cells, which

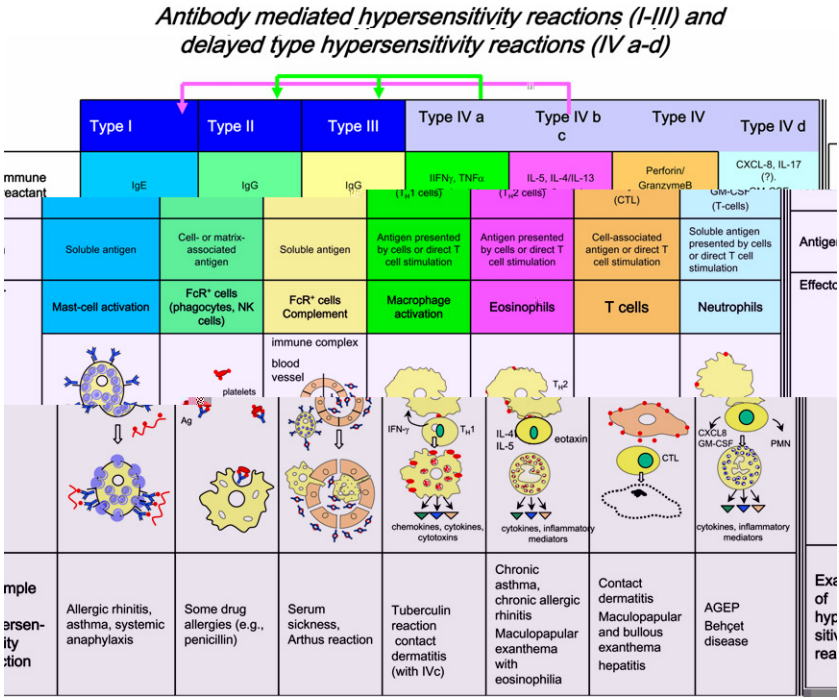


Fig. 4.

orchestrate different forms of inflammation; or as effector T cells mediating cytotoxicity. Based on these findings, as well as studies of immune reactions to drugs in vitro and in vivo, a refined subclassification of T-cell–meditated type IV reactions was developed. It considers the distinct cytokine production by T cells, and thus

incorporates the well-accepted Th1/Th2 distinction of T cells; it includes the cytotoxic activity of CD4 and CD8 T cells (IVc); and it emphasizes the participation of different effector cells such as monocytes (IVa), eosinophils (IVb), or neutrophils (IVd), which are the cells causing inflammation and tissue damage.[7]

Type IVa reactions correspond to Th1-type immune reactions: Th1-type T cells activate macrophages by secreting large amounts of interferon-γ, drive the production of complement-fixing antibody isotypes involved in type II and III reactions (IgG1, IgG3), and are costimulatory for proinflammatory responses (tumor necrosis factor, IL-12) and CD8+ T-cell responses. The T cells promote these reactions by IFNγ secretion and possibly other cytokines (eg, TNFα, IL-18). An in vivo correlate would be a monocyte activation (eg, in skin tests to tuberculin or even granuloma formation, as seen in sarcoidosis), but Th1 cells are also known to help in the activation of CD8 cells, which might explain the common combination of IVa and IVc reactions (eg, in contact dermatitis).

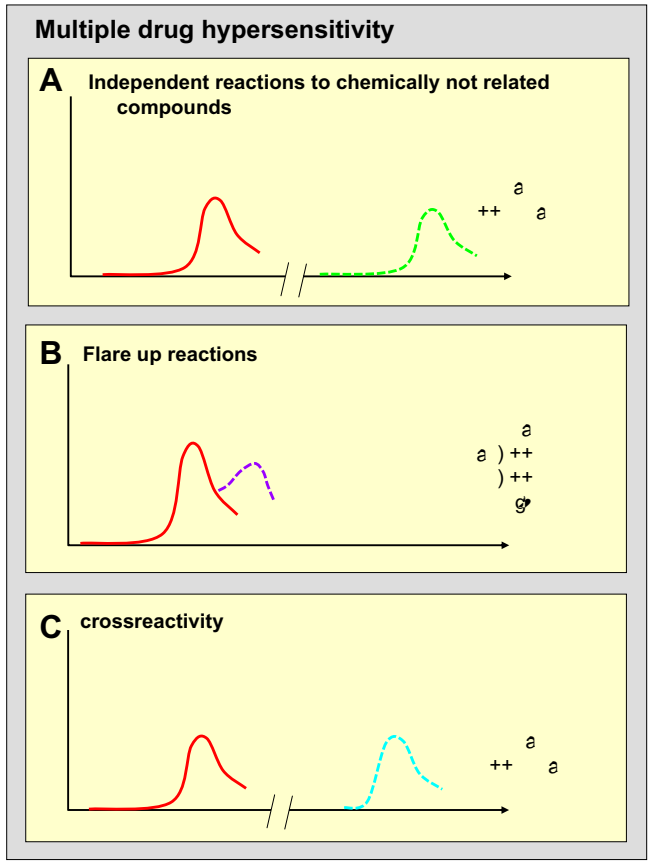
Type IVb corresponds to the Th2-type immune response. Th2 T cells secrete the cytokines IL-4, IL-13 and IL-5, which promote B-cell production of IgE and IgG4, macrophage deactivation, and mast cell and eosinophil responses: The high production of the Th2 cytokine IL-5 leads to an eosinophilic inflammation, which is the characteristic inflammatory cell type in many drug hypersensitivity reactions.[7] In addition, there is a link to type I reactions, as Th2 cells boost IgE production by IL-4/IL-13 secretion. An in vivo correlate might be an eosinophil-rich maculopapular exanthem but also infestations with nematodes, or an allergic inflammation of the bronchi or nasal mucosa (asthma and rhinitis).

