Draft Report on

Severe Cutaneous Adverse Reactions (SCAR)

Council for International Organizations of Medical Sciences (CIOMS)

ISBN: 978-929036107-7

Suggested citation:
Severe Cutaneous Adverse Reactions. A consensus by a CIOMS Working Group. Geneva, Switzerland: Council for International Organizations of Medical Sciences (CIOMS), 2024. doi:

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ACKNOWLEDGEMENTS

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ABBREVIATIONS AND ACRONYMS

ACLE	Acute Cutaneous Lupus Erythematosus
ADR	Adverse Drug Reaction
AE	Adverse Event
AGEP	Acute Generalized Exanthematous Pustulosis
AGPP	Acute Generalized Pustular Psoriasis
aGVHR	Acute Graft Versus Host Reaction
ARDS	Acute Respiratory Distress Syndrome
ART	Antiretroviral Therapy
BSA	Body Surface Area
CBC	Complete Blood Count
CHMP	Committee for Medicinal Products for Human Use of the European Medicines Agency
CI	Confidence Interval
CKD	Chronic Kidney Disease
CIOMS	Council for International Organizations of Medical Science
CMV	Cytomegalovirus
CRP	C-reactive Protein
cADR	Cutaneous Adverse Drug Reaction
CTCAE	Common Terminology Criteria for Adverse Events
CYP	Cytochrome P450
CYP2C9	Cytochrome P450 2C9
DHCP	Dear Healthcare Provider
DHPC	Direct Healthcare Professional Communication
DI SCLE	Drug-Induced Subacute Cutaneous Lupus Erythematosus
DIHS	Drug-Induced Hypersensitivity Syndrome
DPT	Drug Patch Testing
DRESS	Drug Reaction with Eosinophilia and Systemic Symptoms
EBV	Epstein-Barr Virus
ECG	Electrocardiogram
EHR	Electronic Health Record
ELISpot	Enzyme Linked Immunosorbent Spot
EMA	European Medicines Agency
EMM	Erythema multiforme Major
EN	Epidermal or Epithelial Necrolysis
EU	European Union
ExDerm	Exfoliative Dermatitis
FDA	U.S. Food and Drug Administration
FDE	Fixed Drug Eruptions

GBFDE	Generalized Bullous Fixed Drug Eruptions
G-CSF	Granulocyte Colony Stimulating Factor
GM-CSF	Granulocyte/Macrophage Colony-Stimulating Factor
GPP	Generalized Pustular Psoriasis
GWAS	Genome-Wide Association Study
H&E	Hematoxylin and Eosin
HCP	Healthcare Professional
HHV	Human Herpes Virus
HHV6	Human Herpes Virus 6
HIV	Human Immunodeficiency Virus
HLA	Human Leukocyte Antigen
ICD-CM	International Classification of Diseases - Clinical Modification
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICSR	Individual Case Safety Report
ICU	Intensive Care Unit
IQR	Interquartile Range
IRIS	Immune Reconstitution Inflammatory Syndrome
IVIG	Intravenous Immunoglobulin
JAK	Janus Kinase
LE	Lupus Erythematosus
MedDRA	Medical Dictionary for Regulatory Activities
MHC	Major Histocompatibility Complex
MPE	Maculopapular Exanthem
NPV	Negative Predictive Value
NSAID	Non-Steroidal Anti-Inflammatory Drugs
OR	Odds Ratio
PE	Paraneoplastic Erythroderma
PGx	Pharmacogenomic
PPV	Positive Predictive Value
PT	Preferred Term
PV	Pharmacovigilance
PUVA	Psoralen Combined with Ultraviolet A
REMS	Risk Evaluation and Mitigation Strategies
RMP	Risk Management Plan
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
SCAR	Severe Cutaneous Adverse Reaction(s)
SCLE	Subacute Cutaneous Lupus Erythematosus
SLE	System Lupus Erythematosus
SmPC	Summary of Product Characteristics

SJS	Stevens-Johnson Syndrome
SOC	System Organ Class
SSSS	Staphylococcal Scalded Skin Syndrome
SUSAR	Suspected unexpected serious adverse reaction
TARC	Thymus and Activation-Regulated Chemokine
TB	Tuberculosis
TBSA	Total Body Surface Area
TEN	Toxic Epidermal Necrolysis
TEN Like LE	TEN-Like Lupus Erythematosus or Lupus-Associated TEN
TNF	Tumour Necrosis Factor
UK	United Kingdom
US	United States
WHO	World Health Organization
WHO-UMC	WHO Uppsala Monitoring Centre

FOREWORD

Severe Cutaneous Adverse Reactions (SCAR) such as Stevens-Johnson syndrome/toxic epidermal necrolysis (SJS/TEN) are associated with significant patient morbidity and mortality. These reactions may result in death or life-threatening conditions, inpatient hospitalization or prolongation of existing hospitalization, or significant disability/incapacity.

The SCAR Working Group of the Council for International Organizations of Medical Sciences consists of a diverse and comprehensive group of major stakeholders, i.e. academia/research organizations, clinicians, medicinal product[1] developers/industry and regulatory authorities, to assist in establishing a balanced, global perspective on the approach for SCAR detection, susceptibility factors, severity, outcome and probability through causality assessment tools, monitoring and risk management during the medicinal product development and postauthorization phases.

The panel of experts encompassed wide participation, with members from several World Health Organization regions, to ensure comprehensiveness, synergies and global impact.

To increase participation and input from individual experts and leading institutions globally, the draft document was posted for public consultation prior to finalization. This report takes into account the comments received as a result of the public consultation.

CIOMS SCAR Working Group Objectives

The intent is to provide a guidance for medicinal product developers, regulatory authorities, healthcare professionals and scientists in academic and research organizations regarding:

- Diagnosis of SCAR in patients.
- Interpretation and management of SCAR safety signals for a medicinal product considering that SCAR assessments differ between clinical practice, clinical trial and observational studies, and that there is a need to enhance safety of medicinal product development and in medicinal product life-cycle management.
- SCAR data analysis of suspected unexpected serious adverse reactions during clinical trials, individual case safety reports in the postauthorization phase, aggregate data from clinical trials and observational studies using this consensus report on the terminology and level of evidence needed to assess safety, data standards, and data acquisition.
- Data capture and analysis of safety signals of a SCAR for a medicinal product during preauthorization clinical trials through adopting standards for data and biospecimen acquisition and management, to allow future biomarkers development and validation.
- Proposed causality assessment process in clinical trials and the postauthorization phase, including assessment of SCAR data for strength of evidence or degrees of uncertainty in causal association.
- Assessment of SCAR safety data for special populations with impaired immune status, such as cancer patients, patients with autoimmune diseases, the elderly, and paediatric patients.

1 The CIOMS Cumulative Glossary with a Focus on Pharmacovigilance (version 2.0) defines "medicinal product" according to the definition below. "Medicinal product" will be used interchangeably with the term "drug" in this report.

Any substance or combination of substances:
- presented as having properties for treating or preventing disease in humans; or
- which may be used in or administered to humans either with a view to restoring, correcting or modifying physiological functions by exerting a pharmacological, immunological or metabolic action, or to making a medical diagnosis.

Note: In other jurisdictions, this may be called a medicine, medical product or a drug, and may include biologicals and vaccines.

- Validation of traditional and new biomarkers, also through combining large SCAR safety datasets across many clinical trials and postauthorization data in different patient populations to generate sufficient data for detecting rare SCAR induced by a medicinal product

- Prevention and mitigation of SCAR induced by medicinal products. The aim of this report is to create a global consensus reference for regulators, patient organizations, scientists, industry and clinicians involved in product life cycle management or clinical practice.

EXECUTIVE SUMMARY

Following is a brief description of each chapter:

Chapter 1: What are Severe Cutaneous Adverse Reactions?

This chapter describes the differences between cutaneous adverse drug reactions (cADRs) and severe cutaneous adverse reactions (SCAR) in terms of epidemiology, etiology, clinical characteristics, prognosis and outcome of the various SCAR conditions.

Chapter 2: Diagnosis and identification of SCAR cases

The first step in analysing a putative SCAR is to make a tentative diagnosis. DRESS, AGEP and some other SCAR conditions have defined diagnostic criteria which may overlap and can hence be challenging to diagnose in the earliest stages. A SCAR diagnosis should consider patient history, visual assessment (appearance, morphology), severity and the presence of systemic symptoms, followed by a clinical investigation of potential causes or causality assessment in the individual patient.

Chapter 3: Case management in clinical care

Withdrawal of the culprit medicinal product is the cornerstone of care for SCAR. Additionally, management and supportive care are elucidated in this chapter.

Chapter 4: Biomarkers

Numerous investigations have uncovered many promising biomarkers to identify individuals at risk of developing SCAR, confirm and diagnosis of SCAR early, and inform prognosis. Human leukocyte antigen (HLA) variants are consistently associated with the risk for SCAR and testing results are clinically actionable for many culprit medicinal products, most significantly for anti-epileptics and allopurinol. Several histopathologic, blister fluid and serum biomarkers have been identified that appear to be specific to SCAR and could enable earlier diagnosis. Some may even represent possible therapeutic targets. However, more research is needed to confirm their utility in the diagnostic workup of SCAR.

Chapter 5: Causality assessment of SCAR in pre- and postauthorization surveillance

Causality assessments aim to determine the procedure to determine the relationship between the medicinal product and the adverse event (AE). Methods such as Bradford Hill criteria, Global Introspection, operational algorithms, probabilistic approaches are presented for SCAR. Also presented are adjudication, targeted follow-up form, and assessment of the aggregate data.

Chapter 6: Pre-authorization safety data collection and analysis

Prompt recognition of SCAR enhances patient safety and enables the assessment of the impact on the clinical trial programme. Risk factors such as patient population, pharmacology, and pharmacogenomics should all be considered when setting up preauthorization surveillance.

Chapter 7: Postauthorization safety data collection and assessment

Data sources for postauthorization surveillance include spontaneous reports, electronic health records (EHRs), registries, clinical trial data and preclinical data.

Chapter 8: Risk minimization

Prompt evaluation and discontinuation of the potentially offending medicinal product(s) are the most appropriate immediate interventions in the management of drug-induced SCAR once detected, based on the benefit risk balance of the treatment for the given patient. Key developments in SCAR research include new technologies allowing the identification of genetic risk factors with improved sensitivity, specificity and efficiency. Routine risk minimization measures and additional risk minimization measures for SCAR are presented with examples.

INTRODUCTION

An adverse event (AE) is any untoward medical occurrence that may present during treatment with a medicinal product (drug or biological product), but which does not necessarily have a causal relationship with this treatment. An AE therefore can be any unfavourable and unintended sign (for example, an abnormal laboratory finding) symptom or disease that is temporally associated with the use of a medicinal product, whether or not it is related to this medicinal product.

An adverse drug reaction (ADR), as established by regional regulations, guidance, and practices, concern noxious and unintended responses to a medicinal product. The phrase "responses to a medicinal product" means that a causal relationship between a medicinal product and an AE is at least a reasonable possibility.[1]

Skin is the most commonly affected organ by ADRs by not only small molecules in medicinal products, including vaccines and other etiologies. Cutaneous ADRs (cADRs) affect 2% to 3% of all hospitalized patients.[2] cADRs have a wide spectrum of clinical manifestations, are caused by various medicinal products, and result from different pathophysiologic mechanisms. Hence, their diagnosis and management are challenging, but approximately 0.1-1% of patients with medicinal product eruptions are serious ADRs. In regulatory guidelines, a serious AE or adverse reaction to a medicinal product is defined as any untoward medical occurrence that at any dose satisfies any of the following criteria:[1,3]

- results in death,
- is life-threatening,
- requires inpatient hospitalization or prolongation of existing hospitalization,
- results in persistent or significant disability/incapacity,
- is a congenital anomaly/birth defect, or
- other medically important event or reaction.[1,4]

Severe cutaneous adverse reactions (SCAR) are rare, idiosyncratic disorders that are most often induced by medicinal products but may also be reactions to other kinds of exposure, and associated with significant morbidity, usually leading to hospitalization. SCAR consist of Stevens-Johnson syndrome/toxic epidermal necrolysis (SJS/TEN), drug reaction with eosinophilia and systemic symptoms (DRESS), acute generalized exanthematous pustulosis (AGEP), and generalized bullous fixed drug eruptions (GBFDE). The annual incidence of SJS/TEN is estimated at 1-5 per million person-years. Utilizing spontaneous reports of suspected adverse reactions from healthcare professionals (HCPs) and patients may generate a signal for SCAR as a potential ADR even with a single, well-documented report on an individual patient. This may indicate possible causality with the medicinal product, particularly for serious SCAR that are rare in the general population or SCAR that are rare in the absence of medicinal product exposure.[1,4]

Future needs

Medicine-induced SCAR are rare serious AEs that pose substantial hurdles to medicine developers, regulators, healthcare professionals and patients as well as patient acceptance of therapeutic options and adherence. Further work is necessary to continue the advancement of science, medicine and regulation to better identify, characterize and mitigate SCAR risks.

The following highlight some of the main topics that need further progress:

For healthcare professionals:

- The lack of consensus in clinical guidance regarding SCAR in special populations, especially cancer patients, patients with pre-existing autoimmune diseases, the elderly, and children;
- There is mounting concern in relation to the ongoing health burden of SCAR and the emergence of SCAR related to novel biological medicinal products as well as the increasing cost of diagnosis and management.

For regulatory authorities and the biopharmaceutical industry:

- The need for comprehensive, proactive and systematic workflows for safety data capture and analysis during medicinal product development;
- The lack of harmonized case definitions of SCAR types, the need to ensure completeness of safety assessment and management in medicines development, as well as consensus guidance on the design of studies to develop and validate new technologies and biomarkers;
- The lack of evidence-based practice to promote consistent pharmacovigilance and risk management of SCAR in clinical trials and postauthorization studies during medicinal product development and postauthorization phases;
- The lack of specific information provided in the Summary of Product Characteristics (SmPC) about SCAR: the information is overall quite similar for all concerned medicinal products even if they do not carry the same risk of SCAR.

Furthermore, the magnitude of attrition of new chemical entities during medicinal product development that accounts for up to > 80% from phase I to application for marketing authorization has put an unsurpassable barrier for the clinical translation of new medicinal products. This has taken the pharmaceutical industry to a point where a revision of current approaches is necessary.

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CHAPTER 1.

WHAT ARE SEVERE CUTANEOUS ADVERSE REACTIONS?

Chapter summary

- Severe cutaneous adverse reactions (SCAR) comprise Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS), acute generalized exanthematous pustulosis (AGEP) and generalized bullous fixed drug eruptions (GBFDE).
- Clinical phenotypes of cutaneous adverse drug reactions (cADRs) are very diverse and most of them are benign non-life-threatening reactions such as maculopapular exanthema (MEP), urticaria, fixed drug eruptions (FDE), lichenoid eruptions, vasculitis and others. Maculopapular exanthem (MPE) is the most common benign cADR to medicinal products.
- SJS, SJS/TEN-overlap and TEN represent different severity spectra of the same disease, epidermal necrolysis (EN), which needs to be distinguished from erythema multiforme major (EMM) which is exclusively due to infections.
- DRESS is a multi-systemic ADR with a heterogeneous presentation and variable clinical course. Initial symptoms may be prodromal in nature such as fever and malaise. Cutaneous eruptions are extensive and may be polymorphic in presentation, including maculopapular eruptions, infiltrated plaques, pustules, target-like lesions, purpura, eczematous lesions and erythroderma. Facial erythema and swelling are prominent features of DRESS. Various internal organs may be involved including the liver, kidneys, lungs, heart, nervous system and others.
- AGEP is characterized by a sudden onset of numerous pinpoint, non-follicular sterile pustules on oedematous erythematous skin. The most characteristic feature of AGEP is its clinical course. It has a very rapid onset and equally rapid resolution.
- GBFDE is characterized by well-demarcated, round, or oval erythematous, violaceus or dusky red patches with blisters and erosions. Most patients report a positive history of similar eruptions. GBFDE may be confused as SJS/TEN due to the extensive bullous eruption with erosions.

Conclusions or recommendations

It is important to distinguish SCAR from cADRs in terms of epidemiology, etiology, clinical characteristics, prognosis and outcomes.

1.1 Introduction

An ADR, as defined by the World Health Organization (WHO), is “any noxious, unintended and undesired effect of a medicinal product, given at normally used dose in man, for the prevention, diagnosis or treatment of any condition or for the modification of physiological function”.[1] Cutaneous adverse drug reactions (cADRs) are common, comprising 10 to 30% of all reported ADRs.[2,3] Among hospitalized patients, the incidence of cADRs has been estimated to be 2 to 3%.[4] Cutaneous manifestations of ADRs range from benign maculopapular eruption to life-threatening toxic epidermal necrolysis and from those localized only to skin to those associated with systemic disease.

