



Severe cutaneous adverse reactions to drugs

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During the past decade, major advances have been made in the accurate diagnosis of severe cutaneous adverse reactions (SCARs) to drugs, management of their manifestations, and identification of their pathogenetic mechanisms and at-risk populations. Early recognition and diagnosis of SCARs are key in the identification of culprit drugs. SCARs are potentially life threatening, and associated with various clinical patterns and morbidity during the acute stage of Stevens-Johnson syndrome and toxic epidermal necrolysis, drug reactions with eosinophilia and systemic symptoms, and acute generalised exanthematous pustulosis. Early drug withdrawal is mandatory in all SCARs. Physicians' knowledge is essential to the improvement of diagnosis and management, and in the limitation and prevention of long-term sequelae. This Seminar provides the tools to help physicians in their clinical approach and investigations of SCARs.

Introduction

Severe cutaneous adverse reactions (SCARs) to drugs are associated with morbidity, mortality, health-care costs, and drug development challenges. SCARs to drugs cover a broad spectrum of entities mainly consisting of Stevens-Johnson syndrome and toxic epidermal necrolysis, and drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome.¹ Because of the extensive eruption or the possibility of systemic symptoms, physicians also consider acute generalised exanthematous pustulosis (AGEP) a SCAR. This Seminar focuses on these three main entities.

Despite their low annual incidence, SCARs, especially Stevens-Johnson syndrome, toxic epidermal necrolysis and DRESS syndrome, can be life threatening and responsible for severe, potentially chronic sequelae. The incidence of Stevens-Johnson syndrome and toxic epidermal necrolysis is estimated to be two per 1 million people, whereas the incidence of DRESS syndrome in new users of antiepileptic drugs (eg, carbamazepine or phenytoin) is estimated to be one per 1000 to one per 10 000.²

Although they are rare, physicians need to be able to recognise SCARs to enable early drug withdrawal and appropriate management.

Classification and diagnosis

SCAR classification tools and adequate identification of SCARs have been widely emphasised as being key to identification and assessment of the potential culprit drug (table 1).^{3–14} During the past decade, several retrospective validation scores have been developed by a European network of SCAR experts, such as EuroSCAR and RegiSCAR (appendix pp 1–2).^{9,12}

Stevens-Johnson syndrome and toxic epidermal necrolysis

Stevens-Johnson syndrome and toxic epidermal necrolysis are considered variants of epidermal necrolysis. They occur 4–28 days after drug exposure. Clinical classification is defined by the extent of body surface area with skin detachment—ie, Stevens-Johnson syndrome in cases of less than 10% skin detachment, toxic epidermal necrolysis in cases of 30% or greater, and Stevens-Johnson syndrome–

toxic epidermal necrolysis (SJS–TEN) for anything in between.³ In about 30% of cases of Stevens-Johnson syndrome and toxic epidermal necrolysis, no causative drug is identified,^{3,15} and in 15%, drug responsibility is deemed unlikely.¹⁶ *Mycoplasma pneumoniae* has been associated with Stevens-Johnson syndrome and toxic epidermal necrolysis, mainly in children.¹⁷ General physical deterioration, fever, influenza-like illness, ocular symptoms, ear, nose, and throat (ENT) events, and skin pain frequently precede dermatological manifestations, and are key in early diagnosis.¹⁸ Initially, the eruption is distributed on the face, upper trunk (appendix p 7), and proximal extremities,³ whereas distal portions of upper and lower limbs are relatively spared.³ Initial lesions are characterised as erythematous, irregularly shaped, dusky-red macules. Atypical target lesions with dark centres can often be observed without the typical three concentric

Search strategy and selection criteria

We searched PubMed for articles published between Jan 1, 1995, to Feb 25, 2017 (date of last search), with the terms “severe cutaneous adverse drug reactions”, “cutaneous adverse reactions”, “Stevens-Johnson syndrome”, “toxic epidermal necrolysis”, “Lyell syndrome”, “drug reaction with eosinophilia and systemic symptoms”, “hypersensitivity syndrome”, “DRESS syndrome”, “drug-induced hypersensitivity syndrome”, “acute generalized exanthematous pustulosis”, “AGEP”, and the specific terms used in the title of each section—eg, “classification”, “diagnosis”, “immune mechanism”, “genetic factors”, “HLA”, “management”, “treatment”, “outcome”, “sequelae”, and “drug causality”. Articles published in English were selected and reviewed by two of us (TAD and LV-A). Selection criteria were the novelty and importance of the studies or particularly relevant articles. Because of the rarity of severe cutaneous drug reactions (SCARs), we also selected some relevant case reports to illustrate this Seminar. We identified additional references among the references listed in review articles. To verify whether new drugs were suspected of being associated with SCARs, we assessed the websites of drug regulatory agencies—ie, US Food and Drug Administration and European Medicines Agency—to identify drugs under safety monitoring until March, 2017.

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See Online for appendix

	Drug-to-SCAR interval	General symptoms*	Skin features	Laboratory values	Main organs involved	Severity score	Score system for classification	Histological features
SJS and TEN ^{3,5}	4–28 days	Fever $\geq 38^{\circ}\text{C}$, influenza-like syndrome, respiratory tract symptoms	Blisters, large skin detachment, confluent erythema, atypical target lesions, purpura, Nikolsky's sign; skin detachment: Stevens-Johnson syndrome <10%, toxic epidermal necrolysis $\geq 30\%$, SJS-TEN 10–30%; two or more of mucous membranes involved	Lymphopenia, transitory neutropenia, mild cytolysis, renal impairment	Ear, nose, and throat, lung, intestinal tract, liver, kidney	SCORTEN [†]	No [‡]	Full-thickness epidermal necrosis, focal adnexal necrosis, necrotic keratinocytes, mild mononuclear cell dermal infiltrate, negative direct immunofluorescence test
DRESS syndrome ^{6–11}	2–6 weeks	Fever $\geq 38^{\circ}\text{C}$, influenza-like syndrome	Maculopapular rash, erythroderma, facial or extremity oedema, purpura, pustules, focal monopolar mucous-membrane involvement	Eosinophilia >700 cells per μL , atypical lymphocytes, elevated transaminase concentration, impaired renal function, herpesvirus family reactivation (HHV6, HHV7, EBV, CMV), parvovirus B19 reactivation	Liver, kidney, lung, muscle, heart, pancreas, medulla, lymph nodes at two or more sites	None	Yes	Lichenoid infiltrate or eczematous pattern (spongiosis, oedema), focal necrotic keratinocytes, mononuclear infiltrate, focal eosinophil and neutrophil infiltrates, mild vasculitis
AGEP ^{12,13}	1–11 days	Fever $\geq 38^{\circ}\text{C}$	Intertriginous erythema, oedema, widespread non-follicular sterile pustules, post-pustular pinpoint desquamation, Nikolsky's sign, rare oral mucous-membrane involvement	Hyperleukocytosis, neutrophils ≥ 7000 cells per μL , mild eosinophilia	Rare: liver, lung	None	Yes	Subcorneal or intraepidermal spongiform or non-spongiform pustules with or without papillary oedema, focal necrotic keratinocytes, neutrophilic sometimes with eosinophils, mild vasculitis

SCAR=severe cutaneous adverse reaction. SJS=Stevens-Johnson syndrome. TEN=toxic epidermal necrolysis. SCORTEN=SCORE of Toxic Epidermal Necrolysis. DRESS=drug reaction with eosinophilia and systemic symptoms. HHV=human herpesvirus. EBV=Epstein-Barr virus. CMV=cytomegalovirus. AGEP=acute generalised exanthematous pustulosis. *General symptoms can precede or occur at the same time as skin manifestations. †See appendix. ‡Not published.

Table 1: Main clinical and histological characteristics of SCARs

rings of erythema multiforme major (appendix pp 7–8).³ Necrotic lesion confluence leads to extensive erythema, flaccid blisters, and large epidermal sheets, revealing areas of red dermis (appendix p 9). Nikolsky's sign—when the epidermis sloughs off under lateral pressure—is positive on erythematous areas (appendix p 10).³ Two or more mucous membranes are involved in 80% of cases, often preceding skin lesions.³ Erythema, blisters, or erosions involve the nasopharynx, oropharynx, eyes, genitalia, or anus mucous membranes, and occur during the early stage associated with pain and dysfunction (appendix pp 11–12). The lips can develop a vermilion border, and greyish-white pseudomembranes coat oral-cavity haemorrhagic erosions, with crusts being the main lesions (appendix p 13). Conjunctival lesions, including hyperaemia, erosions, chemosis, photophobia, and tearing comprise eye involvement. Severe forms lead to corneal ulceration, anterior uveitis, or purulent conjunctivitis (table 1).¹⁹ Disease progression is time limited (7–10 days).

Visceral involvement associated with Stevens-Johnson syndrome and toxic epidermal necrolysis consists of transient liver or renal enzyme increases or bronchial and digestive tract epithelial necrosis.²⁰ Although rare, specific acute visceral failures in Stevens-Johnson syndrome and toxic epidermal necrolysis should be suspected and documented after eliminating bacterial or viral superinfection. No specific score or diagnostic test is available for the diagnosis of Stevens-Johnson syndrome and toxic epidermal necrolysis. The diagnosis mainly relies on

identification of a broad range of clinical signs and symptoms and histological tests (tables 1, 2). Full-thickness epidermal necrosis (appendix p 14)⁵ and a negative direct immunofluorescence test are mandatory for diagnosis. Differential diagnoses include erythema multiforme major, linear IgA bullous dermatosis (appendix p 15; spontaneous or drug-related), generalised fixed drug eruption (appendix p 16), superficial burns, cytotoxic drug (eg, methotrexate) toxicity, and acute graft-versus-host disease (table 2).^{3,21,22} Toxic epidermal necrolysis-like histological and clinical features were recently described with coxsackievirus A6 infection.²³ Full-thickness epidermal necrolysis associated with acute syndrome of apoptotic pan-epidermolysis with fulminant epidermal cleavage has also been reported in patients with a history of erythema multiforme or lupus erythematosus.²⁴ Diagnostic tests might easily rule out differential diagnoses (table 2).

DRESS syndrome

Since its description in 1996, the R of DRESS syndrome has changed from rash to reaction.⁶ It is also known as hypersensitivity syndrome or drug-induced hypersensitivity syndrome.²⁵ It usually begins 2–6 weeks after drug exposure. The difficulty in diagnosing DRESS syndrome is mainly due to its complex natural course and heterogeneous clinical presentation, involving visceral symptoms with or without dermatological involvement and biological abnormalities.^{9,10} The prodromal stage,

Suggested confirmation tests		Differential diagnosis	
		Clinical diagnosis	Tests
SJS and TEN	Histology	Erythema multiforme major, <i>Mycoplasma pneumoniae</i> infection*, coxsackievirus infection, linear IgA bullous dermatosis, generalised bullous fixed-drug eruption, methotrexate toxicity, graft-vs-host disease, staphylococcal skin scalded syndrome, systemic lupus erythematosus, pemphigus	<i>Mycoplasma pneumoniae</i> serology and PCR, coxsackievirus serology and PCR, direct and indirect immunofluorescence, anti-epidermal basement membrane zone and intercellular antibodies, methotrexate plasma concentration, antinuclear antibodies, anti-Ro-SSA antibodies
DRESS syndrome	Blood cell counts, liver enzyme tests, serum urea, creatininaemia, proteinuria, arterial oxygen saturation, blood gas, chest radiograph, CT scan, heart assessments (troponin I, electrocardiogram, echocardiography)	T-cell lymphoma, pseudolymphoma, viral rash	Sézary cells (ie, atypical T cells found in Sézary disease), cutaneous clonal T-cell rearrangements, viral serology
AGEP	Histology	Pustular psoriasis, cutaneous localisation of fungal or bacterial septicaemia, neutrophilic dermatosis, pustular vasculitis	Bacterial or fungal pustule analysis, blood cultures

SJS=Stevens-Johnson syndrome. TEN=toxic epidermal necrolysis. SSA=Sjögren's-syndrome-related antigen A. DRESS=drug reaction with eosinophilia and systemic symptoms. AGEP=acute generalised exanthematous pustulosis. **Mycoplasma pneumoniae* can trigger SJS and TEN, erythema multiforme, and a specific skin rash with mucosal erosions.

