Severe Delayed Drug Reactions

Role of Genetics and Viral Infections

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KEYWORDS

- Human leukocyte antigen • T-cell receptor • Adverse drug reaction
- Pharmacogenomics • Human herpes virus
- Drug reaction with eosinophilia and systemic symptoms • Steven Johnson syndrome
- Toxic epidermal necrolysis

KEY POINTS

- Severe delayed drug reactions are typically off-target reactions that are immunologically mediated and associated with long-lasting immunologic memory.
- There are many strong associations between these immunologically mediated adverse drug reactions (IM-ADR) and the major histocompatibility complex.
- Despite this, the minority of these have been implemented into clinical practice as cost-effective pretreatment screening tests.
- A heterologous immune model of delayed drug hypersensitivity may explain why, for most drugs, less than 5% of those carrying an HLA risk allele will develop an IM-ADR.
- It is proposed that pathogen-specific T-cell responses generate either migratory or resident memory T-cells which cross-react with drug-modified self-peptide epitopes when the risk drug is introduced later in life.

INTRODUCTION

Adverse drug reactions (ADRs) account for a significant source of patient morbidity and mortality and represent a major burden to the health care and drug development systems. It is estimated that up to 50% of such reactions are preventable.[1–8] Although

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many ADRs can be predicted based on the on-target pharmacologic activity of the drug (Fig. 1),[1–3,6,8–10] ADRs arising from drug interactions with off-target receptors are now more commonly recognized. Off-target ADRs include the immune-mediated ADRs (IM-ADRs) as well as pharmacologic drug effects such as those associated with non–IgE-mediated mast cell activation (see Fig. 1).[11] In this review, we discuss what is known about the immunogenetics and pathogenesis of IM-ADRs and the hypothesized role of preexisting pathogen exposure as a predisposing factor for the development of an IM-ADR.

CLINICAL PHENOTYPES OF IMMUNE-MEDIATED ADVERSE DRUG REACTIONS

IM-ADRs encompass a number of phenotypically distinct clinical diagnoses that include both B-cell (antibody-mediated, Gell Coombs types I–III) and purely T-cell–mediated reactions (Gell-Coombs type IV). T-cell–mediated IM-ADRs have been classified into delayed exanthema without systemic symptoms (ie, maculopapular eruption), contact dermatitis, drug-induced hypersensitivity syndrome, drug reaction with eosinophilia and systemic symptoms (DRESS), hypersensitivity syndrome, Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), acute generalized exanthematous pustulosis, fixed drug eruption, single organ involvement pathologies such as drug-induced liver injury, and the abacavir hypersensitivity syndrome.[12,13]

Drug Reaction with Eosinophilia and Systemic Symptoms

The clinical presentation of DRESS is characterized by a generalized rash of varying severity without skin separation, fever, internal organ involvement (usually hepatitis), and hematologic abnormalities (often atypical lymphocytes and/or eosinophilia). Clinical features of this syndrome are variable, but may also include diffuse lymphadenopathy, pneumonitis, encephalitis, myocarditis, and nephritis. Onset of symptoms typically occurs 2 to 8 weeks after initiation of the inciting drug and the patient may have a protracted clinical course. Prolonged or recurrent symptoms, sometimes weeks after cessation of the offending drug and often related to discontinuation of systemic corticosteroids, is frequently observed and late onset autoimmune diseases including thyroiditis, systemic lupus, and type I diabetes are well-described long-term sequelae that can occur at least up to 4 years after the resolution of acute disease.[14–22]

Stevens–Johnson Syndrome and Toxic Epidermal Necrolysis

SJS and TEN are the most severe cutaneous hypersensitivity syndromes and are thought to represent a spectrum of disease defined by the percentage of total body surface area (TBSA) involvement. Characteristic features include epidermal necrosis leading to the formation of fluid-filled blisters and epidermal sloughing, fever, mucosal and eye involvement, internal organ involvement, and secondary complications such as sepsis. Generally, SJS is diagnosed in cases where less than 10% of TBSA has blistering and epidermal detachment, whereas TEN is diagnosed in instances where more than 30% of the TBSA is affected. SJS/TEN describes the overlap in this spectrum in which 10% to 30% of TBSA is affected. However, patients with severe epidermal detachment and skin necrosis are classified as TEN regardless of the percentage of TBSA involved. These syndromes are often associated with significant mortality as well as short- and long-term morbidity, including respiratory, gastrointestinal, and genitourinary complications, as well as permanent corneal scarring and vision loss.[7,12] The mortality associated with TEN is higher with aging and comorbidities and may reach 30% to 50%.[12,13,23,24]