Three prospective studies which investigated the epidemiology of dermatologist-diagnosed cADRs in a hospital setting documented prevalence rates of 3.6 to 7 per 1000 hospitalized patients. The first study from France detected 48 cADRs among 13 294 hospitalizations over six months, yielding a prevalence of 3.6 per 1000 hospitalized patients.[5]

Reactions were considered serious in 34% of cases because they were responsible for hospitalization (18%), increased the duration of hospitalization (14%) or were life threatening (2%). The second study from Mexico documented a cADR prevalence of 7 per 1000 inpatients (35/4765 hospital discharges over 10 months) and 17% were severe.[6] The third study from Malaysia identified 43 cADRs among 11017 hospitalized patients over a six month period, yielding a prevalence of 3.9/1000 admissions and 51.2% were SCAR.[7]

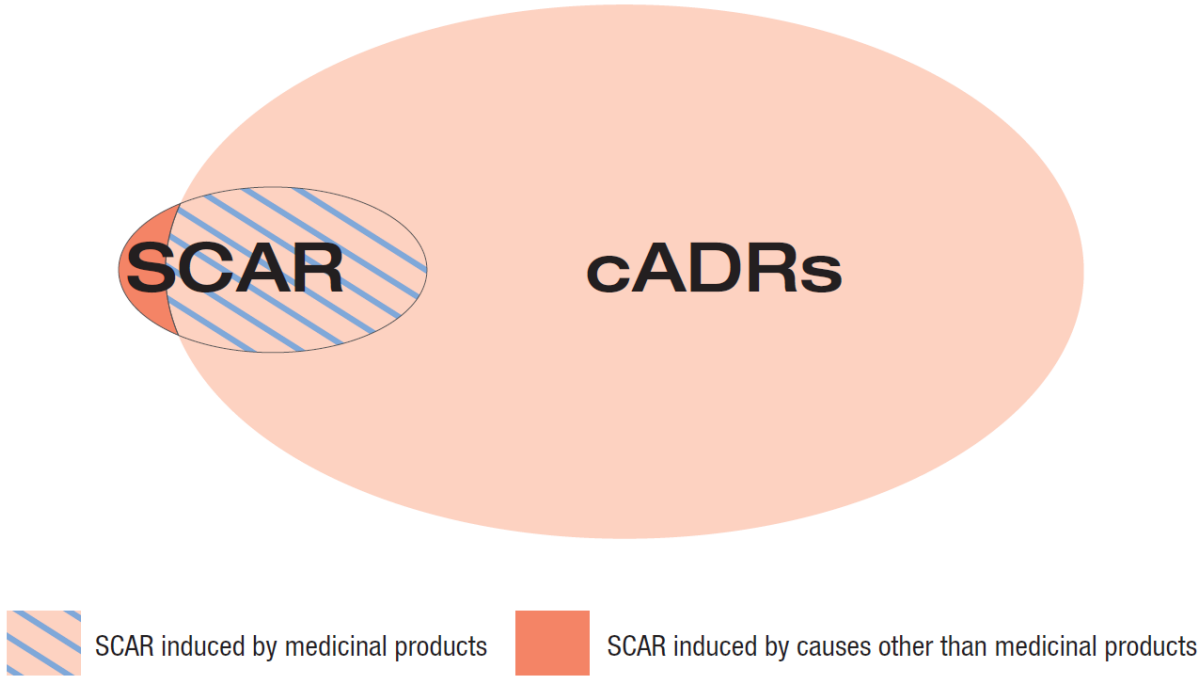
SCAR comprise Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS), acute generalized exanthematous pustulosis (AGEP) and generalized bullous fixed drug eruptions (GBFDE). Medicinal products are responsible for > 85% of SCAR in adults.[8] T-cell-mediated delayed hypersensitivity reactions, triggered by interactions between small-molecule drugs, HLA class I molecules and T-cell receptors, underlie the pathogenesis of most SCAR.

1.2 SCAR and non-SCAR

The majority of cADRs are non-serious and not life-threatening. A serious AE or reaction to a medicinal product is defined as any untoward medical occurrence that at any dose satisfies any of the following criteria:[9,10]

- results in death,
- is life-threatening,
- requires inpatient hospitalization or prolongation of existing hospitalization,
- results in persistent or significant disability/incapacity,
- is a congenital anomaly/birth defect, or
- other medically important event or reaction.[9,11]

SCAR are a heterogeneous group of delayed T-cell-mediated hypersensitivity reactions, which are most frequently triggered by medicinal products.[8] They are life-threatening and therefore, serious reactions with reported case fatality between 5% for SJS and 30% for TEN. However, SCAR are not exclusively caused by medications and can be induced by various non-medicinal product causes including infections.[8-14]



Note:
SCAR = 0.1-1% of all cADRs
SCAR induced by causes other than medicinal products = 5-10% of all SCAR

Figure 1. SCAR and cADRs

For instance, SJS and TEN which represent different severity spectra of the same disease, now termed epidermal or epithelial necrolysis (EN), are not caused by medications in about 1/3 of cases.[13,14] For effective pharmacovigilance and benefit–risk management of medications, accurate estimates of the incidence of SCAR are important to characterize and quantify SCAR risk[9,10]. Based on the CIOMS definition, medicinal product-induced SCAR are attributable to any medicine with a causality grading of at least "possible", which may improve the accuracy of SCAR evaluation in pharmacovigilance.

1.3 Benign cADRs (non-SCAR ADRs)

Clinical phenotypes of cADRs are very diverse and most of them are benign non-life-threatening reactions such as maculopapular exanthem (MPE), urticaria, FDE, lichenoid eruptions, vasculitis and others. A summary of differences between SCAR and non-SCAR is provided in Table 1 below. MPE is the most common benign cADR to medicinal products.[7-13] MPE is characterized by a maculopapular/morbilliform eruption which usually appears one to two weeks after medicinal product exposure but may occur up to one week after stopping it. On re-exposure to the causative or related medicinal product, onset of MPE is much shorter, within one to three days after re-exposure. Medicinal products commonly implicated are penicillin, sulfonamides, cephalosporins and anti-epileptics. MPE resolves within one to two weeks on medicinal product withdrawal. It is a generally benign reaction but may be a first sign of DRESS. Factors favouring DRESS are fever, extensive skin involvement affecting more than 50% body surface area (BSA), facial swelling and a delayed onset of two to six weeks. (Figure 2)

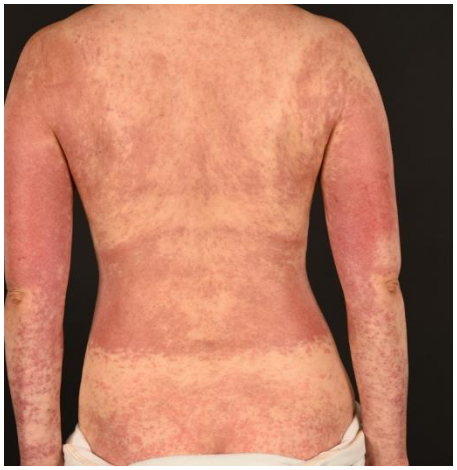


Figure 2 Characteristic morbiliform eruption in a patient with dapsone-induced reaction
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Morbilliform rashes are a common manifestation of viral infections but unlike medicinal product eruptions which usually first appear on the trunk and then spread to the limbs and neck, a viral exanthem usually starts on the face and exhibits a cephalic-caudal spread. MPE is also a well-known eruption seen in patients with infectious mononucleosis after exposure to aminopenicillins. Another notable benign, non-life-threatening cADR is a FDE which characteristically recurs on the same site or sites each time a culprit medicinal product is consumed.[15-17]

Skin lesions are well-demarcated, round, or oval erythematous or violaceus patches which may be surmounted by bullae. FDE typically settled with hyperpigmentation on medicinal product withdrawal. If patient is re-exposed to causative or related medicinal product, the same pigmented patch become red and swollen again and patient may develop more lesions with repeated exposures. The lesions usually develop within 30 minutes to eight hours of taking the medicinal product.

Sites of predilection include hands and feet, lips, eyelids, and genitalia. Blisters and extensive ulceration may occur on mucosal sites (lips, vulva, penis). Medicinal products frequently implicated include non-steroidal anti-inflammatory drugs (NSAIDs), antibiotics (namely sulfamethoxazole, tetracyclines, dapsone), barbiturates and paracetamol/acetaminophen.

FDE may be solitary at first, but with repeated exposure to the culprit medicinal product, new lesions appear, and existing ones may increase in size leading to GBFDE. Hence, patients with FDE should be educated to avoid implicated and cross-reacting medicinal products to prevent potentially life-threatening GBFDE, which has a similar prognosis to SJS/TEN.[16]

	SCAR	Non-SCAR cADRs
Frequency	• SJS/TEN: 1–13 cases per million persons per year.[6-8,12,17-33] • DRESS: 21.8 cases per million persons.[18] • AGEP: 1-5 cases per million persons per year.[19-26]	• 10-30% of all reported ADRs.[2,3] • 2-3% of all hospitalized patients.[4] • 0.36-0.7% (dermatologists diagnosed) of hospitalized patients in 3 prospective studies.[5-7]
Common etiology	• Allopurinol • Antibiotics • Antiepileptic agents • Nonsteroidal anti-inflammatory drugs (NSAIDs) • Sulfonamides	All medicinal products may cause non-SCAR cADRs
Latency period from medicinal product exposure to onset of skin rash	Variable, but for SJS/TEN and DRESS, it is usually longer than for non-SCAR cADRs • SJS/TEN 7-21 days • DRESS: 17-31 days • AGEP: 1-2 days • GBFDE: a few hours	• 1-3 days for urticaria or FDEs • 1-2 weeks for MPE or other non-SCAR cADRs
General symptoms	Fever, general malaise, and sore throat are common	May have mild fever
Skin manifestations	Widespread lesions, rapid progression • Blisters • Targetoid lesions • Pustules • Facial swelling • Purpuric changes • Skin pain (especially in SJS/TEN and GBFDE) • Nikolsky sign in SJS/TEN	Localized or widespread lesions; mainly macular or popular lesions; no blisters/pustules/skin pain/Nikolsky sign
Mucosal involvement	Often	Very rare
Hospitalization for intensive care	Needed	Usually not needed
Laboratory data	Variable, but relatively more common than non-SCAR • SJS/TEN and AGEP: Leukocytosis • DRESS: leukocytosis, eosinophilia, atypical lymphocytosis, abnormal liver/renal function tests	Uncommon, except mild eosinophilia
Visceral organ involvement	Variable, but relatively more common than non-SCAR • Very common in DRESS	Rare
Outcome	Life threatening • SJS/TEN: case fatality 5-30% • DRESS: 2-10% • AGEP: < 5% • GBFDE: ~10%	Benign, non-life threatening

Table 1. Comparison between SCAR and non-SCAR

1.4 Different types of SCAR

1.4.1 SJS/TEN/EMM

1.4.1.1 Epidemiology

SJS, SJS/TEN-overlap and TEN represent different severity spectra of the same disease, namely epidermal necrolysis (EN). The latter, however, is distinct from erythema multiforme major (EMM), which is exclusively the result of infections. In the past, EMM was assumed to be a less severe form of SJS because of similar clinical and histopathologic features, but it is not a SCAR. A number of studies have explored the incidence of drug-induced epithelial necrolysis. Hospital-based studies and studies using large electronic databases documented an annual incidence of 1–13 cases per million persons.[5-33] A prospective population-based study that used the German SCAR registry estimated the incidence of SJS/TEN in Germany to be one to two cases/million population/year.[27] A nation-wide population-based study that used a national health insurance database in South Korea from 2010 to 2013 reported 5.9 cases of SJS/TEN/million/year.[32]

A study conducted in the United Kingdom (UK) using Clinical Practice Research Datalink from 1995 to 2013 validated 551 cases, yielded an incidence of 5.76 SJS/TEN cases/million/year.[33] The twofold increased risk of SJS/TEN observed among Asians and Blacks in this study confirmed the finding of an earlier study from the United States (US), which was based on the Nationwide Inpatient Sample from 2009 to 2012 and documented an incidence of 12.7 cases of SJS /TEN/million adults/year with an increased risk in nonwhite populations (Asians; OR 3.27, 95% CI 3.02, 3.54 and Blacks; OR 2.01, 95% CI 1.92, 2.10).[31] SJS and TEN can occur at any age, but the median age among more than 2200 and 2635 EN incidents in Germany and France, respectively, was about 50 years old with a slight female preponderance.[17,27]

1.4.1.2 Common etiology (medicinal products)

Although SJS and TEN are life-threatening SCAR, infections such as mycoplasma pneumonia and herpes simplex virus were also implicated as causes.[33] No offending agent was identified in about 15-30% of cases. The EuroSCAR group identified allopurinol, anti-infective sulfonamides, antiepileptic agents (namely carbamazepine, phenobarbital, phenytoin and lamotrigine), and NSAIDs of the oxicam type as high-risk drugs for induction of EN based on two case-controlled studies; first, conducted from 1989 to 1995, included 372 cases and 1720 controls and another between 1997 and 2001 of 379 validated cases and 1505 controls.[12,34] A study by the Asian SCAR consortium of 1028 validated cases of SJS/TEN treated from 1998 to 2017 showed that anti-epileptics were the most common culprits followed by anti-infectives and allopurinol.[35] Oxcarbazepine, sulfasalazine, COX-II inhibitors, and strontium ranelate were identified as potentially new causes in Asia.

In addition to sulfa drugs and beta-lactam antibiotics, quinolones were also a common cause while several medications (e.g. oseltamivir, terbinafine, isotretinoin, and sorafenib) labelled as carrying a risk of SJS/ TEN by FDA were not found to have caused any of the cases in the Asian countries investigated in this study.

1.4.1.3 Clinical characteristics (that assist diagnosis by highlighting key clinical manifestations)

SJS/TEN are characterized by EN with varying degree of blistering, skin detachment and sloughing. By consensus, SJS, SJS/TEN overlap and TEN are defined as EN with skin detachment affecting < 10%, 10-30% and >30% of the total body surface area (TBSA) respectively. Drug-induced SJS/TEN usually developed 4-28 days after initiation of culprit drugs. Cutaneous manifestation is often preceded by a prodromal period with symptoms such as fever, malaise, sore throat and cough.

Typical cutaneous lesions start as purpuric macules or atypical target lesions on upper torso, proximal limbs and face before spreading to the rest of body including palms and soles. Skin pain is an important early symptom and lesional skin is tender with dusky or vesicular centres that progress to become confluent areas of dusky erythema or flaccid bullae with a positive Nikolsky sign. Extensive necrolysis leads to sheets of denuded epidermis that exude serum, bleed easily and may become secondarily infected (Figure 3).

Figure 3. Extensive skin detachment characteristic of TEN
This figure was provided by the Working Group and included in the report with appropriate permission

Mucosal involvement is universal, with two or more mucosal surfaces being involved in up to 80% of cases.[36] Oral involvement is most common, with haemorrhagic mucositis and ulceration occurring in 93-100% of cases.[37,38] Ocular involvement is seen in 60-100% of cases with severity ranging from conjunctival hyperaemia to complete epidermal sloughing of the ocular surface. Early ophthalmologist consultation is essential to prevent long term ocular sequelae. Genital involvement is seen in up to 71% of female patients. SJS/TEN may also involve other organs including pulmonary, hepatic, gastrointestinal, otorhinolaryngologic, genitourinary and renal systems.[5,36]

SJS/TEN may be distinguished from EMM, which is characterized by a typical round target lesion with a darker centre with or without a blister surrounded by a raised, lighter, pale pink ring and a bright red outermost ring (Figure 4), whereas atypical target lesions in SJS are irregular in shape and flat.

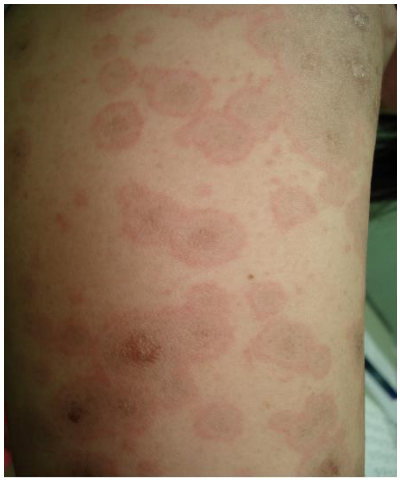

Figure 4. Typical round target lesions with a darker centre surrounded by a lighter, pale pink ring and a bright red outermost ring in a patient with EMM

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Classic target lesions of EMM are predominantly on the limbs and acral regions whereas EN lesions start on the torso before they become generalized. Additionally, EMM occurs in younger patients and is exclusively associated with infections whereas SJS is predominantly a SCAR which affects older adults. German registry data show that 65% of SJS patients were older than 40 years whereas more than 80% of patients with EMM were younger than 40 years and 45% were under 18 years.[27,38]

GBFDE is an important differential diagnosis of SJS/TEN. The classic, discrete, large and well-defined violaceous or brownish round or oval patches with or without a central blister are very characteristic and can be readily distinguished from the confluent purpuric macules and patches of SJS and the large, denuded epidermis of TEN.