Table 2: Severe cutaneous adverse reactions: suggested confirmation tests and main differential diagnoses

including fever, lymphadenopathy, influenza-like symptoms, burning pain, or pruritus, can precede the skin eruption by up to 2 weeks.² Clinical dermatological symptoms consist of facial oedema, erythroderma, distal oedema, purpura, pustules, and sometimes focal mucosal involvement (table 1; appendix pp 17–18).⁹

DRESS syndrome-specific organ involvement results from specific eosinophil or lymphocyte tissue infiltration.² Liver involvement is observed in more than 80% of patients: mainly hepatic cytolysis, sometimes cholestasis, or both, and, rarely, fulminant hepatic failure.² Kidney involvement is characterised by interstitial nephritis.² The lungs are affected in up to 15% of cases, manifested by dyspnoea, cough, eosinophilic pneumonitis, and rare respiratory failure.² Heart involvement—ie, myocarditis and pericarditis—with electrocardiogram, CT scan, or cardiac enzyme abnormalities, can be fatal.² Poor prognoses are also associated with rare visceral effects that can be neurological, muscular, haemophagocytic, or pancreatic.²⁶ To reduce misdiagnosis, several investigations are recommended (table 2), such as those to identify blood abnormalities indicating visceral involvement, virus reactivation, hypereosinophilia, atypical lymphocytes, and hypogammaglobulinaemia during the acute stage.²⁶ As first hypothesised in 1994, DRESS syndrome can lead to reactivation of a single or multiple human herpesvirus (HHV) family members,^{7,8} with HHV6 being the most described. This HHV6 viral reactivation can be detected up to 2–3 weeks after DRESS syndrome onset. Reactivation of other herpesviruses (ie, Epstein-Barr virus [EBV], HHV7, cytomegalovirus) and parvovirus B19 has also been described, occurring in a sequential manner.⁸ Relapses of long duration might occur in the course of DRESS syndrome and are mainly described with the reactivation of HHV6.^{8,27} DRESS histological patterns are non-specific lichenoid or eczematous lesions (table 1; appendix p 19); inflammatory

infiltrate does not necessarily include eosinophils.¹¹ Two published scores contribute to the retrospective validation of DRESS syndrome diagnosis,^{9,10} and one¹⁰ systematically considers HHV6 reactivation (appendix p 1). Both enable the diagnosis of DRESS syndrome to be validated without the presence of cutaneous eruption, emphasising the potential to misdiagnose this syndrome and the necessity to consider it a multiorgan drug-induced reaction.

AGEP

AGEP is considered to be less severe than Stevens-Johnson syndrome, toxic epidermal necrolysis, and DRESS syndrome.²⁸ Its onset is 2–11 days after drug exposure (table 1).¹² Cutaneous symptoms develop simultaneously with high fever and numerous small, primarily non-follicular sterile pustules, arising on large areas of oedematous erythema (table 1; appendix pp 20–21), which can lead to erythroderma.^{12,29} The first involved sites are the major intertriginous zones (the armpits and groin), trunk, and upper extremities. During the early stage, pustule confluence can result in Nikolsky's sign, with superficial detachment, whereas only post-pustular desquamation is observed at the late stage.^{12,29} In less than 20% of cases, pustules or erosions develop on mucous membranes, usually oral.¹² Blood tests reveal elevated neutrophil counts in most patients and eosinophilia in more than a third.¹² AGEP-specific visceral disease—eg, hepatitis, nephritis, or pneumonitis—is rare but has been described; systematic investigations are recommended.^{12,29,30}

The histological findings in most AGEP cases are neutrophil infiltrates, of a spongiform or non-spongiform pattern, and subcorneal or intraepidermal pustules, with or without dermal oedema (appendix p 22).¹³ No significant association has been established between pustular psoriasis and AGEP. The histology of AGEP reveals larger eosinophil infiltrates, more necrotic

keratinocytes, and larger mixed dermal and interstitial infiltrates than in pustular psoriasis, and the absence of dilated blood vessels.^{13,28} For physicians, relapse of pustular eruption without drug re-challenge is the most reliable sign to reject a diagnosis of AGEP, even though authentic drug-induced and non-drug-induced pustulosis have been observed in specific patients with AGEP.^{13,31}

In the absence of specific tests, SCAR diagnosis mainly relies on the analysis of clinical and histological patterns (table 1). Despite some specific patterns, misclassification can still occur—eg, AGEP instead of toxic epidermal necrolysis, AGEP as an initial feature of DRESS syndrome—and even authentic SCARs can have clinical or histological features that overlap with each other—ie, DRESS syndrome with Stevens-Johnson syndrome and toxic epidermal necrolysis, AGEP with DRESS syndrome, and AGEP with Stevens-Johnson syndrome and toxic epidermal necrolysis.³²

Pathogenesis

The clinical heterogeneity of SCARs might be explained by the activation of different effector or regulatory cells secreting specific cytokines.^{33–35} SCARs are considered to be non-immediate hypersensitivity reactions with four proposed subgroups: IVa, mediated by type 1 T helper (Th1) T cells; IVb, mediated by Th2 T cells and interleukins 5, 4, and 13, and eotaxin cytokines (as occurs in DRESS syndrome); IVc, mediated by cytotoxic T cells (as occurs in Stevens-Johnson syndrome and toxic epidermal necrolysis); and IVd, mediated by T cells and neutrophils via chemokine (C-X-C motif) ligand 8 (CXCL-8) and granulocyte-macrophage colony-stimulating factor cytokines (as occurs in AGEP).³⁴

Several mechanistic models have been proposed to explain the recognition by T cells of small compounds (ie, drugs) and the ability of T cells to promote an immune response (figure 1).

In the hapten model, covalent bonds are established between drug molecules and autologous proteins or peptides, leading to a drug-specific humoral or cellular immune response. Haptens are chemically reactive small molecules that are able to bind covalently with larger proteins or peptides, initiating an immune response. By contrast, pro-haptens are not chemically reactive; they become chemically active compounds after being metabolised. An example of a hapten model is the penicillin hypersensitivity model, in which penicillin derivatives bind to serum albumin that then undergoes intracellular processing to generate chemically modified peptides that elicit an immune reaction.³⁶

Another mechanism involves the pharmacological interaction of drugs with immune receptors: the so-called p-i concept. The drug, in its native form or as a metabolite, binds directly and non-covalently to immune receptors such as T-cell receptors, or to specific HLA molecules (ie, MHC proteins), without a specific peptide ligand.³⁴ For example, in the carbamazepine-induced Stevens-Johnson

syndrome and toxic epidermal necrolysis model, carbamazepine directly binds to the protein encoded by the HLA-B*15:02 allele via a non-peptide processing pathway; this was demonstrated by showing that fixation of antigen-presenting cells could still elicit an immune reaction.³⁷ In the p-i model, the antigenic peptide-processing pathway in antigen-presenting cells is not necessary.

Lastly, a new physiopathological hypothesis has emerged, known as the altered peptide repertoire model. In this model, the drug binds non-covalently within the binding pocket of MHC, leading to alteration of both the chemistry of the binding cleft and the self-peptide repertoire. This new self-peptide presentation can lead to cytotoxic T-cell activation.^{38,39} For example, in the abacavir hypersensitivity model, abacavir alters the repertoire of self-peptides by triggering conformational changes in endogenous peptides presented by the protein encoded by the HLA-B*57:01 allele, resulting in the generation of a polyclonal T-cell response and induction of hypersensitivity reactions.³⁸ In this model, the offending drug does not directly interact with the HLA repertoire; rather, the peptides that change the binding cleft of the HLA repertoire, induced by the offending drug, are treated as foreign antigens by antigen-presenting cells and therefore elicit T-cell activation.

Genetic factors

Several genetic factors that cause a predisposition to SCARs have been previously reported—eg, metabolic enzyme mutations, or specific HLA-A, B, or C alleles (appendix p 3).^{40–49}

In AGEP, a mutation of the interleukin-36 receptor antagonist gene (*IL36RN*) was proposed to be a genetic factor in rare cases.⁵⁰ A strong (100%) association has been established between the HLA-B*15:02 allele and carbamazepine-triggered Stevens-Johnson syndrome and toxic epidermal necrolysis, and the HLA-B*58:01 allele and allopurinol-induced Stevens-Johnson syndrome and toxic epidermal necrolysis or DRESS syndrome.⁴² These associations were first identified in countries with a high prevalence of one specific allele and few ethnic groups (eg, Taiwan [Han Chinese]). European studies did not find such an association.⁴⁷ In patients with carbamazepine-induced SCARs, the HLA-A*31:01 allele was reported in patients of northern European ancestry and Japanese ancestry, but not in Taiwanese patients.⁴⁸ These results emphasise that various HLA alleles could be associated with a drug-specific clinical pattern, maybe owing to a similar distribution of key aminoacids at the binding sites (eg, as in carbamazepine-induced SCARs).³⁷ In carbamazepine-induced SCARs, a restricted T-cell receptor clonotype role has been suggested, since a T-cell receptor clonotype role has been associated with individuals with Stevens-Johnson syndrome or toxic epidermal necrolysis who are HLA-B*15:02 positive, whereas it is absent in all carbamazepine-tolerant HLA-B*15:02 carriers.⁵¹

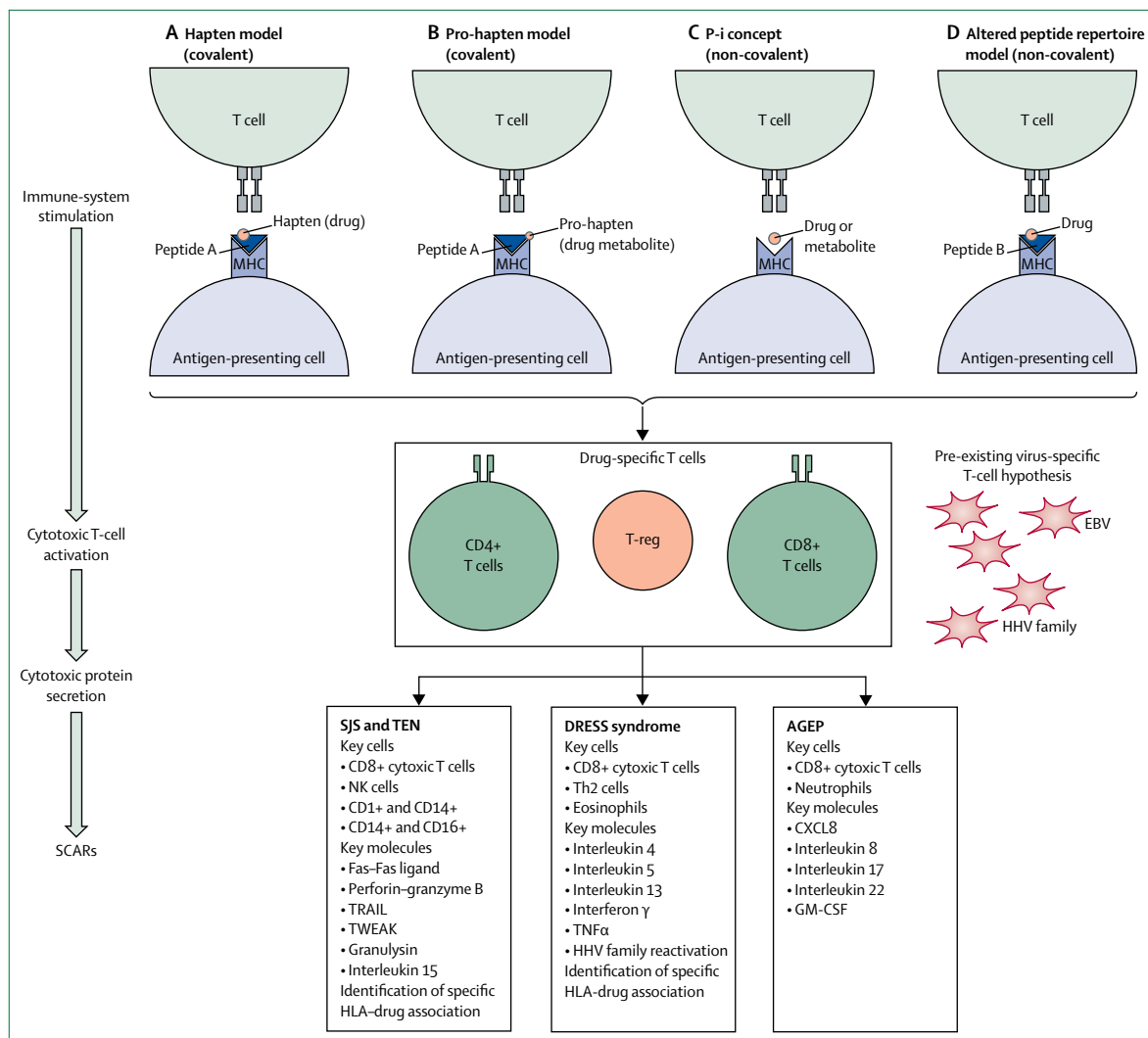


Figure 1: Immune mechanisms of SCARs

Schematic diagram showing the immune stimulation, cytotoxic T-cell activation, and key actors in the development of SCARs, adapted from Pichler and colleagues³⁴. In the hapten (A) and pro-hapten (B) models, the drug or its metabolite, respectively, binds covalently to a peptide carrier (peptide A) and is then presented by MHC proteins to the T-cell receptor (TCR). In the p-i concept (C), the drug or its metabolite interacts directly and non-covalently with the TCR or a peptide-loaded MHC protein. In the altered peptide repertoire model (D), the drug binds directly to the MHC binding pocket and alters its specificity, resulting in presentation of novel ligands (peptide B), leading to cytotoxic T-cell activation. Pre-existing virus-specific T cells might become reactivated during the drug-induced immune response (eg, HHV6, HHV-7, EBV, parvovirus B19). The key actors involved in drug-induced immune reactions leading to SJS or TEN, AGEP, and DRESS syndrome are shown at the bottom of the figure. AGEP=acute generalised exanthematous pustulosis. CXCL8=chemokine (C-X-C motif) ligand 8. DRESS=drug reaction with eosinophilia and systemic symptoms. EBV=Epstein-Barr virus. GM-CSF=granulocyte-macrophage colony-stimulating factor. NK=natural killer. p-i=pharmacological interaction. SCAR=severe cutaneous adverse reaction. SJS=Stevens-Johnson syndrome. TEN=toxic epidermal necrolysis. TRAIL=TNF-related apoptosis-inducing ligand. T-reg=regulatory T cell. TWEAK=TNF-related weak inducer of apoptosis.