In type IVc reactions, T cells can themselves act as effector cells. They emigrate to the tissue and can kill tissue cells such as hepatocytes or keratinocytes in a perforin/granzymeB-, granulysin-, and FasL-dependent manner (Fig. 5).[27,43,44] Such reactions occur in most drug-induced delayed hypersensitivity reactions, usually together with other type IV reactions (monocyte, eosinophil, or PMN recruitment and activation). Cytotoxic T cells thus play a role in maculopapular or bullous skin diseases (with high granulysin production) as well as in neutrophilic inflammations (eg, acute generalized exanthematous pustulosis [AGEP]), and in contact dermatitis. Type IVc reactions seem to be dominant in bullous skin reactions, in which activated CD8+ T cells kill keratinocytes,[7,43,44] but they may also be the dominant cell type in hepatitis or nephritis.[27]

Type IVd reactions involve the new concept that T cells can also coordinate (sterile) neutrophilic inflammations.[45] Typical examples would be sterile neutrophilic inflammations of the skin, in particular AGEP. In this disease, CXCL8 and granulocyte-macrophage colony-stimulating factor (GM-CSF)–producing T cells recruit neutrophilic leukocytes via CXCL8 release, and prevent their apoptosis via GM-CSF release.[46] In addition to AGEP, such T-cell reactions are also found in Behçet disease and pustular psoriasis.[47] To what extent the cytokine IL-17, associated with neutrophilic inflammations, is involved in these reactions is not yet clear.

Tolerance Mechanism

Most patients can take drugs without developing immune-mediated side effects. It could be argued that these patients lack precursor cells able to interact with the drug. However, the great heterogeneity of the immune response to drugs,[7] a high precursor frequency in sensitized patients,[48] and the finding that 2% to 4% of the normal population, but 30% to more than 50% of human immunodeficiency virus–infected patients may react with SMX suggest that, rather than a lack of precursor cells, other factors such as the underlying immune status (preactivation of memory



T cells) and regulatory mechanisms may be important. Thereby regulation may occur on different levels. At present, these regulatory mechanism in immune responses to small molecules are not yet well understood: in DRESS and SJS/TEN, Treg cells were investigated: they were expanded during acute DRESS, but contracted after resolution, leading to an enhanced response to more drugs, as well as to

autoimmunity.[49] In contrast, the functional defects of Tregs in TEN were restored on recovery. Further work is needed, but the frequently observed multiple-drug hypersensitivity syndrome after DRESS may be explained by this Treg defect. Tolerance mechanisms to drugs are[c]

1. Ignorance: even if drugs bind to immune receptors, the interaction (affinity, surface contact) is too weak to elicit a significant reaction
2. Lack of danger signals and preactivation: the hapten-carrier complexes do not sufficiently stimulate the innate immunity, which is necessary to develop a primary immune response. Or, in the case of the p-i concept, TCR stimulation by the drug is not sufficient to induce cytokine production and proliferation, because the T cells are not sufficiently preactivated to react to this signal
3. Regulatory T cells may be insufficiently activated in some patients, making them prone to react to small chemical compounds. These patients may have multiple drug allergies and may also suffer from autoimmunity
4. The liver as a tolerogenic organ: the generation of reactive metabolites in the liver may induce tolerance, which might prevent the development of an immune reaction to the drug in the periphery.

Clinical Symptoms of T-cell–mediated Reactions

The most frequent manifestations of drug allergies are delayed cutaneous reactions; so-called rashes. Rashes comprise a broad spectrum of clinical and distinct histopathological features that usually appear between 6 hours and 10 days after drug intake. The skin is most often affected during drug hypersensitivity, but liver involvement is common if moderate elevations of liver enzymes are considered (they are often attributed to a toxic effect of the drug, but may be immune mediated). Other organs such as kidney, lung, and pancreas may also be involved. (For details of the clinical symptoms see the articles by Harr and colleagues and Scherrer and colleagues elsewhere in this issue for further exploration of this topic).