Patients with GBFDE usually do not have fever and the typical haemorrhagic mucosal involvement of SJS/TEN. Patients with GBFDE often have a history of previous eruptions in which the healed hyper-pigmented patches become inflamed again on re-exposure to culprit medicinal products. Staphylococcal scalded skin syndrome (SSSS) is another disease with blisters and skin detachment, but target or haemorrhagic mucosal lesions are not present and SSSS mainly affects children.

1.4.1.4 Laboratory features

Histopathologically, EN is characterized by variable keratinocytes necrosis and basal layer liquefaction degeneration. With advanced disease, full-thickness epidermal necrosis occurs with sub-epidermal bullae. This is accompanied by mild perivascular mixed infiltrates of predominantly lymphocytes and histiocytes with some eosinophils. SJS/TEN may be distinguished from SSSS by the level of epidermal detachment, which is sub-corneal in SSSS and sub-epidermal in SJS/TEN. Widespread keratinocyte necrosis is characteristic of SJS/TEN. It is difficult to distinguish early stage SJS/TEN from EMM by histology because both diseases are characterized by a vacuolar or lichenoid interface with scattered necrotic keratinocyte and a mixed perivascular infiltrate. As both diseases progress, a sub-epidermal split with increased epidermal necrosis is observed. A heavier lymphocytic infiltrate favours EM while increased eosinophils and confluent epidermal necrosis favours SJS/TEN. Histology is particularly useful to rule out SSSS which is characterized by a superficial sub-corneal blister, lack of epidermal necrosis and minimal inflammatory cells.

1.4.1.5 Prognosis and outcome (long-term sequelae)

EN is a potentially life-threatening SCAR with an overall case fatality between 10% and 20%.[17-31] Potential prognostic markers associated with death include delayed transfer to a specialist unit, advancing age, increasing skin detachment, presence of septicaemia and granulocytopenia. Survivors may have long-term physical sequelae such as cutaneous and ophthalmologic scarring, dyspigmentation, dental complications, genitourinary symptoms and pulmonary disease.[39,40] Long-term psychological outcomes include post-traumatic stress disorder anxiety, depression and decreased health-related quality.[39-42]

A recent survey conducted at 11 academic health centres in the U.S. between 1 January 2009, and 30 September 2019 which included 121 adult survivors of EN showed that the most common physical sequelae were cutaneous problems (84.3%), followed by ocular problems (59.5%) and oral mucosal problems (50.8%). Of screened participants, 53.3% of were positive for depression and 43.3% were positive for anxiety.[40]

1.4.2 DRESS/DIHS

1.4.2.1 Epidemiology

DRESS/DIHS is a rare, multi-systemic SCAR. The epidemiology of DRESS is not well characterized. However, it is estimated to occur in up to 2 per 100,000 patients based on EHRs.[18] and accounts for 10-20% of cADRs seen in a hospitalized setting.[43,44]

1.4.2.2 Common etiology (medicinal products)

Aromatic antiepileptic (such as carbamazepine, phenytoin, lamotrigine, oxcarbazepine, phenobarbital) are the most common causal drugs, accounting for 35% of cases. Other highly associated medications include allopurinol, infective sulfonamides and other antibiotics such as vancomycin, minocycline and amoxicillin.[45] A prolonged latency between drug initiation and the onset of reaction is characteristic of DRESS with a median latency estimated at 22 days (IQR 17-31 days).[44] However, shorter latency periods have been reported for cases due to iodinated contrasts and antibiotics.[46,47]

In recent years, various pharmacogenetic associations between certain medicinal products and ethnicity have been established. These include *HLA-A*32:01* and vancomycin-induced DRESS in Europeans; *HLA-A*3101* and carbamazepine-induced DRESS in European, Japanese and Han Chinese; B*1301 and dapsone-induced DRESS in Han Chinese; and B*13:01, B*15:01 and phenytoin-induced DRESS in Han Chinese and Thai.[48,49]

1.4.2.3 Clinical characteristics (that assist diagnosis by highlighting key clinical manifestations)

DRESS is a multi-systemic ADR with a heterogeneous presentation and variable clinical course. Diagnostic criteria based on the Japanese (J-SCAR) and RegiSCAR criteria are shown in Tables 2 and 3 below. Initial symptoms may be prodromal in nature such as fever and malaise.

1. Maculopapular rash developing > 3 weeks after starting with a number of drugs[a] 2. Prolonged clinical symptoms 2 weeks after discontinuation of the causative drug 3. Fever > 38º C 4. Liver abnormalities (*alanine aminotransferase > 100U/L)*[b] 5. Leukocyte abnormalities (at least one present) a. Leukocytosis (> $11x10^9$/L) b. Atypical lymphocytosis (> 5%) c. Eosinophilia (> $1.5x10^9$/L) 6. Lymphadenopathy 7. Human herpesvirus 6 reactivation
[a] There are eight drugs to treat the majority of cases in Japan: carbamazepine, phenytoin, phenobarbital, zonisamide, mexiletine, dapsone, salazosulfapyridine and allopurinol. [b] This can be replaced by other organ involvement, such as renal involvement

749 **Table 2. J-SCAR diagnostic criteria for drug-induced hypersensitivity syndrome**[50]
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A diagnosis is confirmed by the presence of all seven of the above criteria (typical DIHS) or five of the criteria (1 to 5, atypical DIHS).

Assessment/ Score	-1	0	1	Comment
Fever ≥ 38.5º C	No/U	Yes		Acute episodes
Enlarged lymph nodes		No/U	Yes	>1cm, **≥** 2 different areas (right side plus left side is not adequate)
Eosinophilia ˙Eosinophils≧700/μL or ˙**≥**10% if leukocyte <4000/μL		No/U	Yes	Score 2 for extreme eosinophilia ˙Eosinophils **≥**1500/μL or ˙**≥**20% if leukocyte <4000/μL
Atypical lymphocytes		No/U	Yes	
Skin rash				Onset < 21 days before hospitalization
Extent > 50% body surface area		No/U	Yes	
Rash suggesting DRESS	No	U	Yes	**≥**2 symptoms: purpuric change, facial edema, infiltration, psoriasiform desquamation
Biopsy suggesting DRESS	No	Yes/U		Score -1 if results fit any other specific dermatopathologic diagnosis
Organ involvement				Excluding other causes, score max. of 2
Liver: any criterion		No/U	Yes	ALT>2*UNL, twice on successive dates D-bil.>2*UNL, twice on successive dates AST, T-bil., ALP all>2*UNL, once
Kidney: any criterion			Yes	Creatinine>1.5* patient's baseline Proteinuria above 1g/day
Lung: any criterion			Yes	Evidence of interstitial lung (CT, x-ray) Abnormal bronchoalveolar lavage Abnormal blood gases
Muscle/Heart: any criterion			Yes	Raised creatine kinase Raised troponin T Abnormalities in the echocardiogram
Pancreas			Yes	Amylase >2* UNL
Other organs			Yes	Central nervous system, splenomegaly
Rash resolution ≥ 15 days	No/U	Yes		
Excluding other causes		No/U	Yes	Score 1 if **≥** 3 tests are performed and negative
Hepatitis A, B, C				At least 2 tests are negative and 1 unknown: negative
Mycoplasma/Chlamydia				At least 1 test is negative and 1 unknown: negative
Antinuclear antibody				
Blood culture				Sampling within 3 days of hospitalization
Final Score				

Final scores: <2: excluded; 2-3: possible; 4-5: probable; >5: definite

Abbreviations: ALP, alkaline phosphatase; ALT, alanine transaminase; AST, aspartate transaminase; CT, computed tomography; D-bil., direct bilirublin; max., maximum; T-bil., total bilirulin; U, unknown; UNL: upper normal limit

Table 3. RegiSCAR scoring system for DRESS diagnosis [51]
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Cutaneous eruptions are extensive and may be polymorphic in presentation. These include maculopapular eruptions, infiltrated plaques, pustules, target-like lesions, purpura, eczematous lesions and erythroderma. Facial erythema and swelling are prominent features of DRESS. Mucosal involvement is not a prominent feature, unlike SJS/TEN.

Various internal organs may be involved including the liver, kidneys, lungs, heart, nervous system and others. In a prospective multinational registry, RegiSCAR, the most frequently involved organs are the liver (75%), kidneys (37%) and lungs (32%).[44] Although a cutaneous eruption is the most striking feature, the onset and clinical course of the internal organ may not parallel that of the skin.

***Liver involvement**:* The patterns of liver injury in DRESS can be classified into cholestatic (37%), hepatocellular (19%) and mixed (27%). Up to 50% of cases may have severe involvement with liver enzymes being more than 10 times higher than the upper limit of normal.[52] Acute liver failure is uncommon and transplant is rarely required.

***Kidney involvement**:* Renal involvement in DRESS occurs in up to 40% of patients and up to 8% of patients may develop acute renal failure.[53] Renal involvement occurs more commonly in cases associated with allopurinol and vancomycin.[44-54]

***Cardiac involvement**:* Cardiac involvement occurs in up to 20% of cases and presenting features include tachycardia, dyspnoea, hypotension, chest pain and electrocardiogram (ECG) changes. Myocarditis can occur months after the offending medicinal product has been discontinued and when the cutaneous and laboratory features have abated, leading to its under-diagnosis.

There are two forms of DRESS-associated myocarditis: hypersensitivity myocarditis (acute eosinophilic myocarditis) and a more severe form, acute necrotizing eosinophilic myocarditis. In the more severe form, acute necrotizing eosinophilic myocarditis, case fatality approximates 50%.[55]

***Pulmonary involvement**:* Pulmonary involvement may initially present with dyspnoea, cough or pleurisy. The manifestation is diverse, ranging from impaired pulmonary function tests, interstitial pulmonary infiltrates, pneumonia, pulmonary nodules, effusion and acute respiratory distress syndrome (ARDS). In a systematic review of reported DRESS/DIHS cases with pulmonary involvement, pneumonitis was the most common (50%), followed by ARDS (31%) and pleural effusion (23%).[56]

***Blood**:* Haematologic abnormalities are common in DRESS/DIHS with eosinophilia (95%) and atypical lymphocytes (70%) being the most common. Other findings include, leukocytosis, neutrophilia, lymphocytosis, monocytosis, thrombocytosis and thrombocytopenia.[44]

Other reported systemic involvements include neurological (e.g. encephalitis, Bell's palsy, peripheral neuropathy), gastrointestinal (e.g. cholecystitis, pancreatitis, colitis, intestinal perforation), myositis as well as thyroid dysfunction. The acute phase of the disease is prolonged. 90% of cases persist beyond 15 days and up to 20% of patients persist beyond 90 days.[57]

In addition, the clinical course may be punctuated by relapses and flare-ups. The latter occur in up to 25% of DRESS and such reactions are typically cutaneous, although organ involvement may occur as well.[58]

Flare-up reactions typically occur in patients treated with systemic corticosteroids that has undergone rapid dose tapering and this may be related to a viral reaction of human herpes virus. Relapses can occur with the re-introduction of structurally different drugs, antibiotics in particular, which were administered during the acute phase of the disease.[59]

1.4.2.4 Prognosis and outcome (long-term sequelae)

The case fatality in DRESS vary between 2-10%. The presence of cytomegalovirus (CMV) reactivation is a poor prognostic factor.[60] Long-term sequelae have been reported in up to 12 % of survivors, such sequelae are typically autoimmune in nature and consist of Grave's disease, type 1 diabetes mellitus, vitiligo, alopecia areata, autoimmune hemolytic anemia, lupus erythematosus.[61-63]

1.4.3 AGEP

1.4.3.1 Epidemiology

AGEP was originally classified as a variant of generalized pustular psoriasis (GPP), termed exanthematic pustular psoriasis. In a comprehensive review of 104 GPP cases in 1968, Baker & Ryan, identified five cases of exanthematic GPP which were characterized by acute onset of numerous discrete pustules in patients with no known history of psoriasis. Exanthematic GPP usually develops after upper respiratory tract infection (URTI) or after ingestion of drugs used to treat URTI. It is self-limiting and resolved spontaneously in one to two weeks.[64] Without a prior history of psoriasis and the lack of recurrence, the authors postulated that these skin eruptions were likely triggered by drugs and/or infections[53,65] Baker and Ryan's description of exanthematic GPP is reminiscent of AGEP, a term coined by Beylot et al.[65] in 1980 to describe this distinctive drug-induced eruption.

AGEP is a rare SCAR with reported incidence of one to five cases per million per year.[19] A recent retrospective review of 340 probable or definite cases of AGEP based on EuroSCAR criteria from 10 academic dermatology departments in the U.S. between January 1, 2000, and July 30, 2020 showed a female preponderance (62.9%) with a mean age of 57.8 (±17.4) years.[20] Female preponderance was also observed in the EuroSCAR study of nine cases[21] as well as studies from France[22], Israel[23,24], Malaysia[25], Singapore[26] and Taiwan.[66] Although no gender variation was observed in some studies, a recent literature review of 250 case reports or case series which included 297 AGEP confirmed a female preponderance.[67]

1.4.3.2 Common etiology (medicinal products)

The majority (>85%) of AGEP cases are drug-induced.[64,65] Infections with Parvovirus B19, CMV, Coxsackie B4 and Mycoplasma pneumoniae have been implicated. However, the EuroSCAR case control study of 97 cases of AGEP with 1009 normal controls found no significant risk for infections.[21] Hypersensitivity to mercury, Rhus (lacquer) and spider bites have also been reported as triggers for AGEP.[65] Aminopenicillins, pristinamycin, sulfonamides, quinolones, hydroxychloroquine, terbinafine and diltiazem are frequent causative drugs, but the list of reported culprit medicinal products is very long. A recent review identified 93 drugs, which caused 259 positive patch tests in 248 patients with AGEP. Beta-lactam antibiotics caused the highest number of reactions (25.9%), followed by other antibiotics (20.8%), iodinated contrast media (7.3%), and corticosteroids (5.4%), together accounting for nearly 60% of all AGEP cases. The highest number of AGEP cases to individual drugs was to amoxicillin (n = 36), followed by pristinamycin (n = 25), diltiazem (n = 14), amoxicillin-clavulanic acid (n = 13), clindamycin (n = 11), and iomeprol (n = 8).[68] In the US study of 340 validated cases, AGEP was attributed to medicinal products (85.6%), intravenous contrast agents (2.1%), infection (0.9%), or unknown (11.5%) and β-lactam antimicrobials (41.7%) were the most common drug classes that were implicated, followed by non–β-lactam antimicrobials (33.8%), anticonvulsants (6%) and calcium channel blockers (3.3%).

1.4.3.3 Clinical characteristics (that assist diagnosis by highlighting key clinical manifestations)

AGEP is characterized by a sudden onset of numerous pinpoint, non-follicular sterile pustules on oedematous erythematous skin. The most characteristic feature of AGEP is its clinical course. It has a very rapid onset and equally rapid resolution.(Figure 5)

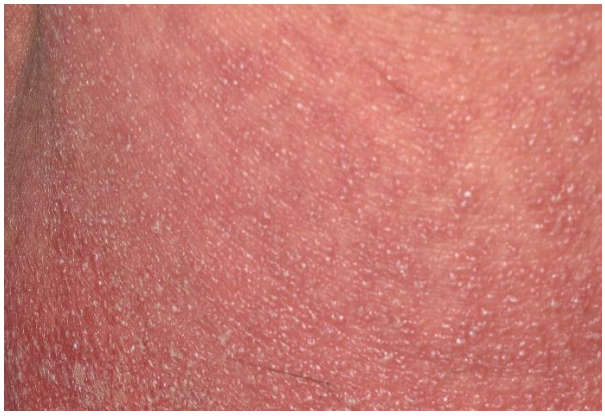

Figure 5. Numerous pinpoint, nonfollicular pustules and confluent pus lakes on oedematous erythematous plaques on the inner thigh of a patient with AGEP

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Skin lesions appear rapidly within 24-48 hours of medicinal product exposure and resolve as rapidly within five to seven days upon medicinal product withdrawal followed by collarette pin-point desquamation. Distribution is usually widespread but may be limited, in which case lesions are usually confined to body folds. Flexural predominance and facial involvement are characteristic. Mucosal involvement is uncommon. It is reported in about 20% and usually manifest as nonerosive cheilitis. Skin eruption is usually pruritic. The pinpoint pustules may coalesce to form bigger, but subcentimetre pustules. Atypical presentations such as huge erosions resembling TEN, purpuric and erythema multiforme-like lesions have been reported.