In allopurinol-induced SCARs, studies have identified a specific T-cell receptor clonotype reacting to its metabolite oxypurinol in addition to the HLA-B*5801 allele.⁵²

HLA studies have identified various SCAR phenotypes with the same drug-HLA association (eg, allopurinol-induced Stevens-Johnson syndrome and toxic epidermal necrolysis or DRESS syndrome and HLA-B*58:01, and carbamazepine-induced Stevens-Johnson syndrome and toxic epidermal necrolysis or DRESS syndrome and HLA-B*15:02), and exclusive drug-HLA associations

with one phenotype—eg, dapsone hypersensitivity with the HLA-B*13:01 allele, or phenytoin-induced Stevens-Johnson syndrome and toxic epidermal necrolysis with the HLA-B*15:02 allele.⁴⁰

Adding to the complexity of the mechanism of SCARs, genome-wide association studies have identified a variant of the cytochrome P450 2C9 enzyme, known to reduce drug clearance, as being an important genetic factor in phenytoin-related SCARs,⁵³ and other studies⁵⁴ have identified an ABC transporter and proteasome pathway

mutation in non-drug-specific Stevens-Johnson syndrome and toxic epidermal necrolysis.

Immunological SCAR mechanisms

After drug stimulation via HLA-encoded MHC proteins, immune mechanisms of SCARs include the activation of drug-specific cytotoxic T cells, inflammatory cells, or regulatory T cells (T-regs) and the differential secretion of inflammatory cytokines.

In Stevens-Johnson syndrome and toxic epidermal necrolysis, drug-specific cytotoxic cells are probably not the sole effector mechanisms of epidermal necrolysis, and their effects might be amplified by massive production of death mediators, altered anti-apoptotic pathways in target cells, or defective negative regulation of drug-specific immune reactions.^{35,55} Inhibition of drug-specific cytotoxic cells by nucleic acid-based blocking agents has been shown.⁵⁶ Analysis of blister fluid from patients with Stevens-Johnson syndrome and toxic epidermal necrolysis first identified MHC-1-restricted cytotoxic T cells, some of which had natural killer (NK) cell markers.⁵⁵ This analysis also identified various proinflammatory and anti-inflammatory cytokines secreted by cytotoxic T cells, NK cells, keratinocytes, CD1a+CD14+ non-lymphoid dendritic cells, or CD14+CD16+ monocytes.^{55,57} Epidermal cell death results from necrosis and massive T-cell-mediated apoptosis via three described pathways: Fas–Fas ligand interaction, a perforin–granzyme B pathway, and a granulysin-induced pathway.^{58,59} Granulysin has been shown to be a major cytotoxic molecule responsible for extensive keratinocyte necrosis through cytotoxic or NK-cell-mediated cytotoxicity without direct cellular contact, whereas Fas–Fas ligand interaction had no detectable effect, and the perforin–granzyme B pathway only a minor one.⁵⁸ Increased concentrations of granulysin and interleukin 15 were significantly correlated with severity of Stevens-Johnson syndrome and toxic epidermal necrolysis, and interleukin 15 was significantly associated with mortality.⁶⁰ High expression of receptor-interacting protein kinase 3 (RIPK3) in a toxic epidermal necrolysis lesion has suggested that RIPK3 is an essential actor in the programmed death and necrosis of keratinocytes.⁶¹

Drug-specific T cells, activated in skin and internal organs, mediate DRESS syndrome, and recruitment of HHV6+ peripheral mononuclear cells to damaged skin is required for virus transmission and replication in CD4+ T cells.^{25,62} A high proportion of CD8+ T cells expressing granzyme B was detected in skin samples of patients with severe DRESS syndrome.¹¹ Involvement of viruses in DRESS syndrome—eg, when a viral disease is triggered through direct reactivation by the drug or a strong immune reaction (eg, graft-*vs*-host disease or organ transplantation)—was not found in *in-vitro* studies. In a study of patients with DRESS syndrome, circulating CD8+ T cells secreting tumour-necrosis factor (TNF) α and interferon γ were identified and nearly half of the activated circulating CD8+ T cells recognised HHV, whereas CD8+ T-cell visceral or

skin infiltrates mainly recognised EBV.⁶³ Culprit drugs could also trigger EBV replication via patients' EBV-transformed B lymphocytes.⁶³

In AGEP, the identification of dermal cytotoxic CD8+ T-cell infiltrates also suggests neutrophil recruitment and activation through drug-specific T cells via interleukin 8.⁶⁴ Increased circulating, interleukin-22-producing, Th17 cells stimulating keratinocyte secretion of interleukin 8 for neutrophil recruitment are reported in patients with AGEP.⁶⁴

To explain the broad phenotypic variability induced by the same drugs, researchers compared Stevens-Johnson syndrome and toxic epidermal necrolysis, DRESS syndrome, and non-SCAR cytokine profiles or levels with type and density of inflammatory cells.^{58,65} Concentrations of granulysin and Fas ligand in serum samples were suggested as predictive factors of phenotype severity and skin detachment in Stevens-Johnson syndrome and toxic epidermal necrolysis, but their clinical relevance needs further assessment.^{66,67} Patients with Stevens-Johnson syndrome or toxic epidermal necrolysis had significantly more proinflammatory cytokines (TNF α , interleukin 6, and interferon γ) and anti-inflammatory cytokines (interleukin 10 and interleukin-1-receptor antagonist) than patients with other cutaneous adverse reactions, including DRESS syndrome.⁶⁷ Analyses of immunoglobulin profiles, white blood cell subsets, and lymphocyte subsets also revealed significant differences between patients with Stevens-Johnson syndrome or toxic epidermal necrolysis and those with DRESS syndrome, suggesting the role of an underlying viral infection coinciding with drug exposure.⁶⁷ This concept of T-cell readiness to react suggests that drug reactions follow a type of non-drug-specific immune activation such as occurs in a viral infection.³⁴

T-reg functions during acute and chronic SCAR stages have also been thought to influence phenotype.⁶⁸ By comparison with healthy controls, T-reg frequency in early and late stages of Stevens-Johnson syndrome and toxic epidermal necrolysis did not differ, whereas non-T-reg cell frequency was increased upon resolution of Stevens-Johnson syndrome and toxic epidermal necrolysis.⁶⁸ In the acute stage of DRESS syndrome, functional T-regs were dramatically expanded, whereas they were profoundly diminished in Stevens-Johnson syndrome and toxic epidermal necrolysis.⁶⁹ By contrast, T-regs became functionally deficient upon resolution of DRESS syndrome, whereas their functionality was restored after Stevens-Johnson syndrome and toxic epidermal necrolysis.⁷⁰

Assessment of SCARs

Case assessment relies on the eruption's clinical appearance (eg, potentially virus-related or drug-related),⁷¹ how long the eruption has been present, associated symptoms (eg, fever, pruritus, lymphadenopathy), and the time elapsed between drug intake and SCAR onset.

Physical examination includes the description of the distribution of SCAR-specific lesions. Cutaneous or mucous membrane involvement in orifices, indicating a severe reaction (external or internal), must be specified. Photos and clinical signs should be collected as often as possible to enable retrospective expert validation of the SCAR. Skin biopsy, including direct immunofluorescence of blistering eruptions and biological tests to eliminate differential diagnoses, are strongly recommended (table 2).

If Stevens-Johnson syndrome, toxic epidermal necrolysis, or DRESS syndrome is confirmed, management by a referral centre or specialised intensive-care unit is strongly recommended.^{72,73} A diagnosis of Stevens-Johnson syndrome or toxic epidermal necrolysis within 7 days of onset is associated with improved survival compared with a more delayed diagnosis.⁷⁴ AGEP is usually a transient and benign reaction, but management by an experienced team is recommended if it mimics toxic epidermal necrolysis with extensive or severe visceral involvement.

Management and treatment

Principles of symptomatic treatment

SCAR-management strategies (table 3) are predominantly symptomatic, aimed at avoiding short-term morbidity and mortality and severe long-term sequelae.^{72,76,77}

For all patients, culprit-drug identification (appendix p 23) and its early withdrawal are the first mandatory steps (figure 2). For Stevens-Johnson syndrome and toxic epidermal necrolysis, early culprit-drug discontinuation is associated with better prognoses, and causative drugs with long half-lives are associated with an increased morbidity risk.⁷⁸

During the acute stage, SCARs can require intensive care because they can lead to multiorgan failure and fluid loss due to skin damage. Supportive care consists of restoration of haemodynamic equilibrium and prevention of life-threatening complications.⁷² Patients with epidermal detachment or erythroderma are exposed to increased fluid and protein loss, hypovolaemia, renal insufficiency, thermal dysregulation, and sepsis. Fluid replacement should be started as soon as possible and adjusted daily. The environmental temperature of the patient should be raised to 28°C. Nutritional hypercaloric and hyperproteic enteral feeding of patients with Stevens-Johnson syndrome and toxic epidermal necrolysis is systematically discussed and often initiated through a nasogastric tube.^{79,80} Peripheral venous lines are placed, when possible, in a region of uninvolved skin.

For Stevens-Johnson syndrome and toxic epidermal necrolysis, opioid agonists are used to limit the pain or stress inherent in mucosal or skin-debris removal,⁷² necessitating respiratory monitoring. Systematic invasive mechanical ventilation is unnecessary and is associated with high risk of in-hospital death.^{80,81} Anxiolytics can be prescribed for the prevention of post-traumatic stress disorder (PTSD). Antibiotic prophylaxis is not recommended, and the prescription of unnecessary or non-vital medications should be avoided.

Dermatological care

Wound care of patients with Stevens-Johnson syndrome or toxic epidermal necrolysis is done daily with antiseptic baths or diluted antiseptic spray. Skin injuries should be avoided to minimise epidermal detachment, so transportation and manipulation of the patient must

Treatment	Treatment		Acute-stage mortality	Outcome	Sequelae	Management after resolution
	Specific	Symptomatic				
SJS and TEN	Drug withdrawal, no RCT-validated curative treatment*	Supportive care strongly recommended, cutaneous and mucous membrane care, enteral feeding, fluid-loss treatment, analgesia, no systematic intubation, environmental temperature $\geq 28^{\circ}\text{C}$, anxiolytics	10–40%	Bacterial superinfection, visceral-specific involvement, lung failure	Dystrophic scars, hyperpigmentation, alopecia, nail loss, visual loss, synechiae, dry eye, symblepharon, dental agenesis, sialadenitis, tooth decay, genital synechiae, psychiatric disorders	Patch testing at month 6; follow-up† at least at month 2, month 6, month 12, and every year for 5 years; specialist consultations: dermatology, ophthalmology, ear, nose, and throat examination, gynaecology, psychiatry, pulmonology
DRESS	Drug withdrawal, no RCT-validated curative treatment‡; topical or systemic corticosteroids (or both) according to disease severity	Symptomatic, antipyretics	1–10%	Acute organ failure, virus reactivation, relapses	Autoimmune diseases, lupus, thyroiditis, diabetes, scleroderma	Patch testing at month 6; follow-up† at month 2, 3, 4, 5, 6, and 12, then annually
AGEP	Drug withdrawal, no RCT-validated curative treatment; topical or systemic corticosteroids (or both) according to disease severity	Symptomatic, antipyretics, no antibiotics	1%	Recovery	None described	Patch testing after 6 weeks

SCAR=severe cutaneous adverse reaction. SJS=Stevens-Johnson syndrome. TEN=toxic epidermal necrolysis. RCT=randomised controlled trial. DRESS=drug reaction with eosinophilia and systemic symptoms. AGEP=acute generalised exanthematous pustulosis. *Thalidomide increased mortality in an RCT that was stopped early; the benefits of intravenous immunoglobulins and systemic corticosteroids are still being debated; a single-arm trial⁷⁵ found some benefits of ciclosporin. †Follow-up is adapted to disease severity and sequelae, a multidisciplinary approach is mandatory for all cases of SJS and TEN and often necessary for DRESS syndrome. ‡Intravenous immunoglobulin had no benefit; the antiviral ganciclovir provided no clear benefit in case reports.

