Severe Delayed Cutaneous and Systemic Reactions to Drugs: A Global Perspective on the Science and Art of Current Practice

Jonathan Grant Peter, MD, PhD[a,*], Rannakoe Lehloenya, MD[b,*], Sipho Dlamini, MD[c], Kimberly Risma, MD[d], Katie D. White, MD, PhD[e], Katherine C. Konvinse, BA[f], and Elizabeth J. Phillips, MD, FIDSA, FAAAAI[e,f,g,h] *Cape Town, South Africa; Cincinnati, Ohio; Nashville, Tenn; and Murdoch, Western Australia, Australia*

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Date of Original Release: May 1, 2017. Credit may be obtained for these courses until April 30, 2018.

Overall Purpose/Goal: To provide excellent reviews on key aspects of allergic disease to those who research, treat, or manage allergic disease.

Target Audience: Physicians and researchers within the field of allergic disease.

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Learning objectives:

1. To recognize the clinical phenotypes of severe delayed cutaneous adverse drug reactions.

2. To describe the management and role of ancillary diagnostic and treatment measures for severe cutaneous adverse drug reactions.

3. To describe the immunopathogenesis of severe cutaneous adverse drug reactions and describe the role of genetic screening to predict and prevent these reactions.

Recognition of Commercial Support: This CME has not received external commercial support.

Disclosure of Significant Relationships with Relevant Commercial Companies/Organizations: S. Dlamini has received lecture fees from Pfizer South Africa and has received travel support from Merck Sharp & Dohme South Africa and Gilead Sciences. K. C. Konvinse has received research support from the National Institutes of Health (grant nos. 1P50GM115305-01 and T32GM007347). K. D. White has received research support from the National Institutes of Health (grant no. 1P50GM115305-01). E. J. Phillips has received research support from the National Health and Medical Research Council Australia, the National Institutes of Health (grant nos. 1P50GM115305-01, 1RO1A1103348-01, and 1P30AI110257-01A1), and the Australian Centre for HIV and Hepatitis Virology Research; receives royalties from UpToDate; has received consultancy fees from honoraria from Biocryst; has received consultancy fees from Aicuris; and is codirector of the company that has a patent for HLA-B* 57:01 testing for abacavir hypersensitivity reaction. The rest of the authors declare that they have no relevant conflicts of interest.

[a]Division of Allergology and Clinical Immunology, Department of Medicine, University of Cape Town, Cape Town, South Africa
[b]Division of Dermatology, Department of Medicine, University of Cape Town, Cape Town, South Africa
[c]Division of Infectious Diseases, Department of Medicine, University of Cape Town, Cape Town, South Africa
[d]Division of Allergy, Cincinnati Children's Hospital Medical Center, Department of Pediatrics, University of Cincinnati College of Medicine, Cincinnati, Ohio
[e]Department of Medicine, Vanderbilt University Medical Center, Nashville, Tenn
[f]Department of Pathology, Microbiology and Immunology, Vanderbilt University Medical Center, Nashville, Tenn
[g]Department of Pharmacology, Vanderbilt University School of Medicine, Nashville, Tenn
[h]Institute for Immunology & Infectious Diseases, Murdoch University, Murdoch, Western Australia, Australia

K.D.W., K.C.K., and E.J.P. are supported by the National Institutes of Health (grant no. 1P50GM115305-01). E.J.P. is additionally supported by the National Health & Medical Research Association, Australia (grant nos. 1R01AI103348-01 and 1P30AI110527-01A1), and the Australian Centre for HIV & Hepatitis Research (ACH2).

Conflicts of interest: S. Dlamini has received lecture fees from Pfizer South Africa and has received travel support from MSD South Africa and GILEAD. K. C. Konvinse has received research support from the National Institutes of Health (grant nos. 1P50GM115305-01 and T32GM007347). K. D. White has received research support from the National Institutes of Health (grant no. 1P50GM115305-01). E. J. Phillips has received research support from National Health & Medical Research Council (Australia), the National Institutes of Health (grant nos. 1P50GM115305-01, 1RO1A1103348-01, and 1P30AI110257-01A1), and the Australian Centre for HIV and Hepatitis Virology

Abbreviations used
ADR- Adverse drug reaction
AGEP- Acute generalized exanthematous pustulosis
HHV- Human herpes virus
IM-ADR- Immune-mediated adverse drug reaction
CADR- Cutaneous adverse drug reaction
PT- Patch testing
SCAR- Severe cutaneous adverse reaction
SJS- Stevens-Johnson syndrome
TEN- Toxic epidermal necrolysis
DRESS- Drug reaction, eosinophilia and systemic syndrome
SCORTEN- SCORe of Toxic Epidermal Necrosis
SS- Serum sickness
SSLR- Serum sickness-like reaction
TB- Tuberculosis
Treg- regulatory T

