TABLE 74-1 CLASSIFICATION OF ADVERSE DRUG REACTIONS BASED ON IMMUNE PATHWAY

Type	Key Pathway	Key Immune Mediators	Adverse Drug Reaction Type
Type I	IgE	IgE	Urticaria, angioedema, anaphylaxis
Type II	IgG-mediated cytotoxicity	IgG	Drug-induced hemolysis, thrombocytopenia (e.g., penicillin)
Type III	Immune complex	IgG + antigen	Vasculitis, serum sickness, drug-induced lupus
Type IVa	T lymphocyte–mediated macrophage inflammation	IFN-γ, TNF-α T_H1 cells	Tuberculin skin test, contact dermatitis
Type IVb	T lymphocyte–mediated eosinophil inflammation	IL-4, IL-5, IL-13 T_H2 cells Eosinophils	Drug-induced hypersensitivity syndrome (DIHS) Morbilliform eruption
Type IVc	T lymphocyte–mediated cytotoxic T lymphocyte inflammation	Cytotoxic T lymphocytes Granzyme Perforin Granulysin (Stevens-Johnson syndrome [SJS]/toxic epidermal necrolysis [TEN)] only)	SJS/TEN Morbilliform eruption
Type IVd	T lymphocyte–mediated neutrophil inflammation	CXCL8, IL-17, GM-CSF Neutrophils	Acute generalized exanthematous pustulosis (AGEP)

Abbreviations: GM-CSF, granulocyte-macrophage colony-stimulating factor; IFN, interferon; IL, interleukin; TNF, tumor necrosis factor.

as drug rash with eosinophilia and systemic symptoms [DRESS]), acute generalized exanthematous pustulosis (AGEP), Stevens-Johnson syndrome (SJS), and toxic epidermal necrolysis (TEN) (Table 74-1). Drug-specific T cells have been detected in these types of drug eruptions. For example, drug-specific cytotoxic T cells have been detected in the skin lesions of fixed drug eruptions and of TEN. In TEN, skin lesions contain T lymphocytes reactive to autologous lymphocytes and keratinocytes in a drug-specific, HLA-restricted, and perforin/granzyme-mediated pathway.

The mechanism(s) by which medications result in T cell activation is unknown. Two hypotheses prevail: first, that the antigens driving these reactions may be the native drug itself or components of the drug covalently complexed with endogenous proteins, presented in association with HLA molecules to T cells through the classical antigen presentation pathway, or alternatively, through direct interaction of the drug/metabolite with the T cell receptor or peptide-loaded HLA (e.g., the pharmacologic interaction of drugs with immune receptors, or p-i hypothesis). Recent x-ray crystallography data characterizing binding between specific HLA molecules to particular drugs known to cause hypersensitivity reactions demonstrates unique alterations to the MHC peptide-binding groove, suggesting a molecular basis for T cell activation and the development of hypersensitivity reactions.

GENETIC FACTORS AND CUTANEOUS DRUG REACTIONS

Genetic determinants may predispose individuals to severe drug reactions by affecting either drug metabolism or immune responses to drugs. Polymorphisms in cytochrome P450 enzymes, drug acetylation, methylation (such as thiopurine methyltransferase activity and azathioprine), and other forms of metabolism (such as glucose-6-phosphate dehydrogenase) may increase susceptibility to drug toxicity or underdosing, highlighting a role for differential pharmacokinetic or pharmacodynamic effects.

Associations between drug hypersensitivities and HLA haplotypes also suggest a key role for immune mechanisms. Hypersensitivity to the anti-HIV medication abacavir is strongly associated with HLA-B*57:01 (Chap. 226). In Taiwan, within a homogeneous Han Chinese population, a 100% association was observed between SJS/TEN (but not DIHS) related to carbamazepine and HLA-B*15:02. In the same population, another 100% association was found between SJS, TEN, or DIHS related to allopurinol and HLA-B*58:01. These associations are drug and phenotype specific; that is, HLA-specific T cell stimulation by medications leads to distinct reactions and may explain why the reaction patterns are so clinically diverse. However, the strong associations found in Taiwan have not been observed in other countries with more heterogeneous populations.

GLOBAL CONSIDERATIONS

Recognition of the HLA associations with drug hypersensitivity has been acknowledged by recommendations to screen high-risk populations. Genetic screening for HLA-B*57:01 to prevent abacavir hypersensitivity, which carries a 100% negative predictive value when patch test confirmed and 55% positive predictive value generalizable across races, is becoming the clinical standard of care worldwide (number needed to treat = 13). The U.S. Food and Drug Administration recently mandated new labeling of carbamazepine recommending HLA-B*15:02 screening of Asian individuals prior to receiving a new prescription of the medication. The American College of Rheumatology has recommended HLA-B*58:01 screening of Han Chinese patients prescribed allopurinol. To date, screening for a single HLA (but not multiple HLA haplotypes) in specific populations has been determined to be cost-effective.

Several investigators have proposed that specific HLA haplotypes associated with drug hypersensitivity indeed play a pathogenic role; stimulation of carbamazepine-specific cytotoxic T lymphocytes (CTL) in the context of HLA-B*15:02 results in production of a putative mediator of keratinocyte necrosis in TEN. Other studies have identified CTLs reactive to carbamazepine that use highly restricted V-alpha and V-beta TCR repertoires in patients with carbamazepine hypersensitivity that are not found in carbamazepine-tolerant individuals. Although not yet clinically available, some investigators have suggested combined genetic testing for specific HLA haplotypes and functional screening for TCR repertoire to best identify patients at risk.

CLINICAL PRESENTATION OF CUTANEOUS DRUG REACTIONS

NONIMMUNE CUTANEOUS REACTIONS

Exacerbation or Induction of Dermatologic Diseases A variety of drugs can exacerbate preexisting diseases or sometimes induce a disease that may or may not disappear after withdrawal of the inducing medication. For example, NSAIDs, lithium, beta blockers, tumor necrosis factor (TNF) α cytokine antagonists, interferon (IFN) α, and angiotensin-converting enzyme (ACE) inhibitors can exacerbate plaque psoriasis, whereas antimalarials and withdrawal of systemic glucocorticoids can worsen pustular psoriasis. The situation of TNF-α inhibitors is unusual, as this class of medications is used to treat psoriasis; however, in other cases, they may induce psoriasis (especially palmar-plantar) in patients being treated for other conditions. Acne may be induced by glucocorticoids, androgens, lithium, and antidepressants. Follicular papular or pustular eruptions of the face and trunk, sometimes mimicking acne, frequently occur with epidermal growth factor (EGF) receptor antagonists. In the case of EGF-receptor antagonists, the severity of the eruption correlates with a better anticancer effect. It