Table 3: SCAR management, outcomes, and main sequelae

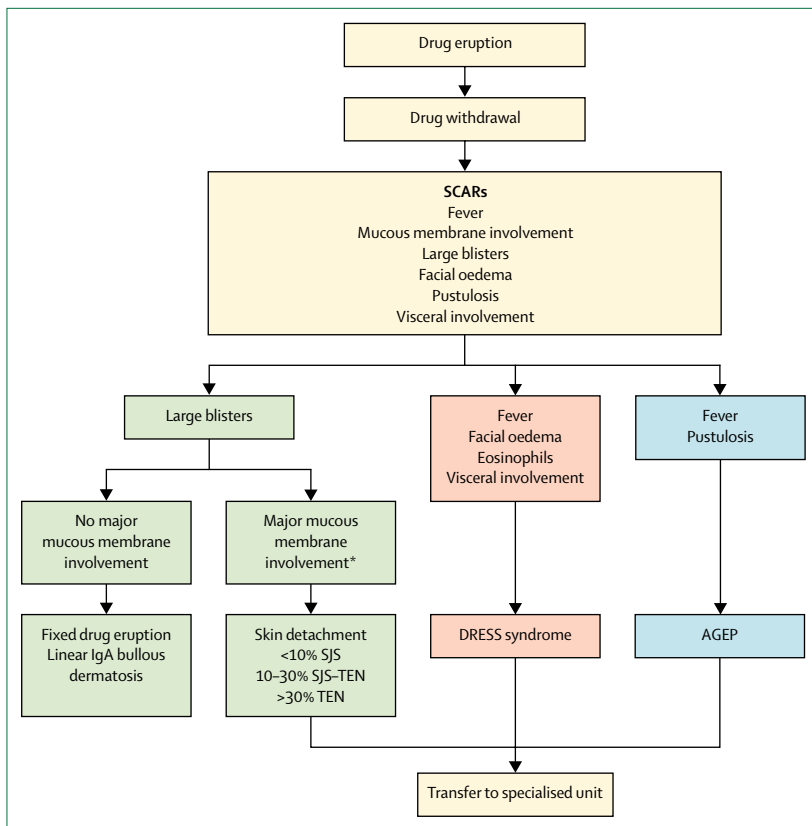


Figure 2: Decisional algorithm for SCARs

Clinical features leading to suspect a SCAR and decisional algorithm helping physicians to classify the SCAR at the first visit. AGEP=acute generalised exanthematous pustulosis. DRESS=drug reaction with eosinophilia and systemic symptoms. SCAR=severe cutaneous adverse reaction. SJS=Stevens-Johnson syndrome. TEN=toxic epidermal necrolysis. *Most patients with SJS or TEN have more than two affected mucous membranes.

be restricted, as should use of adhesive electrocardiogram electrodes. Petroleum jelly should be applied systematically to all areas of detached skin.⁷² Unlike burn management, large and aggressive skin debridement should be avoided, and might delay re-epithelialisation, because necrolytic epidermal sheets act as a natural biological dressing. Topical antimicrobial agents or sulfadiazine cream (containing antibacterial sulphonamides) are not recommended. When necessary, non-adhesive (eg, hydrocellular) dressings are used to cover pressure points, particularly on the back.^{76,82}

During the acute phase, ocular, oral, nasal, genital, or anal mucosa lubrications with emollient are recommended to reduce mucosal adhesion formation and functional sequelae.^{79,83} Mucosal bleeding or erosions are treated with topical analgesia, mouthwashes, application of swabs, local administration of adrenaline, and clotting agents.^{72,79} Ocular management relies on inflammatory debris removal with daily saline rinses, and, after topical anaesthesia, removal with a moist cotton bud or smooth blunt instrument. Prophylactic topical antibiotics, topical ciclosporin, or corticosteroids have been used, but were

shown to have no benefit in terms of ocular sequelae.⁸³ To protect and reduce conjunctival or corneal sequelae, amniotic membrane transplantation has been proposed to prevent eyelid scarring.⁸⁴

For DRESS syndrome and AGEP, dermatological care mainly relies on appropriate skin moisturisation.²⁹ When necessary, mucous-membrane management should be the same as that used for Stevens-Johnson syndrome and toxic epidermal necrolysis.

Targeted therapeutic approaches

In parallel with supportive care, therapeutic approaches for patients with Stevens-Johnson syndrome and toxic epidermal necrolysis are still being debated. Most of the information comes from case reports and small, uncontrolled series.^{85,86} The shortage of large randomised controlled trials (RCTs) comparing treatment strategies reflects the rarity of SCARs. Several immunosuppressants or immunomodulatory treatments (eg, corticosteroids,⁸⁷ cyclophosphamide,⁷⁹ calcineurin inhibitors,⁷⁵ anti-TNF therapies,⁸⁸ intravenous immunoglobulin [IVIg],^{89,90} or plasmapheresis) have had controversial results.

Systemic corticosteroids (eg, intravenous methylprednisolone) administered in pulses of 1–2 mg/kg up to 600–1000 mg per day were considered to be a treatment option for many years in some centres. In large case-control study,⁸⁷ which assessed the preventive effect of corticosteroids on Stevens-Johnson syndrome and toxic epidermal necrolysis, previous exposure to corticosteroids was associated with a longer disease progression—ie, 2.2 days (95% CI 1.1–3.2) longer—than no previous exposure, with no effect on disease severity or mortality.

IVIg as a treatment for Stevens-Johnson syndrome and toxic epidermal necrolysis has had varying results, some supporting their efficacy and others not.^{82,89–92} A meta-analysis of 17 studies yielded a 19.9% overall mortality rate in patients with toxic epidermal necrolysis given IVIg. The pooled odds ratio for mortality from six observational studies comparing IVIg with supportive care was 1.00 (95% CI 0.58–1.75; $p=0.99$), but IVIg dose (high vs low) did not correlate with mortality in a multivariate analysis.⁹¹ In a series of 82 patients with Stevens-Johnson syndrome or toxic epidermal necrolysis that compared corticosteroids with or without IVIg, complication or mortality rates did not significantly differ with the addition of IVIg, whereas hospital stays were significantly shorter for those receiving IVIg.⁹⁰ Furthermore, mortality did not significantly differ in patients receiving IVIg or corticosteroids in comparison with supportive care in a retrospective study.⁸⁵ In a prospective cohort study, no difference with regard to mortality was observed between IVIg and supportive care for patients with Stevens-Johnson syndrome or toxic epidermal necrolysis, suggesting that supportive care alone is optimal.⁸²

Ciclosporin, an anti-apoptotic agent, has also been proposed to inhibit CD8+ T cells, limiting disease

progression after a short-term administration of 3–10 mg/kg.⁷⁵ This potential benefit of ciclosporin on mortality of patients with Stevens-Johnson syndrome and toxic epidermal necrolysis, compared with IVIg, was also established in a single centre study of 71 patients.⁹³

In an uncontrolled series of ten patients with toxic epidermal necrolysis, a single dose of etanercept (an anti-TNF agent) was found to provide prompt healing (in a median of 8.5 days) without complications.⁸⁸ Granulocyte-macrophage colony-stimulating factor might be interesting to investigate further in future trials, because preliminary data⁹⁴ from two patients with toxic epidermal necrolysis suggest that it had an effect on re-epithelialisation via T-reg mobilisation, expansion of tolerogenic myeloid precursors, immature dendritic cell mobilisation, or enhanced cytolytic functions of NKT cells.

In our clinical experience, neither corticosteroids nor IVIg affect mortality,⁸⁹ whereas death occurs more frequently with thalidomide than placebo as shown in an RCT of patients with toxic epidermal necrolysis.⁹⁵ Oral ciclosporin (at decremental doses for 10 days) prevented skin-detachment progression in patients with Stevens-Johnson syndrome or toxic epidermal necrolysis;⁷⁵ only 38% of patients developed progressive disease, as opposed to 65% of those in the open-label IVIg trial.⁸⁹ No severe adverse events, relapse, or deaths occurred in the 29 patients who received oral ciclosporin,⁷⁵ even though the SCORe of Toxic Epidermal Necrolysis (SCORTEN) scale⁴—a prognosis score built on seven independent variables (appendix) that can determine a patient's mortality risk—predicted that three patients would die.⁷⁵

No RCTs have been done for DRESS syndrome or AGEP. Pulse or oral corticosteroids have been administered to patients with DRESS syndrome in retrospective series, but no standardised assessment of outcomes has been done.^{96,97} The role of high-dose corticosteroids in DRESS relapses has not been specifically analysed.^{8,97} The use of corticosteroids in patients with DRESS syndrome enhances cytomegalovirus and HHV6 viral load, but not EBV.²⁷ Despite virus reactivation, antiviral therapy (eg, with ganciclovir) should not be used currently because of both poor demonstrated efficacy in this syndrome and toxic effects.²⁶ IVIg, which has been used to treat patients with DRESS syndrome, has antiviral and immunomodulatory properties, affecting the innate and adaptive immune system.⁹⁸ In a prematurely stopped prospective study,⁹⁸ six patients with severe DRESS syndrome were given IVIg, but three had severe malaise, one had pulmonary embolism, and four required rescue oral corticosteroid treatment. In our retrospective study on the therapeutic management of DRESS syndrome,⁹⁹ patients treated with topical corticosteroids had fewer relapses than those treated with systemic steroids, but this result might be overestimated by the higher severity of DRESS syndrome in patients who received systemic steroids.⁹⁹ An RCT comparing superpotent topical corticosteroids with systemic

corticosteroids in patients with mild-to-moderate DRESS syndrome is ongoing (NCT01987076).