Skin eruptions in AGEP are often accompanied by fever 38.0 °C. AGEP usually resolves fully within 15 days. In a study of 58 patients with AGEP, 17% had internal organ involvement (namely hepatic, renal and pulmonary dysfunction) that resolved on drug withdrawal and supportive treatment with no mortality.[19] Neutrophilia, elevated CRP and re-challenge are identified as risk factors for organ involvement. In a recent U.S. study, 8.4% of 298 patients with AGEP had an acute elevation of aspartate aminotransferase and alanine aminotransferase levels with a peak at 6 (IQR, 3-9) days and 7.8% of 319 patients experienced acute kidney insufficiency, with at 4 (IQR, 2-5) days after onset of AGEP. Reported case fatality of AGEP is 5% mainly due to secondary infections in older patients with comorbidities. All-cause mortality in the study population within 30 days was 3.5%, but none was deemed to be due to AGEP.[64]

1.4.3.4 Laboratory features

AGEP is almost always accompanied by absolute neutrophilia (>7000/mL) which was seen in about 85% of 309 cases with available data in the U.S. study.[64] Thirty to 50% of patients had eosinophilia and 65-75% of patients had hypocalcemia.[21,64] Key histopathologic features of AGEP include intra-corneal, sub-corneal and intra-epidermal spongiform pustules containing a mixed infiltrate of neutrophils and eosinophils.[69] Other epidermal features include keratinocyte necrosis, neutrophilic exocytosis and mild psoriasiform hyperplasia. Characteristic dermal findings are papillary oedema, a neutrophil-rich superficial to mid-dermal perivascular and interstitial infiltrates that regularly contain eosinophils. Red blood cell extravasation and mild leukocytoclasia are common, but frank vasculitis is not a feature.

1.4.3.5 Prognosis and outcome

AGEP is a rare distinctive SCAR. It may be associated with systemic complications in a minority of patients and typically resolves upon withdrawal of culprit medicinal products. Reported case fatality is <5%.

1.4.4 GBFDE

1.4.4.1 Epidemiology

GBFDE may be defined as widespread typical FDE with blisters and erosions affecting more than 10% of BSA on at least three out of six sites:

1) head and neck,
2) anterior trunk,
3) back,
4) upper limbs,
5) lower limbs and
6) genitalia.[17]

FDE is most common in adults, but can affect children and the elderly whereas GBFDE mainly affects elderly patients.[15-17] In a survey of 58 patients with GBFDE, the median age of patients was 78 years (range 68–84 years).[16]

1.4.4.2 Common etiology (medicinal products)

Since GBFDE may evolve from FDE after repeated exposure to the culprit medicinal product, implicated medicinal products are similar to those responsible for FDE, namely NSAIDs, antibiotics (namely sulfamethoxazole, tetracyclines, dapsone), barbiturates and paracetamol/acetaminophen. Other implicated substances include tartrazine in food and cold medication, and quinine in alcoholic beverages made with tonic water. GBFDE has been reported following influenza and COVID-19 vaccination.[70,71]

1.4.4.3 Clinical characteristics (that assist diagnosis by highlighting key clinical manifestations)

GBFDE is characterized by well-demarcated erythematous, violaceous or dusky red round or oval patches with blisters and erosions. Most patients report a positive history of similar eruptions. GBFDE may be confused with SJS/TEN due to the extensive bullous eruption with erosions. Clinical clues which favour a GBFDE diagnosis are (Figure 6):

1) characteristic well-demarcated erythematous, violaceous or dusky red round or oval patches, which resolves with typical hyperpigmentation
2) absence of small spots and targetoid lesions,
3) lack of or minimal mucosal involvement,
4) lack of constitutional symptoms such as fever, and
5) rapid onset of rash within a few hours after drug exposure compared to 1-3 weeks reported in EN.

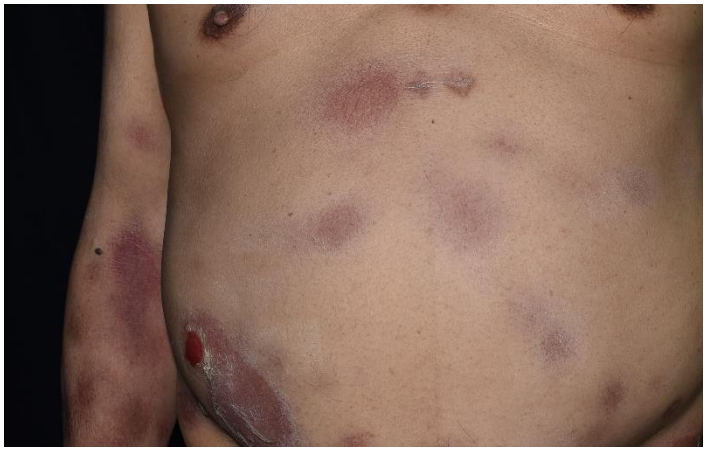

Figure 6. Many well-demarcated, dusky red, round or oval patches with blisters and erosions on the trunk and limbs of a patient with GBFDE

1.4.4.4 Laboratory features

GBFDE and SJS/TEN share overlapping histopathologic features. Histopathologically, GBFDE is characterized by subepidermal blisters, vacuolar interface dermatitis with variable mild to moderate density of perivascular and interstitial infiltrate, composed of eosinophils and lymphocytes in both the superficial and deep dermis. Pigmentary incontinence is a typical feature and discrete apoptotic/necrotic keratinocytes are scattered throughout the epidermis. In contrast, SJS/TEN, especially TEN, is characterized by a near absence of or sparse inflammatory infiltrate and extensive, confluent full-thickness epidermal necrosis.

1.4.4.5 Prognosis and outcome

GBFDE is generally associated with a much better prognosis than SJS/TEN based on case reports and small case series. However, a case control study comparing 58 patients with GBFDE to 170 patients with SJS/TEN showed that there was no significant difference in the case fatality between the two groups. This study population was drawn from patients reported to the EuroSCAR group as potential SJS/TEN and diagnosis of GBFDE was validated based on the presence of at least two of the following criteria:

1) similar reaction in the past,
2) fewer than two mucous membranes involved,
3) absence of spots or target lesions,
4) large and well-demarcated blisters and erosions, and
5) lesions and erosions on at least two different sites of the body regardless of the extent of the lesions.

However, 31% of the 58 patients[16] had at least two affected mucosal sites. A validated international diagnostic criterion for GBFDE is needed to determine the burden of this rare SCAR accurately.

1.5 SJS/TEN/DRESS/AGEP overlap

Because the initial presentation of SCAR may vary, diagnosis is difficult and suggests the possibility of overlap among SCAR may occur. AGEP, with a confluence of pustules resulting in superficial detachment, may manifest similar to TEN.[72] Cases of "overlap" between DRESS and TEN have been reported, suggesting the difficulty in classifying SCAR under certain circumstances.[73] Various T-cell - mediated delayed hypersensitivity reactions can be related to the preferential activation of medicinal product-specific T cells with distinct functions. These complex immune reactions are not exclusive and may be combined. Therefore, an overlap of immune reactions is possible, even if one type is often dominant, and could explain clinical ambiguities among SCAR.

A retrospective study of SCAR cases revealed the frequent occurrence (n = 45; 21%) of SCAR cases that were based on different diagnoses (possible, probable or certain), which reflects the clinical ambiguity among several SCAR.[74] In such situations, the clinician is confronted with an uncertain diagnosis of several disease entities. However, only three "true" overlap SCAR were documented, representing 2.1% of the 145 confirmed SCAR cases.[74] The above results indicate that overlap of SCAR does exist but is rare, if the retrospective analysis was performed using a diagnostic algorithm.

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CHAPTER 2.

DIAGNOSIS AND IDENTIFICATION OF SCAR CASES

Chapter summary

- The first step in analysing a putative SCAR is to make a diagnosis even if tentative. DRESS, SJS/TEN and some other SCAR conditions have defined diagnostic criteria which may overlap and can hence be challenging to diagnose in the earliest stages.
- The HCP must determine medicinal product exposure (name and dosage) and lag period (the time between initiation of the medicinal product and the onset of the first symptoms of the ADR).
- All medications, especially those taken in the eight weeks prior to the cADR, must be considered as possible causative agents.

Conclusions or recommendations

A SCAR diagnosis should consider patient history, visual assessment (appearance, morphology), severity and the presence of systemic symptoms, skin histopathology, followed by a causality assessment in the individual patient.

2.1 Introduction

ADRs have a wide spectrum of clinical manifestations. They are caused by various medicinal products and result from varied pathophysiologic mechanisms. Hence, their diagnosis and management are challenging. cADRs can range in clinical manifestations; from a mild exanthem involving only the skin to a reaction including systemic symptoms in addition to the skin manifestations, which can be fatal such as in the cases of life-threatening ADRs.[1]

Generally, cADRs are either common and mild or rare and severe reactions. However, medicinal products associated with common and severe reactions are typically not approved for clinical use. Rare and mild reactions usually go unnoticed or are not reported by patients. In most cases, cADRs are classified as “simple” or “complex.” A “simple” reaction only involves the skin, while a “complex” reaction includes systemic involvement of organs in addition to involvement of the skin.[2]

2.1.1 Diagnosis

The diagnosis of a cADR is generally based on three key clinical elements:

1) Appearance: the morphology of the cADR including four main categories of the primary lesion: maculopapular (exanthem, enanthem), urticarial, bullous and pustular.

2) Systemic signs that differentiate between a simple reaction involving only the skin and a complex reaction that comprises systemic involvement in addition to the skin.

3) Histology: histopathology and, if relevant, direct immunofluorescence studies of skin biopsies to confirm the clinical impression and to distinguish between a cADR and other skin diseases.

2.1.2 Criteria for diagnosis

If available, validated diagnostic criteria of specific types of cADRs should be used. Currently, only AGEP and DRESS have published validated diagnostic criteria. This chapter provides a practical approach to diagnosing and identifying SCAR cases.[3,4]

2.2 Patient history

2.2.1 Patient history including time to onset

First, the patient's exposure to the medicinal product must be ascertained by the patient, the patient's family, pharmacists or others who might know which medications the patient was taking prior to the AE. Second, it is crucial to carefully analyse the lag period of an ADR when determining the causative agent since different cADRs have different timelines. The lag period can be defined as the time between initiation of the medicinal product and onset of the first symptoms of the ADR.

All medications, especially those taken in the eight weeks prior to the cADR, must be considered as possible causative agents and physicians should ask patients about any over-the counter medications as well as prescription medicinal products. The physician can produce a graphic illustration of the medicinal product exposure timeline so as to visualize the chronology. For each medicinal product, the timeline should include the start date of the medication, dosage and end date as well as any signs or symptoms present throughout this period.

Evaluating systemic signs that differentiate between a simple and a complex reaction is essential. Systemic involvement is determined by assessing the patient's symptoms such as fever, facial oedema, malaise, chills, dyspnoea, cough, palpitations, nausea, vomiting, diarrhoea, sore throat and arthralgia. Additional information to be gathered includes known medicinal product allergies of the patient and his/her family members, and baseline health status including cutaneous diseases.[5,6]

2.2.2 Morphology description and physical exam findings

It is advisable to assess primary lesion morphology of the cutaneous eruption, which includes the four following main types: exanthematous, urticarial, pustular, and blistering. Moreover, diagnosing cADRs involves two major steps, namely determining morphology and examining systemic involvement.

Physical examination includes:

- Assessment of patient's basic signs: heart rate, blood pressure, oxygen saturation and fever,
- Assessment of the morphology of primary and secondary skin lesions,
- Assessment of mucous membrane involvement: ocular, oral and genital,
- Additional assessments: facial oedema perianal area, nails and hair, palpation of lymph nodes.

2.2.3 Additional clinical information

2.2.3.1 Skin biopsy (hematoxylin and eosin stain (H&E), immunofluorescence studies)

Skin biopsy for histology must be conducted, and, if relevant, direct immunofluorescence studies as well.

2.2.3.2 Specialty consultation

In patients with a suspected complex cADR (systemic involvement), it is prudent to conduct a multidisciplinary assessment based on the clinical signs and symptoms in both the acute stage and follow-up period subsequent to recovery.[7-9]

2.2.3.3 Assessing systemic involvement

We recommend that patients with cADRs be assessed for systemic involvement because the severity of skin manifestations does not always mirror the severity of the systemic involvement. In addition to assessing systemic involvement based on the patient's signs and symptoms, basic laboratory screening is advised, which includes a full blood count, liver and renal function tests, and urine analysis.

2.3 Assessing severity

The severity of SCAR depends mostly on the haemodynamic status and the extent of cutaneous and systemic involvement. The following clinical and histopathological findings were found to be validated values for determination of severity in various types of SCAR.

SCORTEN
This scoring system was developed to assess illness severity and predict mortality in patients with TEN. To optimize the predictive value of this tool, SCORTEN is to be performed on days 1 and 3[10] postadmission.[11]

Drug-Induced Hypersensitivity Syndrome and Drug Reaction with Eosinophilia and Systemic Symptoms Severity Score
This scoring system is based on a variety of factors including age, allopurinol exposure, need for pulsed prednisone, duration of medicinal product exposure after symptom onset, fever duration, percent BSA, appetite loss, liver involvement, renal dysfunction and C-reactive protein (CRP). Higher scores (≥4) were associated with CMV reactivation and CMV-related complications, higher steroids doses, longer hospitalizations and higher risk of fatal outcomes.[12]

2.4 SCAR case definition and diagnosis

2.4.1 SJS and TEN

2.4.1.1 Criteria for diagnosis

SJS and TEN can be defined as different degrees of a severe, acute and life-threatening mucocutaneous reaction. Therefore, SJS/TEN can be referred to as a single entity on this disease spectrum. The SJS/ TEN classification as defined by Bastuji-Garin et al., is based on the extent of epidermal detachment and the presence of characteristic skin lesions.

When evaluating the extent of epidermal detachment, only necrotic skin that is already detached (e.g. blisters, erosions), or detachable skin (positive Nikolsky sign whereby slight rubbing of the skin results in exfoliation of the outermost layer) should be considered. Diagnostic criteria based on clinical characteristics of skin and mucous membranes, histology assessment, lag period and systemic signs remain to be defined.[13]

2.4.1.2 Histology

Among the typical histopathologic characteristics are extensive keratinocyte destruction and apoptosis with separation of the epidermis from the dermis at the dermo-epidermal junction. In addition, a pauci-cellular, dermal mononuclear infiltrate has been commonly described as well as lymphocytes that cross the dermo-epidermal junction with moderate infiltration of the epidermis.[14]

2.4.1.3 Genetics

In the last few decades, progress has been made in understanding the pathogenic mechanisms of SJS/TEN, in particular, the important role of HLA alleles. Recognition of the culprit medicinal products by specific HLA molecules contributes to the pathogenesis of inducing cytotoxic responses in SJS/TEN.

Although association with a specific HLA risk allele might be necessary, it is not sufficient for SJS/TEN to develop. Individual differences in medicinal product metabolism or clearance may also be significant in SJS/TEN development, recovery or prognosis.[15]

2.4.1.4 Biomarkers[2]

A rapid immunochromatographic test for serum granulysin was found to be useful in predicting SJS/TEN.[16]

2.4.1.5 Skin testing

The value of medicinal product skin tests in SJS/TEN:

- patch tests can be done but are rarely positive;
- prick tests add no value and intradermal medicinal product tests are forbidden since it may induce a flare up reaction.[17]

2.4.1.6 Pitfalls in diagnosis

The major differential diagnoses of SJS/TEN include:

- Staphylococcal Scalded Skin Syndrome,
- GBFDE,
- Acute Graft-Versus-Host Reaction,
- TEN-Like Lupus Erythematosus or Lupus-Associated TEN
- Autoimmune blistering diseases,
- Bullous phototoxic reactions,
- AGEP,
- DRESS, and
- Erythema multiforme (minor and major).[18]

[2] See also Chapter 4

2.4.2 DRESS and DIHS

2.4.2.1 Criteria for diagnosis

DRESS is characterized by stepwise multi-organ involvement that may include skin, haematological and solid organs. Cutaneous manifestations of DRESS are diverse. There are two diagnostic criteria: the Japanese consensus group criteria (2006) and the RegiSCAR group criteria (2007).