Most immune-mediated adverse drug reactions (IM-ADRs) involve the skin, and many have additional systemic features. Severe cutaneous adverse drug reactions (SCARs) are an uncommon, potentially life-threatening, and challenging subgroup of IM-ADRs with diverse clinical phenotypes, mechanisms, and offending drugs. T-cell—mediated immunopathology is central to these severe delayed reactions, but effector cells and cytokines differ by clinical phenotype. Strong HLA-gene associations have been elucidated for specific drug-SCAR IM-ADRs such as Stevens-Johnson syndrome/toxic epidermal necrolysis, although the mechanisms by which carriage of a specific HLA allele is necessary but not sufficient for the development of many IM-ADRs is still being defined. SCAR management is complicated by substantial short- and long-term morbidity/mortality and the potential need to treat ongoing comorbid disease with related medications. Multidisciplinary specialist teams at experienced units should care for patients. In the setting of SCAR, patient outcomes as well as preventive, diagnostic, treatment, and management approaches are often not generalizable, but rather context specific, driven by population HLA-genetics, the pharmacology and genetic risk factors of the implicated drug, severity of underlying comorbid disease necessitating ongoing treatments, and cost considerations. In this review, we update the basic and clinical science of SCAR diagnosis and management. © **2017 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2017;5:547-63)**

Key words: *Severe cutaneous adverse drug reactions; Immune-mediated adverse drug reactions; HLA; DRESS; SJS/TEN; T-cell*

Therapeutics is a cornerstone of modern medical practice. The US Federal Drug Agency has approved approximately 1450 new molecular entities, with 25 to 35 new molecular entities approved per year.[1] Adverse drug reactions (ADRs) to known and new agents are common, accounting for around 5% and 3% of adult medical and pediatric hospital admissions, respectively.[2,3] ADRs may result from "on-target" effects, predictable based on drug action (type A); in contrast, "off-target" ADRs (type B) are a heterogeneous group with varied clinical manifestations and underlying mechanism. Subspecialists such as hepatologists, allergists/clinical immunologists, and dermatologists are the usual disciplines that investigate and manage off-target ADRs, given the frequency of liver and cutaneous involvement as well as the proposed central role of immunopathology. Figure 1 illustrates how cutaneous, with and without systemic off-target, ADRs can occur through several mechanisms. In this review, we will discuss cutaneous adverse drug reactions (CADRs) with a special focus on severe cutaneous adverse drug reactions (SCARs), which are life-threatening T-cell—mediated off-target CADRs. SCARs include distinct clinical phenotypes with varied complex underlying immunological mechanisms. Clinicians managing patients presenting with possible SCARs face multiple challenges including a growing number of SCAR-causing drugs, continued reliance on case definitions in the absence of either accurate and/or well-standardized diagnostics/biomarkers, and no discriminatory or good prognostic markers to tailor treatment approaches or prevent drug cessation in less severe variants. We outline for practicing clinicians the existing basic and clinical science evidence base for the prevention, diagnosis, and management of severe cutaneous and systemic reactions to drugs.

EPIDEMIOLOGY

CADRs are common, and can be found listed among the side effects of almost all drugs. Non—life-threatening CADRs such as maculopapular exanthema/morbilliform eruptions, photodistributed drug eruptions, fixed drug eruption, and urticaria are frequent, with estimates between 0.3% and 8%, with antibiotics and nonsteroidal anti-inflammatory drugs being the commonest offenders.[6,7] In certain high-risk patient populations, such as persons living with HIV, CADRs have been reported to occur in up to 25% of patients receiving highly active antiretroviral therapy.[8,9] Clinicians need to be able to distinguish the distinct clinical phenotypes of the more severe reactions (detailed in the next section), with high morbidity and mortality, from this high background rate of CADRs.

Figure 2 highlights the estimated prevalence of major SCAR phenotypes in different continents, with the common offenders and regionally important drugs highlighted. The influence of population-specific HLA risk alleles is also shown for abacavir hypersensitivity (HLA-B*57:01), allopurinol drug reaction with eosinophilia and systemic symptoms (DRESS)/drug-induced hypersensitivity syndrome/hypersensitivity with systemic symptoms (HLA-B58*01), and carbamazepine Stevens-Johnson syndrome/toxic epidermal necrolysis (SJS/TEN) (HLA-B*15:02). Globally, SJS/TEN and DRESS are the 2 commonest SCAR clinical phenotypes, with a prevalence of between 1 and 7/million population and 1 and 4/10,000, respectively. SJS/TEN increases almost a 1000-fold to as high as 2/1000 among persons living with HIV.[10-20] Epidemiological data on acute generalized

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Received for publication October 24, 2016; revised January 11, 2017; accepted for publication January 18, 2017.

Corresponding author: Elizabeth J. Phillips, MD, FIDSA, FAAAAI, 1161 21st Ave South, A-2200, Vanderbilt University Medical Center, Nasvhille, TN 37232. E-mail: elizabeth.j.phillips@vanderbilt.edu.

* These authors contributed equally to this work.

2213-2198

http://dx.doi.org/10.1016/j.jaip.2017.01.025