To limit AGEP progression, drug withdrawal might be sufficient, and topical steroids appeared to be favourable in patients with AGEP and visceral involvement, without requiring systemic corticosteroids, in a retrospective study.³⁰ As in mild-to-moderate DRESS syndrome, potent or superpotent topical corticosteroids—eg, clobetasol propionate 30 g per day—are widely used for patients with AGEP, although their efficacy has not yet been assessed in an RCT.^{99,100}

Outcome and sequelae

SCARs—mainly Stevens-Johnson syndrome, toxic epidermal necrolysis, and DRESS syndrome—are life threatening and carry a non-negligible risk of severe sequelae (table 3). During the acute stages of Stevens-Johnson syndrome and toxic epidermal necrolysis, visceral involvement (eg, renal failure, intestinal, ocular-specific pulmonary lesions, or sepsis) is the main complication.^{20,79} Respiratory insufficiency in patients with SCARs can result from direct effects of the SCAR on the organs or inhalation of foreign substances leading to superinfection, and pulmonary infection is significantly associated with severe laryngeal lesions caused by Stevens-Johnson syndrome or toxic epidermal necrolysis.¹⁸ During the acute stage, impaired skin barrier function or translocation of gut bacteria might facilitate bacterial colonisation and bloodstream infections.¹⁰¹ Sepsis is the predominant cause of death attributed to Stevens-Johnson syndrome and toxic epidermal necrolysis.^{79,85} In a study of pregnant women with acute-stage Stevens-Johnson syndrome or toxic epidermal necrolysis, caesarean was the delivery method in 50% of patients; no maternal deaths occurred but fetal outcomes were poor.¹⁰²

Acute-stage mortality ranges from at least 10% for Stevens-Johnson syndrome to around 40% for toxic epidermal necrolysis, with overall in-hospital mortality of 22% in Europe for both conditions.^{82,85} Increased mortality is described in patients with malignancies who develop Stevens-Johnson syndrome or toxic epidermal necrolysis, and several factors contribute to poor prognosis in this population: malnutrition, cancer type, and chemotherapy type.¹⁰³ SCORTEN successfully predicts 3-day mortality and the individual risk of death for patients with Stevens-Johnson syndrome and toxic epidermal necrolysis when assessed at admission to hospital.^{4,82,104} A five-point auxiliary score that does not require laboratory data has also been devised, and might be useful to predict severity of illness in retrospective settings when laboratory data are missing.¹⁰⁵ At 1 year, overall mortality in patients with Stevens-Johnson syndrome or toxic epidermal necrolysis remains high at 34% (95% CI 30–39; 24% [18–29] for Stevens-Johnson syndrome and 49% [36–60] for toxic epidermal necrolysis).⁸⁶

Re-epithelialisation of lesions in patients with Stevens-Johnson syndrome or toxic epidermal necrolysis

usually begins 1 week after disease onset and lasts up to 3 weeks.⁷⁹ After patients with Stevens-Johnson syndrome or toxic epidermal necrolysis go into remission, sequelae, including cutaneous (appendix p 24), ocular (appendix p 25), pulmonary, buccal (appendix pp 26–27), dental, and genital lesions, and psychiatric disorders (eg, PTSD), can occur.^{19,106–108} Routine screening for sequelae is imperative to limit or reduce their burden or impact on quality of life. Cutaneous sequelae (eg, hyperchromic macules, photosensitivity, telogen effluvium, nail loss, vaginal adhesion bands) and ocular sequelae (eg, photophobia and chronic tearing, eyelid malposition, and punctate keratitis) are the most frequent.¹⁰⁸ Regarding mucous membrane sequelae, in our experience their severity is not related to cutaneous disease severity at the acute stage. During the chronic stage, up to 65% of patients develop late ocular complications—eg, dry eyes or synechial visual loss.¹⁹ In a retrospective study that assessed outcomes 15 months after discharge, acute-stage ocular severity was significantly associated with late complications.¹⁹ Management of ocular sequelae involves treatment for dry eye, cornea inflammation, and refractory ocular disease. To rehabilitate visual function, scleral lenses were successfully used, and minor salivary gland or mucous-membrane grafts have been tested to treat symblepharon and dry eyes.^{109,110} Saliva acidity associated with Stevens-Johnson syndrome or toxic epidermal necrolysis can cause chronic sialadenitis, tooth decay, and dental atrophy.¹⁰⁷ Male genital synechiae requiring circumcision are often observed,¹¹¹ whereas strictures of vaginal mucosa or birth-canal stenosis can complicate spontaneous vaginal delivery and normal sexual intercourse.

With regard to DRESS syndrome, acute-stage mortality ranges from 5% to 10%^{2,6,96} and is mainly attributed to specific myocardial or pulmonary lesions, and haemophagocytosis.²⁶ In a cohort study,¹¹² the overall cumulative incidence of long-term DRESS sequelae was 11.5%, and mainly consisted of autoimmune diseases.¹¹² If PTSD, anxiety, or depression are reported at a late stage or after remission of DRESS, systematic psychological or psychiatric screening is likely to be needed.¹¹³ Although increased anti-HHV6 IgG and anti-HHV6 DNA titres were associated with severity and prolonged duration of DRESS syndrome, the role of virus reactivation in the natural chronic course of DRESS and in relapses remains hypothetical.^{8,114} Chronic virus activation is suspected of triggering excessive autoimmune responses and inducing autoimmune diseases, such as scleroderma, lupus erythematosus, diabetes, or thyroiditis arising after DRESS remission.^{115,116} Corticosteroids were shown to limit autoimmune diseases in patients with DRESS syndrome assessed retrospectively.¹¹⁶

AGEP has a good prognosis and no described sequelae.

Medication risk and drug causality

When assessing drug causality in a patient with a SCAR, several factors should be taken into consideration: SCAR

type, day of symptom onset, drug notoriety, and time since drug intake. The interval between exposure and SCAR onset differs according to the type of SCAR; generally, it is short for AGEP, intermediate for Stevens-Johnson syndrome and toxic epidermal necrolysis, and long for DRESS syndrome. For each SCAR, determining the first day of symptoms (index day) is the first step towards identifying a potential causative agent and withdrawing it to assess its role in causing the SCAR prodrome (appendix p 23). Additionally, a drug stopped before disease onset should still be suspected if it has a long half-life. To date, the French pharmacovigilance causality score test¹¹⁷ or the Naranjo algorithm¹¹⁸ have been the most frequently used worldwide to identify culprit drugs. Additionally, ALDEN (ALgorithm for Drug causality in Epidermal Necrolysis)¹⁶ has been validated to improve individual assessment of a suspected drug's role in Stevens-Johnson syndrome and toxic epidermal necrolysis. This specific algorithm, the scores of which strongly correlated with those in the EuroSCAR case-control study for drugs associated with epidermal necrolysis,¹⁶ uses time since drug intake, pharmacokinetics, rechallenge or dechallenge, and drug notoriety to classify drug causality as very unlikely, unlikely, possible, probable, or very probable.

For each phenotype—Stevens-Johnson syndrome, toxic epidermal necrolysis, DRESS syndrome, and AGEP—a few drugs are strongly associated with most cases. European case-control studies on SCAR cases yielded a list of potential high-risk drugs;^{28,119} the main ones are listed in the appendix (pp 5–6).^{2,15,28,96,97,112,116,119–125} Even though the prevalence of non-drug-induced Stevens-Johnson syndrome and toxic epidermal necrolysis is higher in children than in adults, high-risk drugs identified for children were the same as for adults—eg, antibacterial sulphonamides, carbamazepine, phenobarbital, and phenytoin—and no risk has been identified for any vaccines.^{122,123} Paracetamol's inclusion in the list of culprit drugs might be linked to confounding comedication, because it is prescribed for influenza-like syndromes during the early stage of Stevens-Johnson syndrome and toxic epidermal necrolysis.¹²² Drug regulatory agencies also frequently publish alerts for drugs undergoing safety monitoring for the risk of SCARs (appendix pp 5–6). Taken together, acute-stage management, hospital stays, and chronic sequelae care mean that the cost of Stevens-Johnson syndrome and toxic epidermal necrolysis is high; therefore, benefit–risk analysis is warranted for high-risk drugs. For idiopathic Stevens-Johnson syndrome or toxic epidermal necrolysis with no identified culprit drug, drugs in food (eg, phenylbutazone in meat) have been suggested to be a cause. This hypothesis was not confirmed by the concentration of phenylbutazone or its metabolites in plasma in patients with idiopathic or drug-induced Stevens-Johnson syndrome and toxic epidermal necrolysis.¹²⁶

Known risk factors associated with SCARs are HIV infection, specific HLA allele and drug combinations, and systemic lupus erythematosus.^{120,127} The strength of the

HIV association might be affected by the severity of the patient's immunodeficiency or the use of drugs that are high risk for SCARs (eg, co-trimoxazole or abacavir) in this population,^{119,128} even though for nevirapine, hypersensitivity predominated in non-HIV-infected patients with high CD4+ counts who were given nevirapine as a prophylactic treatment after HIV exposure.¹²⁰ For abacavir, in-vitro T-cell reactivity can also occur in drug-naive individuals with the HLA-B*57:01 allele.¹²⁹ Supported by the results of extensive HLA-B*15:02 screening in Taiwanese neurology clinics, the US Food and Drug Administration recommends genetic testing before prescribing carbamazepine to patients of Asian ancestry from China and southeast Asia.¹³⁰ HLA screening is thus only relevant to avoid SCARs caused by a few drugs in specific populations.^{42,131}

Relapsing SCARs are mainly a result of re-exposure to the same high-risk medications as caused the initial SCAR, but incomplete relapse of DRESS syndrome has been reported by Picard and colleagues¹³² following the administration of drugs not previously taken by the patient. These authors hypothesised that a persistent immune stimulation or viral reactivation was responsible for minor DRESS relapses with drugs that were chemically unrelated to the initial causative agent.¹³² For Stevens-Johnson syndrome and toxic epidermal necrolysis, individual susceptibility was postulated to explain a recurrence risk of 7% after a first episode in a cohort of 708 patients.¹³³ This recurrence risk is overestimated by misclassification of Stevens-Johnson syndrome and toxic epidermal necrolysis, and recurrence solely occurs with causative or relative drugs.¹³⁴ Nevertheless, there is no particular recommendation about the prescription of other potential high-risk drugs to a patient with a history of SCARs.⁷² Because relapse can be worse than the initial reaction, and sometimes even fatal, we recommend that patients who have had a SCAR carry an allergy card stating the culprit drug and medication contraindications (including generic and proprietary names of drugs), so that physicians can avoid giving them potential causative drugs, drugs of same structure, and members of the same family of molecules, but not necessarily the entire therapeutic group.

Culprit-drug tests

Methods to link a particular drug to a SCAR are scarce, with no standardised strategy, and none is associated with a 100% negative predictive value. To confirm a potential culprit drug, HLA screening might be useful when a strong association between the suspected drug and a particular HLA allele exists. None of the current tests has sufficient sensitivity and specificity to rule out a potential culprit drug when negative, enabling its rechallenge.⁴⁴

Routine assessment to identify the culprit drug includes establishing the chronology of drug intake and patch testing if several drugs have been taken. Thus far, no standardised protocol of drug quantity or vehicle has

been established for patch testing, but is frequently 10% of native drug in petrolatum.¹³⁵ The allergen-containing patch is usually taped onto the patient's back for 2 days and then assessed at a minimum of 48 h and 96 h. Patch test specificity and sensitivity vary according to the suspected drug and the SCAR subtype (higher sensitivity for AGEP than for Stevens-Johnson syndrome, toxic epidermal necrolysis, and DRESS).¹³⁵ Patch tests are reportedly safe, with few reported relapses or severe reactions. Neither prick nor intradermal tests are recommended, despite the intradermal test having higher sensitivity than the prick test, and an oral drug provocation test is definitely prohibited because of the risk of relapse.¹³⁵ In our experience of DRESS syndrome, tests are done 6 months after the acute stage to avoid relapse.

In-vitro tests can be used to measure peripheral blood mononuclear cell activity in patients with SCARs, with the culprit drug displaying pharmacological activity. For hypersensitivity reactions, two methods to identify the culprit drug have been described: the lymphocyte-transformation test (LTT) and enzyme-linked immunospot assay (ELISPOT). LTT is usually done 1 month after the reaction (5–8 weeks after DRESS onset, and within 1 month of onset of Stevens-Johnson syndrome and toxic epidermal necrolysis), whereas ELISPOT can be done at an earlier stage after SCAR onset.^{136,137} Neither are done routinely. Although LTT shows promise as a culprit-drug test in patients with DRESS syndrome or AGEP, it has low relevance in Stevens-Johnson syndrome and toxic epidermal necrolysis, even after enhancement of its sensitivity after removal of T-reg CD25+ cells.^{136,137} ELISPOT has a higher sensitivity (82%) than LTT (50%), and detects drug-specific T cells or identifies the culprit drug via drug-specific interferon γ , interleukin 4, or granulysin production.¹³⁸ In patients with Stevens-Johnson syndrome or toxic epidermal necrolysis, the combination of the LTT and ELISPOT, detecting granulysin, granzyme B, and cytokines, have been proposed.¹³⁹

Public health and drug-policy issues

At the population level, the avoidance of SCARs should be considered a high-priority public health and drug policy. A specific focus should be accorded to the following approaches: pharmacogenetic tests to select patients at risk for SCARs in specific subpopulations (table 3); epidemiological studies; pharmacovigilance, including systematic reporting of culprit drugs (including a precise assessment of a drug's harm potential and benefit–risk ratio) by practitioners to health authorities, drug companies, or independent registries (eg, RegiSCAR); consumer self-reporting of drugs eliciting severe or prevalent cutaneous adverse reactions;⁷¹ improvement of drug dictionaries, particularly with regard to the description of drugs associated with Stevens-Johnson syndrome and toxic epidermal necrolysis;¹⁴⁰ organisation of experts and referral centres to improve SCAR

For more on RegiSCAR see <http://www.regiscar.org>

For more on Amalyste see
<http://www.amalyste.fr>

management and outcomes; recording of patients' viewpoints and encouraging the use of patient associations such as Amalyste, which have contributed to improving patients', health-care providers', and decision makers' knowledge of outcomes and sequelae associated with Stevens-Johnson syndrome and toxic epidermal necrolysis; and establishment of specific funds to financially compensate patients with SCARs and improvement of patients' awareness of these funds.¹⁴¹

For a potentially high-risk drug, several decisions should be considered: (1) withdrawal from the market (eg, chlormezanone was recommended for withdrawal by the European Medicines Agency in 1997 due to its unfavourable benefit–risk relationship); (2) restriction of its use (eg, since June, 2012, minocycline is no longer recommended in France for acne and rosacea but is still allowed to be marketed for other indications);¹⁴² (3) changes to the prescription (eg, lamotrigine should be initially given at a low dose and then progressively increased to avoid skin reactions);¹⁴³ and (4) establishment of a safer alternative agent as first-line therapy (eg, prescription of an isoxazolyl penicillin such as cloxacillin instead of high-risk co-trimoxazole first for severe methicillin-resistant *Staphylococcus aureus* infection, especially in countries with non-community-acquired strains).¹⁴⁴ However, these approaches might not be suitable for some high-risk drugs such as allopurinol, which is widely prescribed. Fewer SCARs would be expected if allopurinol was prescribed only according to its accepted use or guidelines—ie, for gout and kidney stones rather than for asymptomatic hyperuricaemia accompanied by renal or cardiovascular disease, for example, for which an increased risk of hypersensitivity reaction was noted.¹³¹

Conclusions

We highlight the difficulty and necessity of early and accurate SCAR diagnosis (figure 2). The expertise of the treating physician is vital in the early diagnosis and specific management of SCARs to prevent or limit long-term sequelae. Physicians should be aware of the potential role of high-risk medication in triggering SCARs, especially when predisposing factors are present.