An important distinction between the two scoring systems is the requirement of human herpes virus-6 (HHV6) reactivation for typical DIHS in the Japanese scoring system.[19,4]

2.4.2.2 Histology

Histopathological characteristics of patients with DRESS are generally non-specific. No single finding can be used to distinguish DRESS from other cADRs or inflammatory skin disorders. Several commonly encountered histopathological patterns were identified in skin specimens of patients with DRESS such as spongiosis, interface dermatitis, vascular damage and superficial perivascular infiltration.

A retrospective analysis of patients with DRESS found that spongiosis and keratinocyte damage were the most common epidermal changes. Spongiosis was associated with non-serious DRESS whereas confluent keratinocyte necrosis correlated with serious DRESS and frequent vascular changes.

A moderate, dermal perivascular lymphocytic infiltrate was invariably present, containing eosinophils, neutrophils and/or atypical lymphocytes in most cases.[20] Another study found that the histopathology of DRESS features various associated inflammatory patterns in a single biopsy.[21] Although differentiated histopathological features of patients with DRESS cannot be identified, there are characteristics that might provide clues for diagnosis or indicate severity. The most important of these observations is the co-existence of the aforementioned patterns in a single skin specimen.

Approximately 50–60% of patients with DRESS have at least two of the above-mentioned patterns in a single specimen.[21,22] In addition, patients with three histopathological patterns (spongiosis, interface dermatitis and vascular damage) that co-exist in a single specimen have a considerably higher likelihood of having a definite case of DRESS.[22]

2.4.2.3 Genetics

It is generally believed that DRESS is the result of a complex interaction between exposure to a medicinal product, genetic predisposition and viral reactivation. HLA alleles are among the most important risk factors for DRESS.

Since certain high risk alleles are more present in some ethnicities than in others, ethnicity is a significant predisposing factor for DRESS. More specifically, the culprit medicinal product is believed to interact with a particular HLA to form a complex-hapten which is then presented to naive T cells via the T-cell receptor, thereby stimulating an immune response.[23]

2.4.2.4 Biomarkers[3]

Thymus and activation-regulated chemokine (TARC) recruits Th2-polarized T cells into local inflammation sites, leading to a Th2-type immune reaction. TARC levels were found to be markedly higher in patients with DRESS than in patients with other cADRs. Hence, the baseline serum TARC level can be used as a marker for the early diagnosis of the DRESS in patients presenting with a maculopapular rash.[24]

2.4.2.5 Skin testing

The value of medicinal product skin tests in DRESS:

- patch tests can be useful and must be performed at least six months after the disappearance of the rash and biological disturbances,
- prick tests may add value only in some cases with delayed reactions and intradermal medicinal product tests have to be cautiously applied.[17]

2.4.2.6 Pitfalls in diagnosis

There are many conditions that mimic DRESS. Differential diagnoses include viral infections such as Epstein-Barr virus (EBV), Severe Acute Respiratory Syndrome coronavirus-2 (SARS-CoV-2), CMV and Human Immunodeficiency Virus (HIV) as well as bacterial sepsis, toxic shock syndrome, Kawasaki disease, Still disease, lymphoma, mycosis fungoides, hypereosinophilic syndrome, connective tissue diseases, hemophagocytic syndrome, and angio-immunoblastic lymphadenopathy and other cADRs.[25]

2.4.3 AGEP

2.4.3.1 Criteria for diagnosis

AGEP is defined as a severe acute pustular cutaneous reaction characterized by a rapid clinical course. Generally, the morphology of AGEP is an acute oedematous erythema with a burning sensation and/or itch, which leads to the development of dozens to hundreds of small (pinhead sized) non-follicular sterile pustules with a tendency toward large folds or widespread distribution. Fever and leukocytosis with neutrophilia are almost always present.

The AGEP validation score developed by the Euro-SCAR study group is a standardized scoring system comprising data about clinical features (morphology and clinical course) and histopathology. Based on this score, AGEP cases can be placed into the following categories: no AGEP, possible AGEP, probable AGEP and definite AGEP.[3]

2.4.3.2 Histology

The histopathological features of AGEP consist of sub-/intra-corneal and/or intra-epidermal pustules or a combination thereof. The primary epidermal features are necrotic keratinocytes such as incidental segmental necrosis and spongiosis with neutrophil exocytosis. The primary dermal features are papillary oedema with mixed superficial interstitial and mid/deep-dermal infiltrates containing neutrophils and eosinophils.[26]

2.4.3.3 Genetics

Genetic predisposition plays an important part in the pathogenesis of AGEP. Specific HLAs were found to be more common in AGEP patients than in the general population.[27] Also, mutations in the IL36RN gene were found in some patients with AGEP.[28]

[3] See also Chapter 4

2.4.3.4 Biomarkers[4]

A recent publication stated that IL17E, inducible nitric oxide synthase and arginase1 may serve as new biomarkers in the identification of neutrophilic dermatoses including AGEP.[29]

2.4.3.5 Skin testing

The value of medicinal product skin tests in AGEP:

- patch tests are useful,
- prick tests and intradermal medicinal product tests add no value.[17]

2.4.3.6 Pitfalls in diagnosis

Differential diagnoses of AGEP include a variety of rashes and skin diseases with pustules, mainly pustular psoriasis; subcorneal pustular dermatosis (Sneddon-Wilkinson); pustular vasculitis and DRESS.[30]

2.4.4 GBFDE

2.4.4.1 Criteria for diagnosis

The diagnosis of GBFDE can often be made on clinical grounds based on distinctive appearance and history of a similar eruption with medicinal product exposure. Skin biopsy may be performed to confirm the diagnosis when the clinical presentation is ambiguous. No diagnostic criteria exist.

2.4.4.2 Histology

Characteristic histopathologic findings of GBFDE consist of a sub-epidermal blister or vacuolar alterations at the dermo-epidermal junction and a variable number of necrotic keratinocytes within lesional intact epidermis. Though the infiltrate of inflammatory cells is variable, there is usually a brisk, moderately dense perivascular infiltrate of lymphocytes and interstitial eosinophils. GBFDE shows increased inflammation with eosinophils, fewer necrotic keratinocytes and more melanin-containing dermal macrophages compared with SJS/TEN. Nevertheless, GBFDE may have full-thickness epidermal necrosis, which histologically strongly resembles and may be almost indistinguishable from SJS/TEN.[31]

2.4.4.3 Genetics

In GBFDE, CD8+ T cells play a critical inflammatory role by recognizing certain medicinal products in association with specific major histocompatibility complex (MHC) class I molecules found on keratinocytes. There are several examples of HLA-A or HLA-B associated with GBFDE.[32]

2.4.4.4 Biomarkers[5]

Serum granulysin levels have been found to be significantly lower in GBFDE compared to SJS/TEN, leading some authors to advocate the use of a serum granulysin test as a method to rapidly diagnose SJS/TEN.[33]

[4] See also Chapter 4
[5] See also Chapter 4

2.4.4.5 Skin testing

Patch testing is the best confirmation method. Patch testing is conducted on a hyper-pigmented site in an area of previous FDE, exploiting normal skin as a control. Patch testing should be performed a few weeks after the lesions resolve to avoid a false negative result due to a refractory period.[34] An additional method of FDE confirmation is performed using the lymphocyte transformation test, which aims to measure a sensitized T-cell reaction in response to the in vitro addition of the medicinal product.[35]

2.4.4.6 Pitfalls in diagnosis

The most important differential diagnosis is between GBFDE and SJS/TEN. Patients with GBFDE tend to be older and less likely to have constitutional symptoms than patients with SJS/TEN. Mucosal involvement is less frequent and less severe in GBFDE. GBFDE always presents within one to two weeks (but most frequently within 48 hours) of ingestion of the causative medicinal product, while latency between medicinal product exposure and clinical presentation of SJS/TEN is most commonly one to three weeks. SJS/TEN skin lesions tend to coalesce and may have atypical targets, while GBFDE patches and bullae tend to be well-demarcated and have larger areas of normal skin between lesions. GBFDE heals with hyperpigmentation but no scarring, whereas SJS/TEN is associated with scarring. A history of a similar less severe skin eruption induced by the culprit medicinal product can often be elicited in cases of GBFDE.[36]

2.5 Interactions between patient, family, healthcare professional and regulatory agencies for reporting

2.5.1 Patient and family

Good communication strategies will aid in the interactions with a patient and their family following a suspected SCAR. Physicians are recommended to:

1) Listen to the patient in a respectful and empathetic manner in order to characterize their experience. This is part of the diagnostic process.

2) Acknowledge the reality of the experience for the patient.

3) Offer the patient clear information on his/her suspected SCAR (see Table 4 below), the name of the suspected offending medicinal product if it is known, potential cross-reacting medicinal products, and medicinal product, which can be safely taken as a substitute. In addition, advise the patient to wear a medic-alert bracelet.

4) Include family counselling in the management plan given that the predisposition to some SCAR may be genetic.

2.5.2 Healthcare professionals

Healthcare professional (HCPs) should obtain information about a SCAR such as type and culprit medicinal product(s) and incorporate the information into the patient's medical records.. At a minimum, the HCP should inform the patient and family of which SCAR was experienced using appropriate patient-focused language and the culprit medicinal product(s), if identified.

Severe Cutaneous Adverse Reactions	A group of hypersensitivity reactions with a variety of clinical signs and symptoms that are typically triggered by taking medications.
Stevens-Johnson syndrome and toxic epidermal necrolysis	A hypersensitivity reaction which can involve the skin and mucous membranes (such as the eyes, mouth/throat, genital areas) and cause widespread redness of the skin and blistering with burn-like lesions from large areas of detached skin.
Drug reaction with eosinophilia and systemic symptoms and drug-induced hypersensitivity syndrome	A hypersensitivity reaction which can include fever, widespread skin rash, multiple organ involvement (such as liver, heart, and lung), and an increase of eosinophils in the blood.
Acute generalized exanthematous pustulosis	A hypersensitivity reaction that presents with fever, increased white blood cells, and widespread redness of the skin with small pustules. The small pustules can merge and lead to large areas of detached skin.
Generalized bullous fixed drug eruption	A hypersensitivity reaction that typically starts with round red/purple or hyperpigmented lesions that can have blistering within the lesions. With repeated occurrence, more lesions appear and can be widespread and appear similar to Stevens-Johnson syndrome/toxic epidermal necrolysis.

Table 4. Example of information to be provided to the patient and the patient's family

2.5.3 Regulatory agencies

If a SCAR has occurred subsequent to treatment with a medicinal product, patients and healthcare professionals should report it to the manufacturer and appropriate regulatory agencies, using the applicable regional pharmacovigilance reporting system. Manufacturers are required by law to report suspected ADRs to regulatory agencies and some regulatory agencies are required to report ADRs that have occurred outside their jurisdictions, which has led to the creation of global databases, e.g. MedWatch, the FDA Safety Information and Adverse Event Reporting Program[37] and EudraVigilance maintained by European Medicines Agency (EMA)[38] for the European Union (EU) regulatory network. Many countries are members of the WHO Programme for International Drug Monitoring and in this context provide their national suspected ADR reports to the WHO Collaborating Centre Uppsala Monitoring Centre (UMC) which maintains the global database VigiBase for collecting and analysing the reports.[39]

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CHAPTER 3.

CASE MANAGEMENT IN CLINICAL CARE

Chapter summary

- Treatment goals in the management of SCAR include withdrawal of the culprit medicinal product, symptom management, avoidance of acute morbidity and fatal outcomes as well as the long-term monitoring and treatment of chronic sequelae.
- The culprit medicinal product that is responsible for the SCAR should be identified and withdrawn immediately. SCAR cases should be managed in reference centres.
- Supportive care is the cornerstone of treatment and involves fluid and nutrition optimization, skin care and dressings, thermoregulation, pain management as well as the monitoring and treatment of organ complications and infections.
- Various systemic treatments have been proposed for SJS/TEN, DRESS and AGEP, but the level of evidence remains low.
- Long-term follow up of SCAR cases is required in order to prevent and mitigate long-term sequelae.

Conclusions or recommendations

Early diagnosis and transfer of SCAR to a reference centre is vital. Key management principles include the withdrawal of the culprit medicinal product and supportive care. The use of specific immunomodulatory treatments requires further validation.

3.1 Introduction

In all cADRs, identification and withdrawal of the culprit medicinal product is the cornerstone of care. Withdrawal of drugs, particularly those with a short half-life, has been shown to improve outcomes in SJS/TEN.[1]

In some cases, the decision to “treat-through” the reaction can be made if the benefits outweigh the risks such as in the context of life-sustaining treatments for which there are no alternative medicinal products, the disease phenotype is benign and there are no features of progression to SCAR. Investigations, supportive care and specific therapy are tailored according to phenotype, severity and clinical course.

3.1.1 Management of benign cADRs (non-SCAR)

Exanthematous drug eruptions (also known as morbilliform drug eruptions, maculopapular rash) are the most common cADRs, accounting for up to 80% of cases.[2] However, an exanthematous reaction may be the initial presentation of SCAR as such, serial examination and follow-up is warranted.

Exanthematous drug eruptions are self-limiting. Emollients and antihistamines may provide symptomatic relief of pruritus. Potent topical corticosteroids are often prescribed to reduce the inflammation and symptoms associated with the rash. However, clinical evidence for such an approach is lacking. Systemic corticosteroids are rarely required.[2]

3.1.2 Management of SCAR

The treatment goals in SCAR include symptom management, avoidance of short-term morbidity, prevention of death as well as prevention and treatment of long-term sequelae. It involves both supportive care and specific treatment for each disease entity. It is recommended that SJS/TEN cases should be managed in reference centres. These are usually specialized dermatological centres, burn or intensive care units (ICU) with significant experience and protocols in place for the management for such rare conditions. It has been shown that delayed transfer to such units is associated with poorer outcomes.[3] Similarly, prognosis is improved when care is delivered in centres with higher volumes.[4]

3.1.3 Supportive care

The extensive involvement of the skin in SCAR impairs its physiological function, resulting in increased fluid loss, hypovolemia, hypothermia, protein loss, risk of bacteraemia and multi-organ failure. The aim of supportive care is to restore homeostatic function and manage the complications associated with skin failure.

Components of supportive care include the following:

3.1.3.1 Fluids and nutrition

SCAR are catabolic states and there is also increased transepidermal water loss, particularly in SJS/TEN. This is compounded by decreased oral intake in many patients with severe oropharyngeal involvement, particularly in SJS/TEN. Strict monitoring of fluid intake and output is essential. Fluid resuscitation and replacement is necessary.

Fluid and electrolyte derangements are most marked in SJS/TEN, and an initial resuscitation of 2ml/kg/% TBSA detached has been proposed and subsequent fluid requirements should achieve urinary output of 0.5 to 1ml/kg/h.[5] Enteral feeding is preferred. However, oral intake of food may be limited by pain, and a nasogastric tube may be required in order to achieve nutritional demands. Estimated caloric requirements is at 20-25 cal/kg/d during the initial catabolic state of SJS/TEN and 25-30 cal/kg/d during the period of anabolic recovery.[5]

3.1.3.2 Thermoregulation

The ambient temperature should be maintained at 28°C to prevent hypothermia.

3.1.3.3 Skin, mucosal and wound care

In a SCAR without epidermal detachment (DRESS, AGEP), liberal application of emollients and potent/ultrapotent corticosteroids has been advocated. Patients with SJS/TEN should be nursed in single rooms with reverse barrier nursing, if available. The ideal wound care strategy in SJS/TEN has not been established and remains variable across centres. Generally, it may involve either a surgical approach whereby the detached epidermis is removed operatively and replaced with either biologic membranes or dressings or a conservative approach whereby the detached/detachable skin is left in situ as a biological dressing.

In the conservative approach, minimal manipulation of the skin is advocated. Saline or antiseptic baths can be used, followed by petrolatum jelly and non-adhesive dressing. Secondary dressings may be applied to absorb the exudate. To date, there have been no controlled studies that evaluate these two approaches. However, a conservative approach may result in less severe postinflammatory skin changes and avoid the risks associated with sedation and anaesthesia in the surgical approach.[6,7]

During the acute phase of a SCAR, mucosal surfaces can be involved, particular in SJS/TEN. The use of emollients and topical corticosteroids are recommended to reduce mucosal adhesions and long-term scarring. Oral mouthwash and topical oral analgesia may be helpful in reducing the mucosal discomfort. Similarly, urogenital involvement can affect up to 70% of patients. Early assessment by urologists/gynaecologists may be necessary to avoid long-term scarring.[8] In addition, the use of non-adhesive dressings, topical corticosteroids and vaginal moulds/dilators can be used to reduce strictures.