Multiple drug hypersensitivity syndrome and flare-up reactions

The term multiple drug hypersensitivity is widely used for different side effects to various drugs: it is used to characterize patients with multiple drug intolerance (pseudoallergy to various, structurally distinct NSAID, and so forth); others reserve this term for well-documented repeated immune-mediated reactions to structurally unrelated drugs.[50] Cross-reactivity due to structural similarity is not included.

In our experience, about 10% of patients with well-documented drug hypersensitivity (positive skin or lymphocyte transformation test) have multiple drug allergies[51]: they may have reacted to an injected lidocain with a massive angioedema; years later the same patient develops an allergy to corticosteroids. Both drugs are positive in skin and lymphocyte transformation tests. Alternatively, a patient reacts to amoxicillin, phenytoin, and SMX within a few months, but with different symptoms (maculopapular exanthema [MPE], drug-induced hypersensitivity syndrome [DiHS]/DRESS, erythrodermia). Most patients with multiple drug hypersensitivity have had severe reactions to at least 1 drug. An IgE-mediated reaction might be followed by a T-cell–mediated reaction. The pathomechanism of this syndrome is unknown, but it

[c] *From* Pichler WJ. Drug hypersensitivity: classification and relationship to T cell activation. In: Pichler WJ, editor. Drug hypersensitivity. Basel (Switzerland): Karger; 2007. p. 168–89; with permission.

is tempting to speculate that the tolerance mechanism to small molecular compounds fail in these patients (see Fig. 5).

An immune reaction to a drug, via a hapten or p-i mechanism, can be seen as a failure of tolerance, and the same patient might not only develop other drug allergies but also autoimmunity.[49] Preliminary data suggest that a previous drug allergy might be a risk factor for the development of a delayed hypersensitivity reaction to contrast media.[33]

Multiple drug hypersensitivity should be differentiated from flare-up reactions and true cross-reactivity (see Fig. 5). Flare-up reactions are clinically important and frequent: patients with systemic drug allergies show a massive activation of their immune system,[52] similar to acute viral infections. This immune activation may make existing drug allergies risk factors for future drug allergies (see earlier discussion). Flare-up reactions occur when, as a result of an existing drug allergy, drug therapy is changed to a new drug: the second drug may then exacerbate the existing drug allergy (more symptoms of exanthema, increased alanine aminotransferase [ALAT], and fever after 1 or 2 days), and it is often confused with a new drug allergy. Such flare-up reactions are common in severe reactions such as DiHS/DRESS (see earlier discussion). With some exceptions,[27] they are normally not dangerous. The mechanism is unclear, but possibly related to the p-i concept explained earlier: the second drug may not have caused its own, specific immune reaction, but the drug may still bind to the immune receptors of preactivated T cells, and thus briefly augment the symptoms. However, later, in remission, the second drug may again be tolerated, as the costimulatory conditions no longer exist. However, there are also accounts of sensitizations to the second drug, which occurred during the DRESS/DiHS disease.

SUMMARY

Small chemical compounds can interact with the immune system in 2 ways: by forming hapten-carrier complexes, which can stimulate innate and adaptive immunity (T and B cells) and cause localized or systemic reactions due to an immune response against the hapten-carrier complex; alternatively, chemicals that are unable to form covalent bonds can directly interact with proteins by van der Waals and other forces. Some of these labile interactions occur with immune receptors (pharmacologic interaction with immune receptors, p-i concept). Because the immune system offers more than 10^{12} different TCR and a few hundred MHC molecules, some of these drug-protein interactions are affine enough to elicit signaling in the receptor-bearing T cell. The type of immune response may differ as a function of the primary interaction of the drug with a particular MHC class I molecule or with the TCR. Full activation of the reactive T cell always requires TCR interaction with the MHC molecule. The consequence of the hapten and p-i mechanisms are drug-allergic diseases, which can appear within minutes to hours. They are mainly caused by mast cell degranulation due to drug-specific IgE or by a direct effect of the drug on mast cells. Delayed reactions start after 6 hours; some even after many days. Delayed reactions become manifest as different types of exanthems, with or without internal involvement, in which the function of drug-specific T cells and their cytokines regulate the type of allergic reaction. This process leads to the further subclassification of type IV reactions as types IVa, IVb, IVc, and IVd, corresponding to T-cell reactions with monocyte/DC (IVa), eosinophil (IVb), cytotoxic T cell (IVc), and neutrophil (IVd) activations.

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