Contributors

All authors contributed equally to the literature search, analysis, manuscript writing, and critical revision of this Seminar.

Declaration of interests

LV-A has received personal fees from Janssen Cilag for a booklet on cutaneous adverse reactions to telaprevir and educational presentations, Cephalon for review of phosphogluconol in cutaneous adverse reactions, Pinnacle Biologics for expertise regarding cutaneous reactions to amifostine, Boehringer Ingelheim for expert consultancy on severe cutaneous adverse reactions, and Pierre Fabre for educational presentations. PW is a principal investigator of a clinical trial (NCT01412892) on neurofibromatosis funded by Novartis and has received personal fees from Pierre Fabre and Expanscience for his expertise on isotretinoin for acne. OC has received personal fees from Roche for a trial assessing the preventive role of doxycycline in cutaneous-related anti-EGFR toxicities, and Jansen Cilag for a meeting dedicated to the Centocor registry for ustekinumab side-effects, as

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References

- Roujeau JC, Stern RS. Severe adverse cutaneous reactions to drugs. *N Engl J Med* 1994; **331**: 1272–85.
- Kardaun SH, Sekula P, Valeyrie-Allanore L, et al. Drug reaction with eosinophilia and systemic symptoms (DRESS): an original multisystem adverse drug reaction. Results from the prospective RegiSCAR study. *Br J Dermatol* 2013; **169**: 1071–80.
- Auquier-Dunant A, Mockenhaupt M, Naldi L, Correia O, Schröder W, Roujeau J-C. Correlations between clinical patterns and causes of erythema multiforme majus, Stevens-Johnson syndrome, and toxic epidermal necrolysis: results of an international prospective study. *Arch Dermatol* 2002; **138**: 1019–24.
- Bastuji-Garin S, Fouchard N, Bertocchi M, Roujeau JC, Revuz J, Wolkenstein P. SCORTEN: a severity-of-illness score for toxic epidermal necrolysis. *J Invest Dermatol* 2000; **115**: 149–53.
- Valeyrie-Allanore L, Bastuji-Garin S, Guégan S, et al. Prognostic value of histologic features of toxic epidermal necrolysis. *J Am Acad Dermatol* 2013; **68**: e29–35.
- Bocquet H, Bagot M, Roujeau JC. Drug-induced pseudolymphoma and drug hypersensitivity syndrome (Drug Rash with Eosinophilia and Systemic Symptoms: DRESS). *Semin Cutan Med Surg* 1996; **15**: 250–57.
- Descamps V, Valance A, Edlinger C, et al. Association of human herpesvirus 6 infection with drug reaction with eosinophilia and systemic symptoms. *Arch Dermatol* 2001; **137**: 301–04.
- Kano Y, Hirahara K, Sakuma K, Shiohara T. Several herpesviruses can reactivate in a severe drug-induced multiorgan reaction in the same sequential order as in graft-versus-host disease. *Br J Dermatol* 2006; **155**: 301–06.
- Kardaun SH, Sidoroff A, Valeyrie-Allanore L, et al. Variability in the clinical pattern of cutaneous side-effects of drugs with systemic symptoms: does a DRESS syndrome really exist? *Br J Dermatol* 2007; **156**: 609–11.
- Shiohara T, Iijima M, Ikezawa Z, Hashimoto K. The diagnosis of a DRESS syndrome has been sufficiently established on the basis of typical clinical features and viral reactivations. *Br J Dermatol* 2007; **156**: 1083–84.
- Ortonne N, Valeyrie-Allanore L, Bastuji-Garin S, et al. Histopathology of drug rash with eosinophilia and systemic symptoms syndrome: a morphological and phenotypical study. *Br J Dermatol* 2015; **173**: 50–58.
- Sidoroff A, Halevy S, Bavinck JN, Vaillant L, Roujeau JC. Acute generalized exanthematous pustulosis (AGEP)—a clinical reaction pattern. *J Cutan Pathol* 2001; **28**: 113–19.
- Kardaun SH, Kuiper H, Fidler V, Jonkman MF. The histopathological spectrum of acute generalized exanthematous pustulosis (AGEP) and its differentiation from generalized pustular psoriasis. *J Cutan Pathol* 2010; **37**: 1220–29.
- Pirmohamed M, Aithal GP, Behr E, Daly A, Roden D. The phenotype standardization project: improving pharmacogenetic studies of serious adverse drug reactions. *Clin Pharmacol Ther* 2011; **89**: 784–85.
- Roujeau JC, Kelly JP, Naldi L, et al. Medication use and the risk of Stevens-Johnson syndrome or toxic epidermal necrolysis. *N Engl J Med* 1995; **333**: 1600–07.

- 16 Sassolas B, Haddad C, Mockenhaupt M, et al. ALDEN, an algorithm for assessment of drug causality in Stevens-Johnson Syndrome and toxic epidermal necrolysis: comparison with case-control analysis. *Clin Pharmacol Ther* 2010; **88**: 60–68.
- 17 Tomaino J, Keegan T, Miloh T, et al. Stevens-Johnson syndrome after *Mycoplasma pneumoniae* infection in pediatric post-liver transplant recipient: case report and review of the literature. *Pediatr Transplant* 2012; **16**: E74–77.
- 18 Bequignon E, Duong TA, Sbidian E, et al. Stevens-Johnson syndrome and toxic epidermal necrolysis: ear, nose, and throat description at acute stage and after remission. *JAMA Dermatol* 2015; **151**: 302–07.
- 19 Gueudry J, Roujeau J-C, Binaghi M, Soubrane G, Muraine M. Risk factors for the development of ocular complications of Stevens-Johnson syndrome and toxic epidermal necrolysis. *Arch Dermatol* 2009; **145**: 157–62.
- 20 Lebargy F, Wolkenstein P, Gisselbrecht M, et al. Pulmonary complications in toxic epidermal necrolysis: a prospective clinical study. *Intensive Care Med* 1997; **23**: 1237–44.
- 21 Chanal J, Ingen-Housz-Oro S, Ortonne N, et al. Linear IgA bullous dermatosis: comparison between the drug-induced and spontaneous forms. *Br J Dermatol* 2013; **169**: 1041–48.
- 22 Cho YT, Lin JW, Chen YC, et al. Generalized bullous fixed drug eruption is distinct from Stevens-Johnson syndrome/toxic epidermal necrolysis by immunohistopathological features. *J Am Acad Dermatol* 2014; **70**: 539–48.
- 23 Chung WH, Shih SR, Chang CF, et al. Clinicopathologic analysis of coxsackievirus a6 new variant induced widespread mucocutaneous bullous reactions mimicking severe cutaneous adverse reactions. *J Infect Dis* 2013; **208**: 1968–78.
- 24 Klimas NK, Dominguez AR, Vandergriff TW. Bullae and atypical target lesions in a young woman. *JAMA Dermatol* 2016; published online Dec 21, 2016. DOI:10.1001/jamadermatol.2016.4809.
- 25 Shiohara T, Inaoka M, Kano Y. Drug-induced hypersensitivity syndrome (DIHS): a reaction induced by a complex interplay among herpesviruses and antiviral and antidrug immune responses. *Allergol Int* 2006; **55**: 1–8.
- 26 Eshki M, Allanore L, Musette P, et al. Twelve-year analysis of severe cases of drug reaction with eosinophilia and systemic symptoms: a cause of unpredictable multiorgan failure. *Arch Dermatol* 2009; **145**: 67–72.
- 27 Ishida T, Kano Y, Mizukawa Y, Shiohara T. The dynamics of herpesvirus reactivations during and after severe drug eruptions: their relation to the clinical phenotype and therapeutic outcome. *Allergy* 2014; **69**: 798–805.
- 28 Sidoroff A, Dunant A, Viboud C, et al. Risk factors for acute generalized exanthematous pustulosis (AGEP)-results of a multinational case-control study (EuroSCAR). *Br J Dermatol* 2007; **157**: 989–96.
- 29 Choi MJ, Kim HS, Park HJ, et al. Clinicopathologic manifestations of 36 Korean patients with acute generalized exanthematous pustulosis: a case series and review of the literature. *Ann Dermatol* 2010; **22**: 163–69.
- 30 Hotz C, Valeyrie-Allanore L, Bouvresse S, et al. Systemic involvement in acute generalized exanthematous pustulosis: a retrospective study of 58 cases. *Br J Dermatol* 2013; **169**: 1223–32.
- 31 Navarini AA, Simpson MA, Borradori L, Yawalkar N, Schlapbach C. Homozygous missense mutation in IL36RN in generalized pustular dermatosis with intraoral involvement compatible with both AGEP and generalized pustular psoriasis. *JAMA Dermatol* 2015; **151**: 452–53.
- 32 Bouvresse S, Valeyrie-Allanore L, Ortonne N, et al. Toxic epidermal necrolysis, DRESS, AGEP: do overlap cases exist? *Orphanet J Rare Dis* 2012; **7**: 72.
- 33 Morel E, Alvarez L, Cabañas R, et al. Expression of α -defensin 1-3 in T cells from severe cutaneous drug-induced hypersensitivity reactions. *Allergy* 2011; **66**: 360–67.
- 34 Pichler WJ, Naisbitt DJ, Park BK. Immune pathomechanism of drug hypersensitivity reactions. *J Allergy Clin Immunol* 2011; **127**: S74–81.
- 35 Takahashi R, Kano Y, Yamazaki Y, Kimishima M, Mizukawa Y, Shiohara T. Defective regulatory T cells in patients with severe drug eruptions: timing of the dysfunction is associated with the pathological phenotype and outcome. *J Immunol* 2009; **182**: 8071–79.
- 36 Padovan E, Mauri-Hellweg D, Pichler WJ, Weltzien HU. T cell recognition of penicillin G: structural features determining antigenic specificity. *Eur J Immunol* 1996; **26**: 42–48.
- 37 Wei C-Y, Chung W-H, Huang H-W, Chen Y-T, Hung S-I. Direct interaction between HLA-B and carbamazepine activates T cells in patients with Stevens-Johnson syndrome. *J Allergy Clin Immunol* 2012; **129**: 1562–69.e5.
- 38 Illing PT, Vivian JP, Dudek NL, et al. Immune self-reactivity triggered by drug-modified HLA-peptide repertoire. *Nature* 2012; **486**: 554–58.
- 39 Ostrov DA, Grant BJ, Pompeu YA, et al. Drug hypersensitivity caused by alteration of the MHC-presented self-peptide repertoire. *Proc Natl Acad Sci USA* 2012; **109**: 9959–64.
- 40 Cheng C-Y, Su S-C, Chen C-H, Chen W-L, Deng S-T, Chung W-H. HLA associations and clinical implications in T-cell mediated drug hypersensitivity reactions: an updated review. *J Immunol Res* 2014; **2014**: 565320.
- 41 Chung W-H, Hung S-I, Hong H-S, et al. Medical genetics: a marker for Stevens-Johnson syndrome. *Nature* 2004; **428**: 486.
- 42 Hung SI, Chung WH, Liou LB, et al. HLA-B*58:01 allele as a genetic marker for severe cutaneous adverse reactions caused by allopurinol. *Proc Natl Acad Sci USA* 2005; **102**: 4134–39.
- 43 Lonjou C, Borot N, Sekula P, et al. A European study of HLA-B in Stevens-Johnson syndrome and toxic epidermal necrolysis related to five high-risk drugs. *Pharmacogenet Genomics* 2008; **18**: 99–107.
- 44 Mallal S, Phillips E, Carosi G, et al. HLA-B*57:01 screening for hypersensitivity to abacavir. *N Engl J Med* 2008; **358**: 568–79.
- 45 Saag M, Balu R, Phillips E, et al. High sensitivity of human leukocyte antigen-B*57:01 as a marker for immunologically confirmed abacavir hypersensitivity in white and black patients. *Clin Infect Dis* 2008; **46**: 1111–18.
- 46 Kaniwa N, Saito Y, Aihara M, et al. HLA-B*15:11 is a risk factor for carbamazepine-induced Stevens-Johnson syndrome and toxic epidermal necrolysis in Japanese patients. *Epilepsia* 2010; **51**: 2461–65.
- 47 Génin E, Schumacher M, Roujeau J-C, et al. Genome-wide association study of Stevens-Johnson syndrome and toxic epidermal necrolysis in Europe. *Orphanet J Rare Dis* 2011; **6**: 52.
- 48 McCormack M, Alfirevic A, Bourgeois S, et al. HLA-A*31:01 and carbamazepine-induced hypersensitivity reactions in Europeans. *N Engl J Med* 2011; **364**: 1134–43.
- 49 Carr DF, Chaponda M, Jorgensen AL, et al. Association of human leukocyte antigen alleles and Nevirapine hypersensitivity in a malawian HIV-infected population. *Clin Infect Dis* 2013; **56**: 1330–39.
- 50 Navarini AA, Valeyrie-Allanore L, Setta-Kaffetzki N, et al. Rare variations in IL36RN in severe adverse drug reactions manifesting as acute generalized exanthematous pustulosis. *J Invest Dermatol* 2013; **133**: 1904–07.
- 51 Ko TM, Chung WH, Wei CY, et al. Shared and restricted T-cell receptor use is crucial for carbamazepine-induced Stevens-Johnson syndrome. *J Allergy Clin Immunol* 2011; **128**: 1266–76.e11.
- 52 Chung WH, Pan RY, Chu MT, et al. Oxypurinol-specific T cells possess preferential TCR clonotypes and express granulysin in allopurinol-induced severe cutaneous adverse reactions. *J Invest Dermatol* 2015; **135**: 2237–48.
- 53 Chung WH, Chang WC, Lee YS, et al. Genetic variants associated with phenytoin-related severe cutaneous adverse reactions. *JAMA* 2014; **312**: 525–34.
- 54 Nicoletti P, Bansal M, Lefebvre C, et al. ABC transporters and the proteasome complex are implicated in susceptibility to Stevens-Johnson syndrome and toxic epidermal necrolysis across multiple drugs. *PLoS One* 2015; **10**: e0131038.
- 55 de Araujo E, Dessirier V, Laprée G, et al. Death ligand TRAIL, secreted by CD1a+ and CD14+ cells in blister fluids, is involved in killing keratinocytes in toxic epidermal necrolysis. *Exp Dermatol* 2011; **20**: 107–12.
- 56 Wang CW, Chung WH, Cheng YF, et al. A new nucleic acid-based agent inhibits cytotoxic T lymphocyte-mediated immune disorders. *J Allergy Clin Immunol* 2013; **132**: 713–22.e11.
- 57 Tohyama M, Watanabe H, Murakami S, et al. Possible involvement of CD14+ CD16+ monocyte lineage cells in the epidermal damage of Stevens-Johnson syndrome and toxic epidermal necrolysis. *Br J Dermatol* 2012; **166**: 322–30.