3.1.3.4 Pain management

In general, most SCAR are not painful with the exception of SJS/TEN. SJS/TEN is an intensely painful disease and the pain is aggravated by movement and wound manipulation. Pain severity should be monitored via a visual analogue scale of 0-10. Appropriate analgesia (paracetamol/acetaminophen, opioids) should be administered with the aim of reducing the pain score to two or below.

3.1.3.5 Monitoring of internal organ complications

SCAR are systemic conditions and the degree and characteristic of internal organ involvement vary according to the specific type of SCAR. Serial monitoring of routine investigations such as complete blood count (CBC), liver function tests, renal panel, cardiac and muscle enzymes may be required. In some setting, imaging studies such as radiographs, ultrasound, computed tomography and magnetic resonance imaging may be required. Due to the systemic nature of SCAR, a collaborative, multi-disciplinary approach is necessary.

3.1.3.5.1 AGEP

Systemic complications occur in about 15% of cases of AGEP, with the liver being the most commonly affected organ. Other affected organs include kidneys, lungs and bone marrow. These complications are generally mild and typically improve subsequent to medicinal product withdrawal.[9,10]

3.1.3.5.2 DRESS/DIHS

Systemic complications occur in at least 90% of patients and up to 20% of patients may have more than two organs involved.[11] The onset and clinical course of visceral involvement may not parallel skin involvement, hence, systematic follow-up and monitoring are needed. The liver is the most common visceral complication, occurring in up to 50-90% of cases.

Other organs involved include the kidneys, lungs, cardiac, bone marrow, and central and peripheral nervous system involvement. Multiple organ involvement, such as pulmonary and cardiac involvement, and human herpes viral reactivation may confer a poorer prognosis.[12,13]

3.1.3.5.3 SJS/TEN

Systemic complications are common in SJS/TEN and may be renal, pulmonary, gastrointestinal, or haematologic in nature though can arise in other organs as well. Pulmonary complications occur in up to 40% of patients and include specific changes such as trachea/bronchial mucosal sloughing as well as non-specific presentation of infection, pulmonary oedema and atelectasis.[14] Pulmonary involvement is a poor prognostic factor for mechanical ventilation and death. Acute renal failure occurs in up to 20% of patients with SJS/TEN. Risk factors for acute renal failure include sepsis, allopurinol, NSAIDs and antibiotics as culprit drugs as well as hypoalbuminemia and chronic kidney disease.[15]

Disseminated intravascular coagulation occurs in up to 20% of cases, and blood component transfusion may be necessary.[16] Leukopenia can occur during the acute phase of the disease and granulocyte-colony stimulating factor (G-CSF) may be required.[17] In view of multi-organ involvement, facilities and expertise for mechanical ventilation, organ support and ICU care should be made available.

3.1.3.6 Management of bacteraemia

Bacteraemia and sepsis can be SCAR complications, particularly in SJS/TEN. Sepsis increases the risk of fatal outcomes for SJS/TEN by three- to four-fold and accounts for up to 50% of all fatal outcomes for SJS/TEN.[18,19] The routine use of prophylactic antibiotics is not recommended in SJS/TEN, however, empirical antibiotics should be started once infection is suspected. Frequent sampling of the blood and skin may aid in the early diagnosis and management of bacteraemia.

Hypothermia and raised procalcitonin may be predictive of positive blood cultures.[17] Skin sampling has a good negative predictive value for bacteraemia. If skin cultures are negative for Staphylococcal aureus or Pseudomoinas aeruginosa, it is unlikely that the blood cultures would be positive for such organisms.[20] Antimicrobial therapy should be culture directed, and dependent on the institutional microbiogram. Initial empirical therapy should include coverage for Staphylococcal aureus, Pseudomonas aeruginosa and other gram-negative bacteria. In burn units and ICUs, coverage for nosocomial organisms should be considered.

3.1.3.7 Management of ocular complications

Acute eye involvement occurs in up to 80% of patients with SJS/TEN.[21] The presentation ranges from conjunctival hyperaemia to extensive corneal ulcerations. As such, ophthalmic review and management during the acute and chronic phase of SJS/TEN is mandatory. During the acute phase of disease, in addition to topical eye drops such as lubricants, corticosteroids and antibiotics, systemic corticosteroids and amniotic membrane transplantation may be p.[22]

3.1.3.8 Laboratory tests

In view of systemic complications and the involvement of internal organs in SCAR, various laboratory tests and investigations may be performed, as indicated.

- CBC, renal function, LFT, muscle/cardiac enzymes, thyroid function tests, arterial blood gases, coagulation profile,
- Blood/wound/urine cultures, procalcitonin as indicated,
- Hepatitis serology, mycoplasma, chlamydia serology, anti-nuclear antibodies as indicated (particularly in DRESS),
- Human herpes viral serology (HHV6, EBV, CMV) may be needed to confirm diagnosis as well as a prognostic factor in DIHS/DRESS,
- Imaging studies: Ultrasound/computed tomography/magnetic resonance imaging may be needed to assess for internal organ involvement,
- ECG/Echocardiography may be necessary to assess for cardiac involvement.

3.1.4 Specific treatment

Although specific therapy is dependent on the type of SCAR, treatment recommendations are generally limited by the quality of the evidence.

3.1.4.1 SJS/TEN

Supportive care remains the cornerstone of management. Current evidence is unable to support the routine use of any immunomodulatory agent over another. Various immunomodulatory agents have been proposed. These agents include systemic corticosteroids, cyclosporine, intravenous immunoglobulins (IVIG) with/without corticosteroids, anti-tumour necrosis factor (TNF)-alpha with/without corticosteroids and plasmapheresis. There have been two randomized controlled studies evaluating therapy in SJS/TEN. The first trial by Wolkenstein et al. evaluated the use of thalidomide, an inhibitor of TNF-alpha, was prematurely stopped due to increased mortality in the active arm.[23] The second, by Wang et al., evaluated the efficacy of etanercept, also a TNF-inhibitor, versus systemic corticosteroids.

There was no significant difference in terms of fatal outcomes, although both interventions showed a decrease in case fatality compared to that predicted by SCORTEN.[24] Several recent meta-analysis suggested that cyclosporine, etanercept, systemic corticosteroids as well as IVIG in combination with corticosteroids may have survival benefits. However, there was significant heterogeneity in these studies and study quality was poor.[25-27] Until improved evidence emerges, specific immunomodulatory treatments cannot be recommended in a routine manner.

3.1.4.2 DRESS

There are no randomized trials that evaluate treatment for DRESS. In view of disease heterogeneity, a step ladder approach has been proposed.[28] In mild disease (no internal organ involvement, or mild liver involvement), systemic corticosteroids may be withheld and symptomatic treatment consisting of emollients and potent to ultrapotent topical corticosteroids may be sufficient.[29] If systemic corticosteroids are used, a slow taper is required to reduce the likelihood of flares. In severe disease (severe organ involvement, e.g. liver, renal, pulmonary, neurological, cardiac involvement), systemic corticosteroids are recommended. As systemic corticosteroid treatment increases the risk of infections, careful surveillance of infective complications are warranted. Various other immunomodulatory agents such as cyclosporine, IVIG, janus kinase (JAK) inhibitors have been utilized but evidence remains limited. In addition to immunomodulatory agents, organ support and emergent transplantation may be required in fulminant cases.

3.1.4.3 AGEP

AGEP is generally self-limiting, although in some cases, it may cause fatal oucomes. Symptomatic treatment with emollients and topical potent to ultrapotent corticosteroids may suffice.[10,11]

3.1.4.4 GBFDE

GBFDE is an extensive, bullous variant of FDE and may be challenging to differentiate from SJS/TEN. The prognosis of GBFDE is comparable to cases of SJS/TEN matched for age and extent of epidermal involvement. As such, similar supportive management principles to SJS/TEN should be carried out.[30] Likewise, supportive care is the most important component of care. Although the use of various immunomodulators such as corticosteroids and cyclosporine has been reported, evidence for such treatments remains anecdotal.

3.2 Special populations

3.2.1 Paediatric SJS/TEN

The prognosis of paediatric SJS/TEN is better compared to adult cases with an overall case fatality of 3% in TEN.[31] Unlike adult cases, which are attributed to medications in close to 80-90%, medications account for only 50% of paediatric cases with infections and idiopathic cases accounting for the rest.[32] As such, investigations evaluating for infective triggers such as *Mycoplasma pneumoniae* and *Chlamydia pneumoniae*, as well as appropriate antimicrobial treatment is warranted. In addition, recurrences of up to 18% have been reported,[33] and this may be due to higher incidence of infections as a trigger and possible misclassification of paediatric cases as EMM, which is more frequently recurrent compared to TEN.

Similar to the adult population, no immunomodulatory therapy has been shown to confer conclusive benefit. Whilst adult cases are recommended to be transferred to SJS/TEN reference centres, in paediatric populations, this may need to be balanced with the availability of paediatric expertise and facilities.[34]

3.2.2 Pregnancy

SJS/TEN is rare in pregnant patients due to the reduced medicinal product intake during gestation and younger age. The majority of reports are from HIV-positive patients who developed the reaction following the use of nevirapine.[35] Acute uro-gynaecological care in such patients is essential to prevent strictures as well as for normal vaginal delivery after the initial episode of SJS/TEN. Other specific pregnancy complications include premature labour and the need for emergent caesarean section, which accounts for up to 50% of all pregnancies in SJS/TEN.

Specific treatment recommendations mirror that for the general adult population. Maternal-fetal transmission of SJS/TEN is rare and has been anecdotally reported.[36] In a systematic review, maternal and neonatal mortality in SJS/TEN has been reported as 2.1% and 4.9%, respectively.[37] Pregnant cases of SJS/TEN should be managed in facilities with access to obstetric and neonatal expertise and facilities.

3.2.3 Renal failure

In a multi-centre cohort in the U.S., dialysis prior to presentation of SJS/TEN was the strongest independent prognostic factor for fatal outcomes (Odds Ratio of 16).[38]

3.2.4 Coloured skin

In the U.S., SJS/TEN was associated with skin colour or genetic factors, particularly Asians and Blacks with respective odds ratio of 3.3 and 2, respectively.[39] Such differences might be due to the inherent pharmacogenetic risks in certain ethnicities and the causal medicinal product. The initial presentation of SCAR may be under-recognized in skin of colour and may lead to a delay in diagnosis and treat.

3.3 cADRs induced by targeted therapy[6] or immunotherapy

The spectrum of cADRs is varied, ranging from common and benign to severe. Such reactions are typically classified according to the Common Terminology Criteria for Adverse Events (CTCAE) grading and management is grade dependent. Maculopapular rash or MPE is the most common presentation, but SCAR such as SJS/TEN have been reported. In SCAR, immunotherapy should be permanently discontinued.

Prednisolone/methylprednisolone is recommended based on consensus, however, evidence for this or other immunomodulatory agents is lacking. In severe cases, urgent dermatological consultation, inpatient care and transfer to reference centres may be necessary.[40]

3.4 Guidance and investigation postreaction

Following the acute phase of the reaction, treatment/management goals include:

- Permanent discontinuation of culprit medicinal product, medicinal product allergy notification, allergy alert/bracelet. Cross-reactive medications to the culprit medicinal product should be avoided as well. For example, all oxicam NSAIDs such as meloxicam and piroxicam should be avoided in any case of oxicam NSAID-induced SCAR. Similarly, aromatic anticonvulsants such as phenytoin, phenobarbital and carbamazepine should be avoided in any aromatic anticonvulsant-induced SCAR.
- Long-term multi-disciplinary follow up to detect and manage any chronic complications from SCAR. (See also Chapter 1.4.1.5 and Chapter 1.4.2.4)
  Additional allergological evaluation to confirm medicinal product causality including both skin tests and in vivo tests may be available in specialty/research centres. (See also Chapter 2.4 and Chapter 5.3.1)

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CHAPTER 4.

BIOMARKERS FOR SCAR

Chapter summary

Life-threatening ADRs should be routinely reported to identify possible biomarkers associated with the reaction, but underreporting is a major limitation in the real world. Additionally, the understanding of all the factors associated with disease progression and the long-term outcomes of ADRs is limited. Therefore, collaborative efforts are needed to improve global surveillance to decrease reporting bias and provide more accurate estimates of disease epidemiology, causes and effects of the disease.[1] In addition, it is critical to collect biospecimens from incident cases at various time points, and follow patients long-term to ascertain outcomes, so that biomarker discovery efforts can take advantage of more complete and comprehensive data to discover and validate biomarker-based approaches to guide care.

Conclusions or recommendations

Race and ethnicity have been recognized as a major factor contributing to interindividual variability in response. For example, abacavir hypersensitivity syndrome is more prevalent in white populations due to a higher frequency of the *HLA-B*57:01* allele in this population, whereas the frequency of carriers of the *HLA-B*58:01* allele is higher in Asian populations.[2-4] The predictive value of any biomarker depends on the frequencies of that marker and the associated ADR in the study population.[3] For this reason, further research is needed to identify genomic markers for particular demographic clusters in admixed populations that may have increased risk for developing certain ADRs.

Except for *HLA-B*1502*/carbamazepine in some Asian populations, HLA testing is not yet being routinely performed pre-emptively in clinical practice.[4] Large randomized controlled pharmacogenomic (PGx) trials are often expected to show the clinical utility of HLA testing, but this may not be feasible for such rare ADRs. Additional implementation studies will further characterize barriers to testing and find the best solutions, such as overcoming obstacles in information technology and infrastructure, translating raw genotyping lab results to actionable information to guide prescribing and improving HCP awareness and education.

4.1 Introduction

SCAR such as SJS/TEN, and DRESS are associated with significant patient morbidity and mortality. These ADRs are the result of complex, heterogeneous, and distinct immunological responses following exposure to various medicinal products. Leveraging the knowledge of biomarkers to predict the risk of SCAR or its outcome can greatly improve the safe use of medications. A great deal of progress has been made in understanding the biological underpinnings of SJS/TEN and other forms of SCAR to enable the development of biomarkers that may be used across the continuum of patient care to mitigate risks and improve outcomes.

A biomarker is “a characteristic that is objectively measured as an indicator of normal biological processes, pathogenic processes, or biological responses to an exposure or intervention, including therapeutic interventions.” To that extent, biomarkers may include molecular, histologic, radiographic or physiologic characteristics.[5] Safety biomarkers, a category of biomarkers, are “biomarkers measured before or after an exposure to a medical product or an environmental agent to indicate the likelihood, presence, or extent of toxicity as an adverse effect.”[5]

Safety biomarkers can be used to identify patients in whom initiation of a particular medicinal product may lead to significant risk of ADR, such as different HLA alleles or polymorphisms in medicinal product-metabolizing encoding genes;[6-8] when used in this way, this type of biomarker may also be referred to as a predictive biomarker. Safety biomarkers also may be used to detect or monitor ADRs (e.g. when tissue damage occurs, certain proteins may be detectable in the blood like transaminase elevations in the setting of liver injury); when used in this way this type of biomarker may also be referred to as a monitoring biomarker. In addition, biomarkers may be used as part of the diagnostic evaluation to confirm the presence of a particular ADR, and once diagnosed, to evaluate prognosis or the likelihood of a particular outcome. The functions of a biomarker are not mutually exclusive; a biomarker that is used for diagnosis may also predict response to certain therapies.

Overall, biomarkers can play a critical role in 1) identifying patient populations who are more likely to respond to medical treatments and those who are susceptible to ADRs, both of which are major goals of precision medicine, 2) enabling early diagnosis to distinguish SCAR from less critical conditions before significant damage occurs, and 3) characterizing the likely course of progression. Therefore, this chapter provides an overview of biomarkers that have been scientifically validated to predict the risk of SCAR, as well as some areas of continued biomarker development, to maximize the benefits and reduce the risk of harm associated with administering medicinal products.

4.2 HLA and immune-related genetic biomarkers

The most extensively studied biomarkers for SCAR risk are genetic variations in the HLA system. The HLA system is a member of the MHC, a region of the human genome located on the short arm of chromosome 6p21.3. HLA is a highly polymorphic gene system and an important modulator for immune responses and hypersensitivity reactions to specific medicinal products. HLA antigens are expressed on the surface of many cells and play a major role in self-recognition, evoking the immune response to an antigenic stimulus and the orchestration of cellular and humoral immunity.[9]

Because HLA molecules need to present such a wide variety of “self” and “non-self” molecules, the HLA genes are both numerous and highly polymorphic. More than 9000 HLA-B alleles have been identified and could play a significant role in the pathogenesis of many immunologic ADRs.[10] For example, HLA-B variants have been associated with severe hypersensitivity reactions to abacavir, allopurinol, carbamazepine and phenytoin.[6,11,12] HLA-B molecules present endogenous or processed exogenous antigens to T cells, thereby eliciting an adaptive immune response. HLA restriction is required for the activation of medicinal product-specific T cells by the culprit medicinal product. The T-cell receptor of the effector T cell is thought to recognize the medicinal product–peptide complex bound by the specific HLA-B molecule on the antigen presenting cell, resulting in the release of immune mediators and leading to robust adaptive immune reactions such as SCAR.[13] The relationships between different HLA alleles and the risk of medicinal product-induced SJS/TEN, DRESS and other skin reactions are well established and guidelines for genetic testing have been developed in some regions of the world with high frequencies of certain HLA alleles.[6-15] The most widely reported HLA genotypes associated with SCARs include *HLA-B*15:02* for carbamazepine and phenytoin (Han Chinese), *HLA-A*31:01* for carbamazepine (Europeans and Koreans), *HLA-B*58:01* for allopurinol (East Asians), *HLA-B*59:01* for methazolamide (Koreans and Japanese), and *HLA-B*13:01* for dapsone (Asians).[16,17] The following sections summarize available evidence related to predisposing genetic factors for selected medicinal products and SCAR-related events.

4.2.1 SJS/TEN

The development of SJS/TEN in response to medicinal product exposure is the result of many genetic and non-genetic factors.[13] While the exact immunohistopathology of SJS/TEN is not fully understood, a variety of factors and characteristics are implicated. Medicinal product-specific CD8+ T cells and NK cells have been shown to be the major inducer of keratinocyte apoptosis. Specific T-cell receptors recognize a medicinal product (or its metabolites) presented by specific HLA alleles, which can lead to activation of medicinal product-induced cytotoxic T cells with release of multiple cytokines, chemokines, signals, and soluble cytotoxic mediators, such as Fas-Fas ligand, granulysin, perforin, granzyme B and tumour necrosis factor alpha (TNF-α).[13] The IL-15 cytokine, a major NK cell priming signal, passes through the JAK-STAT pathway with downstream effects on the PI3K/AKT/mTOR pathway and with effects on NK and CD8+ T cells, playing a vital role in most cellular processes, such as proliferation, adhesion, migration and invasion.[18,19]

Numerous studies have demonstrated a strong association between select HLA alleles and drug-induced SCAR.[20] A sampling of different alleles that have been identified as risk factors for SJS/TEN in different populations are summarized in Table 5.

Drug	Risk alleles	Populations Studied
Allopurinol	A*32:02, B*58:01, C*03:02	European, Korean, Vietnamese, Han Chinese, Japanese, Thai
Carbamazepine	A*24:02, A*31:01, B*15:02, B*15:11, B*15:21, B*57:01	European, Han Chinese, Japanese, Korean, Indian, Malaysian, Thai, Taiwanese, Filipino
Lamotrigine	A*31:01, A*68:01, B*58:01, C*07:18, DQB1*06, DRB1*13	Han Chinese, European, Thai, Korean
Methazolamide	B*55:02, B*59:01	Han Chinese, Japanese, Korean
Phenytoin	B*13:01, B*15:02, B*56:02, B*15:13, Cw*08:01, DRB1*1602	East Asian, Han Chinese, Malaysian, Thai
Sulfamethoxazole	A*29, B*38, B*44, DR*07, A*11:01	European, Japanese

Table 5. HLA alleles associated with SJS/TEN
Adapted from Gibson, et al. 2023[20]
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Chung, et al. were the first to identify an association between carbamazepine-induced SJS/TEN and HLA genetic polymorphisms, particularly the *HLA-B*15:02* allele, in Han Chinese patients in Taiwan, with 100% sensitivity and 97% specificity.[21] This finding has been replicated in a large number of populations in Southeast Asia. Even though SJS/TEN is an infrequent AE, the risk is significant among carriers of the *HLA-B*15:02* allele (OR 26.01; 95% CI 15.88–42.60; $p < 0.00001$) in meta-analyses of data from different populations.[22] While the incidence of SJS/TEN is lower in non-Asian populations, efforts have uncovered additional genetic variants that increase the risk for SJS/TEN in carbamazepine-treated patients. Specifically, *HLA-A*31:01* was reported to be a significant risk factor in European populations, although the relative risk is much more modest than that observed for *HLA-B*15:02*.[22] Several similar studies have also demonstrated that *HLA-B*15:02* is also with a higher risk of SJS/TEN in patients treated with phenytoin. In addition, drugs that are structurally related to carbamazepine such as oxcarbazepine and eslicarbazepine also likely carry the same risk, and experimental studies have identified structural elements that selectively interact with *HLA-B*15:02*.[23] As such, many anti-epileptics carry some shared HLA-related risk for developing SJS/TEN.

Collectively, these findings represent an opportunity for broader implementation of routine HLA genotyping in clinical practice to prevent medicinal product-induced SCAR and reinforce the need for racial and ethnic diversity in developing and validating novel biomarkers to optimally manage ADRs. Following extensive replication of HLA alleles as a risk factor for SJS/TEN, certain geographical regions have implemented prospective genetic testing prior to administration of carbamazepine. A study including 23 hospitals in Taiwan demonstrated reductions in the incidence of carbamazepine induced SJS/TEN by screening patients for *HLA-B*15:02* and avoidance of carbamazepine in *HLA-B*15:02* carriers.[24] Unfortunately, the overall incidence of SJS/TEN was not reduced in part because of a shift to other drugs that also cause SJS/TEN.[25]

Allopurinol, a widely prescribed drug for the management of gout and hyperuricemia, is another major cause of SJS/TEN. Extensive studies have linked SJS/TEN induced by allopurinol to genetic polymorphisms in the HLA system, mainly *HLA-B*58:01.*[26] For example, a study investigated the relationship between SJS/TEN and *HLA-B*58:01* in a Thai population that has a high allelic frequency of this allele. Twenty-seven allopurinol-induced SJS/TEN and 54 allopurinol-tolerant patients were enrolled in the study. The presence of *HLA-B*58:01* and HLA-B genotypes in these patients were analysed. All 27 (100%) allopurinol-induced SJS/TEN patients who were examined carried *HLA-B*58:01* whereas only seven (12.96%) of the control patients had this allele. The risk of allopurinol-induced SJS/TEN was significantly greater in patients with *HLA-B*58:01* when compared with those who did not carry this allele, with an odds ratio of 348.3 (95% confidence interval=19.2-6336.9, $P = 1.6\times10^{-13}$). The sensitivity and specificity of the *HLA-B*58:01* allele for prediction of allopurinol-induced SJS/TEN were 100% and 87%, respectively.[27]. This association however is less strong in Japanese where only 36–40% of allopurinol-induced SCAR patients are *HLA-B*58:01* positive, or in European patients where only 55–64% of patients with SJS/TEN carry this allele. Although the frequency of *HLA-B*58:01* in different populations varies significantly (up to 20% in Taiwan and less than 2% in Europeans), which consequently influence the frequency of SCAR in the different populations, race and ethnicity also seems to have some influence on the capacity to develop this reaction.[25,28] The percent of *HLA-B*58:01* negative individuals with allopurinol-induced SCAR is higher in Europeans and Japanese, suggesting other possible risk factors.[29]

To evaluate the use of prospective screening for the *HLA-B*58:01* allele to identify Taiwanese individuals at risk of SCARs induced by allopurinol treatment, a national cohort study enrolled 2926 people who had an indication for allopurinol treatment but had not previously taken allopurinol.[30] Participants who tested positive for *HLA-B*58:01* (19.6%, n=571) were advised to avoid allopurinol and were referred to an alternate drug treatment or advised to continue with their study treatment. SCAR did not develop in any of the participants receiving allopurinol who screened negative for *HLA-B*58:01.*[30] By contrast, seven cases of SCAR were expected, based on the estimated historical incidence of allopurinol-induced SCARs nationwide (0.30% per year, 95% confidence interval 0.28-0.31%; *P*=0.0026).[30]

These results suggest that *HLA-B*58:01* screening of about 110,000 new users of allopurinol in Taiwan each year could prevent about 330 cases of allopurinol-induced SCARs every year.[30] Prospective screening of the *HLA-B*58:01* allele, coupled with an alternative medicinal product treatment for carriers, could significantly decrease the incidence of allopurinol-induced SCAR in high-risk patients.

From a pathophysiological standpoint, trigger medicinal products are thought to constitute the main target of the immune response. However, the strength of association between medicinal products and SJS/TEN is modulated by interindividual and interethnic variations in the HLA repertoire. In fact, distinct HLA variants might segregate with selected ethnicities and different ancestral population groups. Additional inherited factors may promote altered medicinal product metabolism and variably combine with HLA-related factors to contribute to SJS/TEN susceptibility.[31]

4.2.2 DRESS

In drug hypersensitivity, several models were proposed for recognition of the small drug compounds by T cells with subsequent initiation of the immune response. Traditionally, DRESS is classified as a type IVb reaction that corresponds with CD8+ and CD4+ T-cell responses underlying the production of interferon-γ, IL-4, IL-5, and IL-13, resulting in eosinophilia.[32] DRESS is a complex syndrome with a broad spectrum of clinical features.

As with SJS/TEN, several studies have been conducted to identify genetic susceptibilities to DRESS in various populations. *HLA-A*31:01* has surfaced in a several studies of patients with Chinese, Japanese, European and North African ancestry as a risk factor for carbamazepine-induced DRESS. Other similar studies have been conducted to compare HLA allele frequencies in population or tolerant controls.[20] Selected drugs where multiple loci have been identified are shown in Table 6.

Drug	Risk alleles	Populations studied
Allopurinol	A*32:02, B*58:01, C*03:02	Korean, European, Han Chinese, Thai, Vietnamese
Carbamazepine	A*31:01, B*15:11, B*58:01	Japanese, European, Han Chinese, Korean
Lamotrigine	A*02:07, A*31:01, A*68:01, B*58:01, C*07:18, DQB1*06, DRB1*13	European, Thai, Korean
Nevirapine	C*08:02, B*14:02, CW4, DRB1*01:01	Japanese, European, Han Chinese
Sulfamethoxazole	A*11:01, B*13:01	Japanese, Asian, Han Chinese

Table 6. HLA alleles associated with DRESS
Adapted from Gibson, et al. 2023[20]
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For vancomycin, a study was conducted through an EHR-connected biobank that was coupled with prospective case ascertainment, in which 23 cases of DRESS were compared to 46 matched, vancomycin-tolerant controls. *HLA-A*32:01* was present in 83% of the cases and none of the controls ($p=1x10^{-8}$). In an enzyme linked immunosorbent spot (ELISpot) assay wherein case or control peripheral blood mononuclear cells were incubated with vancomycin showed that almost all ELISpot-positive cases carried *HLA-A*32:01* (11/12, 92%) but none of 24 controls. In silico molecular docking analysis was used to evaluate interactions between *HLA-A*32:01* and vancomycin, showing that vancomycin can potentially bind the antigen binding clef of this variant.[33]

4.2.3 AGEP

AGEP is a SCAR characterized by the acute onset of many pinpoint (< 5 mm), non-follicular sterile pustules scattered on edematous and erythematous skin.[34,35] The pathophysiology of AGEP has been classified as an immune T cell-mediated disease.[35] This immune process is initiated upon exposure to an offending agent, leading to formation of a medicinal product epitope by antigen presenting cells. This causes activation and proliferation of medicinal product-specific $CD4^+$ and $CD8^+$ T cells and the subsequent release of cytotoxic proteins such as perforin, granzyme B and Fas ligand.

These cytotoxic proteins induce apoptosis of keratinocytes in the epidermis, resulting in tissue destruction and vesical formation. The $CD4^+$ T cells release an increasing amount of C-X-C motif chemokine ligand 8 (CXCL8), INF-γ, and granulocyte/macrophage colony-stimulating factor (GM-CSF). CXCL8 is a potent neutrophilic chemotactic cytokine that recruits neutrophils into the vesicles and transforms the vesicles into sterile pustules. Increased levels of INF-γ and GM-CSF synergistically enhances viability of neutrophils and amplifies formation of sterile pustules.

Very little information is available regarding clinical biomarkers for AGEP. A recent case series identified variants in the IL36 receptor antagonist (*IL36RN*) gene that may have potential significance in the pathogenesis of AGEP.[36] IL-36 R blocks pro-inflammatory cytokines IL-36-α, -β and -γ. Variants in the *IL36RN* gene results in increased downstream production and release of these pro-inflammatory cytokines and chemokines such as IL-1, IL-6, IL-12, IL-23 and IL-17, leading to inflammation and potentially a predisposition to AGEP.[36] However, while psoriasis was not documented in any of the cases in this study, *IL36RN* variants are also present in generalized pustular psoriasis, which could potentially be a confounding factor.

4.2 Medicinal product metabolism-related genetic biomarkers

Polymorphisms in the genes encoding medicinal product-metabolizing enzymes or medicinal product-transporter proteins can significantly influence systemic concentrations of medicinal products, and for many medicinal products variability in systemic exposure can result in ADRs. To this end, the inter-individual variability in medicinal product metabolism and the formation of active metabolites could modulate this degree of engagement between the HLA-B molecule and T cells.

Cytochrome P450 (CYP) 2C9 (CYP2C9) is a drug metabolizing enzyme that is involved in the metabolism of numerous drugs, notably phenytoin. A genome-wide association study (GWAS) that compared differences in the frequency of nearly one million variants in 48 SJS/TEN cases and 130 tolerant controls (from Taiwan, Japan and Malaysia), found that the *CYP2C9*3* variant, which results in an amino acid change (p.Ile359Leu) and decreases enzyme activity, was overrepresented in patients who received phenytoin and developed SJS/TEN compared to phenytoin-tolerant controls (from Taiwan, Japan and Malaysia).[37] Additional studies confirmed this finding, and a subsequent meta-analysis has shown a significant association between phenytoin induced SJS/TEN and *CYP2C9*3*, especially in the Thai population.[38] Phenytoin is primarily metabolized to an inactive metabolite by CYP2C9, and therefore, reduced CYP2C9 activity leads to higher systemic phenytoin concentrations, which may increase the risk of SCAR. Patients who are intermediate or poor metabolizers of CYP2C9 (e.g. have variant genotypes such as *1/*3, *2/*2 or *3/*3, which reduce CYP2C9 activity) exhibit higher plasma phenytoin concentrations compared to patients who are normal metabolizers (e.g. *1/*1).[12]

The GWAS also found that patients with SJS/TEN had higher phenytoin concentrations than tolerant controls. Thus, patients who are known to be intermediate or poor metabolizers may ultimately require lower doses of phenytoin to maintain similar steady-state concentrations compared to normal metabolizers, and higher concentrations may increase the risk for SCAR.