- 58 Chung W-H, Hung S-I, Yang J-Y, et al. Granulysin is a key mediator for disseminated keratinocyte death in Stevens-Johnson syndrome and toxic epidermal necrolysis. *Nat Med* 2008; **14**: 1343–50.
- 59 Viard-Leveugle I, Gaide O, Jankovic D, et al. TNF- α and IFN- γ are potential inducers of Fas-mediated keratinocyte apoptosis through activation of inducible nitric oxide synthase in toxic epidermal necrolysis. *J Invest Dermatol* 2013; **133**: 489–98.
- 60 Su S-C, Mockenhaupt M, Wolkenstein P, et al. Interleukin-15 is associated with severity and mortality in Stevens-Johnson syndrome/toxic epidermal necrolysis. *J Invest Dermatol* 2016; published online Dec 21, 2016. DOI:10.1016/j.jid.2016.11.034.
- 61 Kim SK, Kim W-J, Yoon J-H, et al. Upregulated RIP3 expression potentiates MLKL phosphorylation-mediated programmed necrosis in toxic epidermal necrolysis. *J Invest Dermatol* 2015; **135**: 2021–30.
- 62 Hashizume H, Fujiyama T, Kanebayashi J, Kito Y, Hata M, Yagi H. Skin recruitment of monomyeloid precursors involves human herpesvirus-6 reactivation in drug allergy. *Allergy* 2013; **68**: 681–89.
- 63 Picard D, Janela B, Descamps V, et al. Drug reaction with eosinophilia and systemic symptoms (DRESS): a multiorgan antiviral T cell response. *Sci Transl Med* 2010; **2**: 46ra62.
- 64 Fili L, Cardilicchia E, Severino MG, et al. Hapten-specific TH17 cells in the peripheral blood of β -lactam-induced AGEP. *Allergol Int* 2014; **63**: 129–31.
- 65 Schlapbach C, Zawodniak A, Irla N, et al. NKp46+ cells express granulysin in multiple cutaneous adverse drug reactions. *Allergy* 2011; **66**: 1469–76.
- 66 Fujita Y, Yoshioka N, Abe R, et al. Rapid immunochromatographic test for serum granulysin is useful for the prediction of Stevens-Johnson syndrome and toxic epidermal necrolysis. *J Am Acad Dermatol* 2011; **65**: 65–68.
- 67 Nomura Y, Aihara M, Matsukura S, et al. Evaluation of serum cytokine levels in toxic epidermal necrolysis and Stevens-Johnson syndrome compared with other delayed-type adverse drug reactions. *J Dermatol* 2011; **38**: 1076–79.
- 68 Yoshioka N, Suto A, Abe R, et al. Disturbed balance in three subpopulations of CD4(+)Foxp3(+) regulatory T cells in Stevens-Johnson syndrome and toxic epidermal necrolysis patients. *Clin Immunol* 2013; **148**: 89–91.
- 69 Morito H, Ogawa K, Fukumoto T, et al. Increased ratio of FoxP3+ regulatory T cells/CD3+ T cells in skin lesions in drug-induced hypersensitivity syndrome/drug rash with eosinophilia and systemic symptoms. *Clin Exp Dermatol* 2014; **39**: 284–91.
- 70 Hanafusa T, Azukizawa H, Matsumura S, Katayama I. The predominant drug-specific T-cell population may switch from cytotoxic T cells to regulatory T cells during the course of anticonvulsant-induced hypersensitivity. *J Dermatol Sci* 2012; **65**: 213–19.
- 71 Stern RS. Clinical practice. Exanthematous drug eruptions. *N Engl J Med* 2012; **366**: 2492–501.
- 72 Haute Autorité de la Santé. Necrolyse epidermique toxique syndrome de Stevens Johnson et de Lyell. Protocole national de soins. June, 2010. https://www.has-sante.fr/portail/upload/docs/application/pdf/2011-06/synthese_medecin_traitant_sur_la_necrolyse_epidermique_toxique.pdf (accessed Feb 28, 2017).
- 73 Kaffenberger BH, Rosenbach M. Toxic epidermal necrolysis and early transfer to a regional burn unit: is it time to reevaluate what we teach? *J Am Acad Dermatol* 2014; **71**: 195–96.
- 74 Palmieri TL, Greenhalgh DG, Saffle JR, et al. A multicenter review of toxic epidermal necrolysis treated in U.S. burn centers at the end of the twentieth century. *J Burn Care Rehabil* 2002; **23**: 87–96.
- 75 Valeyrie-Allanore L, Wolkenstein P, Brochard L, et al. Open trial of ciclosporin treatment for Stevens-Johnson syndrome and toxic epidermal necrolysis. *Br J Dermatol* 2010; **163**: 847–53.
- 76 Struck MF, Hilbert P, Mockenhaupt M, Reichelt B, Steen M. Severe cutaneous adverse reactions: emergency approach to non-burn epidermolytic syndromes. *Intensive Care Med* 2010; **36**: 22–32.
- 77 Creamer D, Walsh SA, Dziewulski P, et al. UK guidelines for the management of Stevens-Johnson syndrome/toxic epidermal necrolysis in adults 2016. *Br J Dermatol* 2016; **174**: 1194–227.
- 78 Garcia-Doval I, LeCleach L, Bocquet H, Otero XL, Roujeau JC. Toxic epidermal necrolysis and Stevens-Johnson syndrome: does early withdrawal of causative drugs decrease the risk of death? *Arch Dermatol* 2000; **136**: 323–27.
- 79 Rajaratnam R, Mann C, Balasubramaniam P, et al. Toxic epidermal necrolysis: retrospective analysis of 21 consecutive cases managed at a tertiary center. *Clin Exp Dermatol* 2010; **35**: 853–62.
- 80 Weinand C, Xu W, Perbix W, et al. 27 years of a single burn centre experience with Stevens-Johnson syndrome and toxic epidermal necrolysis: analysis of mortality risk for causative agents. *Burns* 2013; **39**: 1449–55.
- 81 de Prost N, Mekontso-Dessap A, Valeyrie-Allanore L, et al. Acute respiratory failure in patients with toxic epidermal necrolysis: clinical features and factors associated with mechanical ventilation. *Crit Care Med* 2014; **42**: 118–28.
- 82 Firoz BF, Henning JS, Zarzabal LA, Pollock BH. Toxic epidermal necrolysis: five years of treatment experience from a burn unit. *J Am Acad Dermatol* 2012; **67**: 630–35.
- 83 Lin A, Patel N, Yoo D, DeMartelaere S, Bouchard C. Management of ocular conditions in the burn unit: thermal and chemical burns and Stevens-Johnson syndrome/toxic epidermal necrolysis. *J Burn Care Res* 2011; **32**: 547–60.
- 84 Liu J, Sheha H, Fu Y, Giegengack M, Tseng SCG. Oral mucosal graft with amniotic membrane transplantation for total limbal stem cell deficiency. *Am J Ophthalmol* 2011; **152**: 739–47e1.
- 85 Schneck J, Fagot J-P, Sekula P, Sassolas B, Roujeau JC, Mockenhaupt M. Effects of treatments on the mortality of Stevens-Johnson syndrome and toxic epidermal necrolysis: a retrospective study on patients included in the prospective EuroSCAR Study. *J Am Acad Dermatol* 2008; **58**: 33–40.
- 86 Sekula P, Dunant A, Mockenhaupt M, et al. Comprehensive survival analysis of a cohort of patients with Stevens-Johnson syndrome and toxic epidermal necrolysis. *J Invest Dermatol* 2013; **133**: 1197–204.
- 87 Lee HY, Dunant A, Sekula P, et al. The role of prior corticosteroid use on the clinical course of Stevens-Johnson syndrome and toxic epidermal necrolysis: a case-control analysis of patients selected from the multinational EuroSCAR and RegiSCAR studies. *Br J Dermatol* 2012; **167**: 555–62.
- 88 Paradisi A, Abeni D, Bergamo F, Ricci F, Didona D, Didona B. Etanercept therapy for toxic epidermal necrolysis. *J Am Acad Dermatol* 2014; **71**: 278–83.
- 89 Bachot N, Revuz J, Roujeau JC. Intravenous immunoglobulin treatment for Stevens-Johnson syndrome and toxic epidermal necrolysis: a prospective noncomparative study showing no benefit on mortality or progression. *Arch Dermatol* 2003; **139**: 33–36.
- 90 Chen J, Wang B, Zeng Y, Xu H. High-dose intravenous immunoglobulins in the treatment of Stevens-Johnson syndrome and toxic epidermal necrolysis in Chinese patients: a retrospective study of 82 cases. *Eur J Dermatol* 2010; **20**: 743–47.
- 91 Huang YC, Li YC, Chen TJ. The efficacy of intravenous immunoglobulin for the treatment of toxic epidermal necrolysis: a systematic review and meta-analysis. *Br J Dermatol* 2012; **167**: 424–32.
- 92 Lee HY, Lim YL, Thirumoorthy T, Pang SM. The role of intravenous immunoglobulin in toxic epidermal necrolysis: a retrospective analysis of 64 patients managed in a specialized centre. *Br J Dermatol* 2013; **169**: 1304–09.
- 93 Kirshhof MG, Miliszewski MA, Sikora S, Papp A, Dutz JP. Retrospective review of Stevens-Johnson syndrome/toxic epidermal necrolysis treatment comparing intravenous immunoglobulin with cyclosporine. *J Am Acad Dermatol* 2014; **71**: 941–47.
- 94 de Sica-Chapman A, Williams G, Soni N, Bunker CB. Granulocyte colony-stimulating factor in toxic epidermal necrolysis (TEN) and Chelsea & Westminster TEN management protocol. *Br J Dermatol* 2010; **162**: 860–65.
- 95 Wolkenstein P, Latarjet J, Roujeau J-C, et al. Randomised comparison of thalidomide versus placebo in toxic epidermal necrolysis. *Lancet* 1998; **352**: 1586–89.
- 96 Chen YC, Chiu HC, Chu CY. Drug reaction with eosinophilia and systemic symptoms: a retrospective study of 60 cases. *Arch Dermatol* 2010; **146**: 1373–79.
- 97 Natkunarajah J, Goolamali S, Craythorne E, et al. Ten cases of drug reaction with eosinophilia and systemic symptoms (DRESS) treated with pulsed intravenous methylprednisolone. *Eur J Dermatol* 2011; **21**: 385–91.
- 98 Joly P, Janela B, Tétart F, et al. Poor benefit/risk balance of intravenous immunoglobulins in DRESS. *Arch Dermatol* 2012; **148**: 543–44.

- 99 Funck-Brentano E, Duong T-A, Bouvresse S, et al. Therapeutic management of DRESS: a retrospective study of 38 cases. *J Am Acad Dermatol* 2015; **72**: 246–52.
- 100 Ingen-Housz-Oro S, Hotz C, Valeyrie-Allanore L, et al. Acute generalized exanthematous pustulosis: a retrospective audit of practice between 1994 and 2011 at a single centre. *Br J Dermatol* 2015; **172**: 1455–57.
- 101 de Prost N, Ingen-Housz-Oro S, Duong TA, et al. Bacteremia in Stevens-Johnson syndrome and toxic epidermal necrolysis: epidemiology, risk factors, and predictive value of skin cultures. *Medicine (Baltimore)* 2010; **89**: 28–36.
- 102 Knight L, Todd G, Muloiwa R, Matjila M, Lehloenyia RJ. Stevens Johnson syndrome and toxic epidermal necrolysis: maternal and foetal outcomes in twenty-two consecutive pregnant HIV infected women. *PLoS One* 2015; **10**: e0135501.
- 103 Wu J, Lee YY, Su SC, et al. Stevens-Johnson syndrome and toxic epidermal necrolysis in patients with malignancies. *Br J Dermatol* 2015; **173**: 1224–31.
- 104 Guégan S, Bastuji-Garin S, Poszepczynska-Guigné E, Roujeau J-C, Revuz J. Performance of the SCORTEN during the first five days of hospitalization to predict the prognosis of epidermal necrolysis. *J Invest Dermatol* 2009; **126**: 272–76.
- 105 Sekula P, Liss Y, Davidovici B, et al. Evaluation of SCORTEN on a cohort of patients with Stevens-Johnson syndrome and toxic epidermal necrolysis included in the RegiSCAR study. *J Burn Care Res* 2011; **32**: 237–45.
- 106 Duong TA, de Prost N, Ingen-Housz-Oro S, et al. Stevens-Johnson syndrome and toxic epidermal necrolysis: follow-up of pulmonary function after remission. *Br J Dermatol* 2015; **172**: 400–05.
- 107 Gaultier F, Rochefort J, Landru M-M, et al. Severe and unrecognized dental abnormalities after drug-induced epidermal necrolysis. *Arch Dermatol* 2009; **145**: 1332–33.
- 108 Yang CW, Cho YT, Chen KL, Chen YC, Song HL, Chu CY. Long-term sequelae of Stevens-Johnson syndrome/toxic epidermal necrolysis. *Acta Derm Venereol* 2016; **96**: 525–29.
- 109 Sant' Anna AE, Hazarbasanov RM, de Freitas D, Gomes JÁP. Minor salivary glands and labial mucous membrane graft in the treatment of severe symblepharon and dry eye in patients with Stevens-Johnson syndrome. *Br J Ophthalmol* 2012; **96**: 234–39.
- 110 Tougeron-Brousseau B, Delcampe A, Gueudry J, et al. Vision-related function after scleral lens fitting in ocular complications of Stevens-Johnson syndrome and toxic epidermal necrolysis. *Am J Ophthalmol* 2009; **148**: 852–59.e2.
- 111 Struck MF, Illert T, Liss Y, Bosbach ID, Reichelt B, Steen M. Toxic epidermal necrolysis in pregnancy: case report and review of the literature. *J Burn Care Res* 2010; **31**: 816–21.
- 112 Chen YC, Chang CY, Cho YT, Chiu HC, Chu CY. Long-term sequelae of drug reaction with eosinophilia and systemic symptoms: a retrospective cohort study from Taiwan. *J Am Acad Dermatol* 2013; **68**: 459–65.
- 113 Lew TT, Creamer D, Mackenzie J, Walsh SA. Post-traumatic stress disorder following drug reaction with eosinophilia and systemic symptoms. *Br J Dermatol* 2015; **172**: 836–37.
- 114 Tohyama M, Hashimoto K, Yasukawa M, et al. Association of human herpesvirus 6 reactivation with the flaring and severity of drug-induced hypersensitivity syndrome. *Br J Dermatol* 2007; **157**: 934–40.
- 115 Kano Y, Ishida T, Hirahara K, Shiohara T. Visceral involvements and long-term sequelae in drug-induced hypersensitivity syndrome. *Med Clin North Am* 2010; **94**: 743–59, xi.
- 116 Ushigome Y, Kano Y, Ishida T, Hirahara K, Shiohara T. Short- and long-term outcomes of 34 patients with drug-induced hypersensitivity syndrome in a single institution. *J Am Acad Dermatol* 2013; **68**: 721–28.
- 117 Bégaud B, Evreux JC, Jouglard J, Lagier G. Imputation of the unexpected or toxic effects of drugs. Actualization of the method used in France. *Thérapie* 1985; **40**: 111–18 (in French).
- 118 Naranjo CA, Busto U, Sellers EM, et al. A method for estimating the probability of adverse drug reactions. *Clin Pharmacol Ther* 1981; **30**: 239–45.
- 119 Mockenhaupt M, Viboud C, Dunant A, et al. Stevens-Johnson syndrome and toxic epidermal necrolysis: assessment of medication risks with emphasis on recently marketed drugs. The EuroSCAR-study. *J Invest Dermatol* 2008; **128**: 35–44.
- 120 Chaponda M, Pirmohamed M. Hypersensitivity reactions to HIV therapy. *Br J Clin Pharmacol* 2011; **71**: 659–71.
- 121 Kuehn BM. FDA: Acetaminophen may trigger serious skin problems; *JAMA* 2013; **310**: 785.
- 122 Levi N, Bastuji-Garin S, Mockenhaupt M, et al. Medications as risk factors of Stevens-Johnson syndrome and toxic epidermal necrolysis in children: a pooled analysis. *Pediatrics* 2009; **123**: e297–304.
- 123 Raucci U, Rossi R, Da Cas R, et al. Stevens-Johnson syndrome associated with drugs and vaccines in children: a case-control study. *PLoS One* 2013; **8**: e68231.
- 124 Roujeau J-C, Mockenhaupt M, Tahan SR, et al. Telaprevir-related dermatitis. *JAMA Dermatol* 2013; **149**: 152–58.
- 125 Valeyrie-Allanore L, Poulalhoun N, Fagot J-P, et al. Stevens-Johnson syndrome and toxic epidermal necrolysis induced by amifostine during head and neck radiotherapy. *Radiother Oncol* 2008; **87**: 300–03.
- 126 Haddad C, Chosidow O, Valeyrie-Allanore L, et al. Are idiopathic Stevens-Johnson syndrome/toxic epidermal necrolysis related to drugs in food? The example of phenylbutazone. *J Invest Dermatol* 2017; published online Jan 17. DOI:10.1016/j.jid.2016.11.041.
- 127 Ziemer M, Kardaun SH, Liss Y, Mockenhaupt M. Stevens-Johnson syndrome and toxic epidermal necrolysis in patients with lupus erythematosus: a descriptive study of 17 cases from a national registry and review of the literature. *Br J Dermatol* 2012; **166**: 575–600.
- 128 Wolkenstein P, Loriot M-A, Flahault A, et al. Association analysis of drug metabolizing enzyme gene polymorphisms in AIDS patients with cutaneous reactions to sulfonamides. *J Invest Dermatol* 2005; **125**: 1080–82.
- 129 Adam J, Wuillemin N, Watkins S, et al. Abacavir induced T cell reactivity from drug naive individuals shares features of allo-immune responses. *PLoS One* 2014; **9**: e95339.
- 130 Chen P, Lin JJ, Lu CS, et al. Carbamazepine-induced toxic effects and HLA-B*15:02 screening in Taiwan. *N Engl J Med* 2011; **364**: 1126–33.
- 131 Yang CY, Chen CH, Deng ST, et al. Allopurinol use and risk of fatal hypersensitivity reactions: a nationwide population-based study in Taiwan. *JAMA Intern Med* 2015; **175**: 1550–57.
- 132 Picard D, Vellar M, Janela B, Roussel A, Joly P, Musette P. Recurrence of drug-induced reactions in DRESS patients. *J Eur Acad Dermatol Venereol* 2015; **29**: 801–04.
- 133 Finkelstein Y, Macdonald EM, Li P, Hutson JR, Juurlink DN. Recurrence and mortality following severe cutaneous adverse reactions. *JAMA* 2014; **311**: 2231–32.
- 134 Stern RS. Recurrence of Stevens-Johnson syndrome and toxic epidermal necrolysis. *JAMA* 2014; **312**: 1590–91.
- 135 Barbaud A, Collet E, Milpied B, et al. A multicentre study to determine the value and safety of drug patch tests for the three main classes of severe cutaneous adverse drug reactions. *Br J Dermatol* 2013; **168**: 555–62.
- 136 Kano Y, Hirahara K, Mitsuyama Y, Takahashi R, Shiohara T. Utility of the lymphocyte transformation test in the diagnosis of drug sensitivity: dependence on its timing and the type of drug eruption. *Allergy* 2007; **62**: 1439–44.
- 137 Srinoulprasert Y, Pichler WJ. Enhancement of drug-specific lymphocyte proliferation using CD25-depleted CD3(+) effector cells. *Int Arch Allergy Immunol* 2014; **163**: 198–205.
- 138 Polak ME, Belgi G, McGuire C, et al. In vitro diagnostic assays are effective during the acute phase of delayed-type drug hypersensitivity reactions. *Br J Dermatol* 2013; **168**: 539–49.
- 139 Porebski G, Pecaric-Petkovic T, Groux-Keller M, Bosak M, Kawabata TT, Pichler WJ. In vitro drug causality assessment in Stevens-Johnson syndrome—alternatives for lymphocyte transformation test. *Clin Exp Allergy* 2013; **43**: 1027–37.
- 140 Haddad C, Sidoroff A, Kardaun SH, et al. Stevens-Johnson syndrome/toxic epidermal necrolysis: are drug dictionaries correctly informing physicians regarding the risk? *Drug Saf* 2013; **36**: 681–86.
- 141 Isvy-Joubert A, Ingen-Housz-Oro S, Vincent R, et al. Severe cutaneous adverse reactions to drugs: from patients to the national office for compensation of medical accidents. *Dermatology (Basel)* 2014; **228**: 338–43.
- 142 Lebrun-Vignes B, Kreft-Jais C, Castot A, Chosidow O. Comparative analysis of adverse drug reactions to tetracyclines: results of a French national survey and review of the literature. *Br J Dermatol* 2012; **166**: 1333–41.
- 143 Ketter TA, Greist JH, Graham JA, Roberts JN, Thompson TR, Nanry KP. The effect of dermatologic precautions on the incidence of rash with addition of lamotrigine in the treatment of bipolar I disorder: a randomized trial. *J Clin Psychiatry* 2006; **67**: 400–06.
- 144 Phoenix G, Das S, Joshi M. Diagnosis and management of cellulitis. *BMJ* 2012; **345**: e4955.