DRESS is a severe T-cell-mediated hypersensitivity reaction to a medication or its active metabolites, which may be associated with enzymatic defects in drug metabolism.[39] Polymorphisms in genes encoding drug-metabolizing enzymes, such as CYP enzymes, N-acetyltransferase or drug transporter proteins have been associated with several ADRs and may possibly contribute to the pathogenesis of DRESS.[7,13]

The GWAS that identified *CYP2C9*3* as a significant risk factor for SJS/TEN also showed that DRESS risk was increased among *CYP2C9*3* carriers.[40]

The precise mechanism by which CYP2C9 variants increase SCAR risk in phenytoin treated patients is not established though it appears to be related to drug or metabolite concentrations. A study involving the immediate reactions to metamizole identified an association between the higher frequency of slow arylamine N-acetyltransferase type 2 (activity (commonly referred to as slow acetylators) and the increased risk of agranulocytosis.[13,41] Impairment of these enzymes causes a reduced degradation of toxic metabolites such as 4-methylaminoantipyrine or 4-aminoantipyrine.[41] As such, other metabolic disturbances that result in the accumulation of immunogenic metabolites could be at play. Other medications including aromatic anticonvulsants are metabolized by the hepatic CYP450 enzymes and oxidation by aromatic hydroxylase may produce the arene oxides, which are the toxic metabolites.[42] Overall, alteration in the activity of drug-metabolizing enzymes leads to the accumulation of toxic metabolites which dysregulate the immune response, stimulating cell necrosis and/or apoptosis.[13]

4.3 Circulating and tissue specific biomarkers to aid in the clinical evaluation of SCAR

Numerous studies have identified potential biomarkers in serum or skin (including blister fluid) that are diagnostic, prognostic or predictive. Granulysin has emerged as a biomarker that is present in various forms of SCAR. Granulysin is a cytotoxic molecule that is released from cytotoxic T lymphocytes and natural killer cells that plays a role in host defenses against pathogens. Granulysin is present in the blister fluid of patients with SJS/TEN and was shown to be toxic to keratinocytes.[43] Histopathology studies have also shown higher skin granulysin expression in various forms of SCAR, including SJS/TEN and DRESS,[44] and it is also found in the serum of patients with SJS/TEN.[45] While granulysin appears to not be specific to SJS/TEN it could be an earlier indicator of SCAR. Similarly, several studies have also shown that various other immune mediators such as soluble Fas ligand[46] granzyme B, and perforin[47] are also consistently elevated among patients with SCAR at various stages following clinical presentation. A body of literature is also available to suggest that various cytokines may be detected. However, the data for most biomarkers are less consistent with respect to correlations with disease severity and prognosis. It is possible that multicomponent biomarkers could be developed to differentiate SCAR from less severe skin reactions, the likelihood of progression to TEN and potentially long-term outcomes.[48,49] Similar studies have also been conducted in DRESS. Biomarkers that have demonstrated promise include granulysin, TARC/CCL/17, soluble ST2, sOX40, CCL-27, IL15, galectin-7, RIP-3, and a variety of cytokines, which have been measured in either serum or skin lesions, some of which appear to track with disease onset and severity.[32,48,49]

Beyond the traditional drug specific immune response, DRESS can be also sustained by viral reactivation.[50] Clinical viral reactivation occurs up to two weeks after the onset of DRESS symptoms and is associated with worse prognosis in disease duration, relapse, constitutional symptoms and organ involvement compared with patients with no viral reactivation.[50]

Viral reactivation may take part in DRESS pathogenesis in the following four ways:

- direct organ damage,
- induction of antiviral immune responses,
- enhancement of systemic inflammation reactivation due to immune cell proliferation.[50]

A typical feature of DRESS is the reactivation of latent HHV), namely HHV6, HHV7, EBV, and CMV. High viral load and antibody titres are considered poor prognostic markers in DRESS treatment outcomes.[13,50] DRESS is the result of complex interplay of genetic factors, especially HLA alleles, immunological response (T cell), and abnormality of medicinal product metabolizing enzymes and herpesviruses family member reactivation (HHV6, HHV7, EBV, CMV).[13,50] Nevertheless, clinical viral reactivation is a probable cause of chronic recurrence of DRESS-related skin rash despite cessation of the culprit medicinal product.[13,50]

4.4 Developing and implementing biomarker testing recommendations

Prescribing guidelines generated by different national and international working groups for translation of HLA-pharmacogenetic testing into clinical practice are operational in many countries. The Clinical Pharmacogenomics Implementation Consortium (CPIC) and the Dutch Pharmacogenomics Working Group (https://www.knmp.nl/richtlijnen) have written prescribing guidelines based on HLA genotype for carbamazepine,[51,52] oxcarbazepine,[51,52] phenytoin,[12] allopurinol, [6,53] flucloxacillin[52] and lamotrigine.[52] Genetic testing coupled with a robust clinical decision support system may enable clinicians to optimize medicinal product selection. To this end, these genotype-based treatment guidelines may help to facilitate the use of pharmacogenetic tests for patient care. However, testing is not routine in many parts of the world primarily because of the rarity of SCAR. Alternatively, in regions where the incidence is lower, testing may be targeted to certain subsets of patients in which the allele frequency and risk for the ADR is higher. An example of this is seen for carbamazepine where regulatory authorities have incorporated testing recommendations in medicinal product labelling for patients of Asian ancestry:

> *Carbamazepine Boxed Warning (U.S. Prescribing Information): SERIOUS AND SOMETIMES FATAL DERMATOLOGIC REACTIONS, INCLUDING TOXIC EPIDERMAL NECROLYSIS (TEN) AND STEVENS-JOHNSON SYNDROME (SJS), HAVE BEEN REPORTED DURING TREATMENT WITH [CARBAMAZEPINE]. THESE REACTIONS ARE ESTIMATED TO OCCUR IN 1 TO 6 PER 10,000 NEW USERS IN COUNTRIES WITH MAINLY CAUCASIAN POPULATIONS, BUT THE RISK IN SOME ASIAN COUNTRIES IS ESTIMATED TO BE ABOUT 10 TIMES HIGHER. STUDIES IN PATIENTS OF CHINESE ANCESTRY HAVE FOUND A STRONG ASSOCIATION BETWEEN THE RISK OF DEVELOPING SJS/TEN AND THE PRESENCE OF HLA-B*1502, AN INHERITED ALLELIC VARIANT OF THE HLA-B GENE. HLA-B*1502 IS FOUND ALMOST EXCLUSIVELY IN PATIENTS WITH ANCESTRY ACROSS BROAD AREAS OF ASIA. PATIENTS WITH ANCESTRY IN GENETICALLY AT-RISK POPULATIONS SHOULD BE SCREENED FOR THE PRESENCE OF HLA-B*1502 PRIOR TO INITIATING TREATMENT WITH [CARBAMAZEPINE]. PATIENTS TESTING POSITIVE FOR THE ALLELE SHOULD NOT BE TREATED WITH [CARBAMAZEPINE] UNLESS THE BENEFIT CLEARLY OUTWEIGHS THE RISK (SEE WARNINGS AND PRECAUTIONS, LABORATORY TESTS).*

Novartis Pharmaceuticals. “Tegretol (Package Insert).” (2023).

Race and ethnicity have been recognized as a major factor contributing to interindividual variability in SCAR. For example, abacavir-hypersensitivity syndrome is more prevalent in white populations due to a higher frequency of the *HLA-B*57:01* allele in this population, whereas the frequency of carriers of the *HLA-B*58:01* allele is higher in Asian populations.[54-,55,56] The predictive value of any biomarker depends on the frequencies of that marker and the associated ADR in the study population.[55] For this reason, further research is needed to identify genomic markers for particular demographic clusters in admixed populations that may have increased risk for developing certain ADRs.

Regardless of the approach, biomarker testing recommendations from regulatory authorities or developers of clinical guidelines have to consider many factors including: 1) the extent of evidence to support the association and information on the relevant population, because the rarity of the events makes populations studies difficult to conduct so experimental evidence and replication of findings is critical; 2) allele distributions for genetic factors because the frequency of variants that increase risk may vary widely based on ancestry; 3) screening considerations because the rarity of events tends to make the yield of screening quite low so identification of multiple factors that increase risk can help make testing more efficient; 4) clinical recommendations to guide prescribing because the potential benefits and risks of alternative treatment strategies may influence outcomes; and 5) uncertainty and limitations because any predictor of SJS/TEN or other SCAR is likely to be imperfect and patients may remain at risk despite having negative test results.

Application of HLA genotyping as a screening tool has significant limitations and should never be a substitute for appropriate clinical vigilance and individualized patient management. Clinicians should diligently monitor patients for development of hypersensitivity reactions, regardless of the absence or presence of a biomarker associated with the ADR.

Additionally, other factors can contribute to the risk for development of an ADR, such as medicinal product dose and duration, concomitant medications and the risk for drug-drug interactions, comorbidities, age and environmental factors. Therefore, clinicians should consider the totality of information and manage each patient individually.

The evidence base for other circulating and tissue biomarkers has not yet reached a level to support routine clinical testing yet remain an area of ongoing research.

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CHAPTER 5.

CAUSALITY ASSESSMENT OF SCAR IN PRE- AND POSTAUTHORIZATION SURVEILLANCE

Chapter summary

Causality assessment is the procedure by which the relationship between a product and AE is established. Standard methods such as Bradford Hill criteria, global introspection, operational algorithms, probabilistic approaches are described for SCAR. Adjudication, targeted follow-up forms and assessment of aggregate data are also presented.

Conclusions or recommendations

1) The standard causality methods may be used to evaluate a potential causal relationship between a product and adverse skin events.

2) The Algorithm for Assessment of Drug Causality for Epidermal Necrolysis (ALDEN) was created to assess causality of individual reports of SJS/TEN takes into account the most relevant factors such as latency and medicinal product half-life, class effect and alternative etiologies.

3) When possible, additional tools such as patch testing or delayed intradermal testing and expert adjudication of individual cases can further support a causal relationship.

4) SCAR-specific targeted questionnaires offer valuable information for a timely and comprehensive assessment of causality.

5.1 Introduction

Causality assessment is a procedure whose purpose is to determine the relationship between an intervention, namely a medicinal product, and an AE. If a causal relationship with the AE is considered at least a reasonable possibility, the event is considered an ADR. The assessment of causality is at the heart of pharmacovigilance, which relies on the information collected from healthcare professionals including clinical trial investigators.

Once a SCAR diagnosis is confirmed, a detailed medical history including all medicinal products and/or supplements will inform the assessment of a causal relationship between the AE and the medicinal product. In general, it is recommended to conduct a review of medical events and exposures, including dates and timelines over an eight-week period prior to the reported onset of the SCAR[1] and the patient's skin risk profile.[2]

In certain circumstances, it may be useful to consider medicinal product exposures over a longer timeline, taking into account factors such as treatment indication, patient population characteristics, and medicinal product mechanism of action. Validated medicinal product causality assessment tools also help to avoid implicating the medicinal product(s) introduced for early symptoms of SCAR and are discussed in this chapter.

In the pre-authorization phase, clinical trial participants benefit from close safety surveillance and any suspected ADR will be investigated, which will include a causality assessment of the individual case. In the postauthorization phase, patients and healthcare professionals are encouraged to report suspected ADRs to their regional reporting schemes. Also, it is important to note that causality assessment of individual cases is not required for reporting purposes.

When a suspected ADR is reported by a healthcare professional or patient, the manufacturer may perform a causality assessment of that reaction, although this is not mandatory. However, even if the causality assessment considers a causal relationship of the AE and the medicinal product as an unlikely cause or is excluded altogether, the company is still required to report the case to the appropriate regulatory bodies. The causality assessment outcome can be part of this submission.

Manufacturers and regulatory bodies are required to perform continuous safety surveillance in the postauthorization phase based on the totality of all available evidence. However, such surveillance does not only include causality assessment of individual cases if this is feasible based on the nature of these cases and available information about them, but more importantly, also includes causality assessment of safety concerns. Whereas causality assessment at case level investigates if an AE in a given patient is caused by a medicinal product, causality assessment conducted on the basis of all evidence examines whether the medicinal product can cause the AE in patients who will receive the medicinal product in the future. Approaches for causality assessment on the basis of all evidence are also discussed in this chapter.

5.2 Global introspection methods

Global introspection methods rely on detailed clinical information for individual cases of suspected ADRs. The WHO-UMC for International Drug Monitoring has developed a practical tool which combines the assessment of clinical and pharmacological case information and the quality of this information to assess causality. The WHO/UMC causality tool takes into account the temporal relationship, laboratory values, dechallenge and rechallenge outcomes, as well as the presence of possible alternative etiologies to classify the likelihood of a causal relationship of a given case into Certain, Probable/Likely, Possible, Unlikely, Conditional/Unclassified, and Unassessable/Unclassifiable.[3]The global introspection method implicitly relates to the diagnosis-making process which remains subjective and demonstrated poor intra- and interrater reproducibility.[4-7]

5.2.1 Operational algorithms

The second category of causality assessment methods consists of questionnaire-based operational algorithms for individual cases of suspected ADRs.[3] Algorithms are designed to reduce intra- and interrater variability, increase reliability and validity of causality assessment. The **Naranjo scale** is the commonly used algorithm to assign a probability scale to medicinal product-event relationship.[8] It was originally developed by pharmacologists/physicians and psychiatrists at the University of Toronto for use in controlled trials and registration studies of new drugs.[8,9] The Naranjo approach is simple to apply in the assessment of causality of individual case reports from spontaneous postauthorization reporting[10], or observational studies.[11,12] The Naranjo scale can be used for assessment of adverse skin events.[13] However, the high variability of weighting assigned to each causality criterion can lead to the imprecise expression of the final result.[14] Slight variations of the Naranjo scale, such as the **Liverpool algorithm**, have been shown to reduce interrater variability.[15]

5.2.2 Probabilistic methods

Probabilistic methods calculate the probability of causality based on available knowledge of the type of suspected medicinal product, its potential to cause a specific ADR (prior estimate) and specific findings in individual case reports of suspected ADRs, in combination with background information (posterior estimate).[8]

The probabilistic approach derived from Bayes' theorem, offers a formal causal assessment in determining the probability of medicinal product causation. While highly reliable, these methods remain too complex and time consuming for routine practice.[7,16]

These tools are not specific to an ADR and can be further refined to the type of medicinal product-induced injury such as the Roussel Uclaf Causality Assessment Method for drug-induced liver injury[17] or the Algorithm for Assessment of Drug Causality for Epidermal Necrolysis (ALDEN) that is specific to cases of SJS/TEN.[18]

5.2.2.1 ALDEN

ALDEN is a probabilistic method aimed at assessing the causality of individual cases of SJS/TEN. ALDEN was developed for use in case–control studies (SCAR and EuroSCAR)[19,20] and a case registry (RegiSCAR).

The ALDEN score also takes into account the latency between start of medicinal product intake and index day (day of SJS/TEN symptom onset), presence/availability of the medicinal product in the body before index day (taking into account the medicinal product's half-life and the patient's hepatic and renal function), information on previous and later intake as well as the discontinuation of the medicinal product (if available), type of medicinal product and its possible induction potential (based on medicinal product lists that have to be updated regularly), and alternative reasons.

The ALDEN criteria includes a criterion on medicinal product "notoriety" for SJS/TEN assigning no points for medicinal products not previously identified as culprits, 'including those newly released to the market"[18] and thus a new medicinal product culprit would not contribute to the total score and causality classification. Numeric score values allow the causality assessment of every single medicinal product a patient used four weeks before the SJS/TEN. The numeric score values are classified as "very improbable", "improbable", "possible", "probable", or "very probable". Given that ALDEN is more sensitive than global introspection or operational algorithms, it can be considered a reference tool in SJS/TEN.[18]

5.2.3 The Bradford Hill criteria

The Bradford Hill criteria consist of nine principles that can be useful in establishing a causal relationship between an observation at population level and a suspected cause based on all available evidence. These criteria have been widely used in epidemiology and public health research and include the strength in terms of effect size, consistency across clinical findings, specificity, temporal sequence, biological gradient in terms of dose-response relationship, biologic plausibility, coherence with non-clinical findings, experimental evidence and analogous evidence.[21]

In pharmacovigilance, the Bradford Hill criteria are considered relevant for causality assessment[21] and have become the basis for several methods, which have five criteria in common: challenge, dechallenge, rechallenge, previous bibliographic description and etiologic alternatives.[21]

5.3 Tools to support investigation of causality between medicinal product and SCAR

5.3.1 Tests

Patch or delayed intradermal testing provide evidence to support the assessment of causality. In general, diagnostic patch testing (DPT) is performed after but within one year of the acute phase of the hypersensitivity reaction.

DPT is generally safe but has been associated with a high incidence of non-life-threatening systemic reactions among HIV-infected patients with antituberculosis drug-related cADRs, including SJS/TEN.[22,23] For SJS/TEN the optimum time for a diagnostic rechallenge is during the acute stage. In DRESS, which formed the majority of the cases, it should be performed 5-8 weeks after the initial cADR. Other authors have suggested that rechallenge following cADR should be deferred by a period equivalent to over five times the elimination half-life of the drug and not earlier than four weeks after the episode. This could be related to transient, nonspecific residual reactivity to drugs often induced by persisting viral or immune reactivation during the acute stage, causing high background proliferation and activity, regardless of stimulus.[22,23]

These tests are of particular interest when several medicinal products are co-administered and/or to clarify the phenotype.[24] For abacavir, DPT has helped define the phenotype of immunologically-mediated abacavir hypersensitivity with a diagnostic sensitivity of 87%.[25-27] The in vivo skin testing has shown a negative predictive value (NPV) of approximately 90% for skin reactions depending on the drug tested. The negative results may support a rechallenge in the absence of safe, alternative treatments.[28]

DPT has also been used to investigate the cross-reactivity to anti-epileptic agents that are considered as therapeutic alternatives.[29] A large multi-centre study showed a high degree of variability of the DPT results in both drug and clinical phenotype in patients diagnosed with DRESS, AGEP or SJS/TEN within one year of event resolution.[30]

In vitro testing, such as lymphocyte proliferation assays and those to identify and characterize drug-specific immune cell populations or key cytokines involved in skin reactions are still under development and are not used for routine diagnostic testing.[31,32] HLA pharmacogenomic testing can be used in a clinical setting to identify if patients are at risk for SCAR.[33]

5.3.2 Adjudication

5.3.2.1 Independent clinical trial review board

Event adjudication is a process where an independent review board of medical specialists assesses relevant events for fulfilment of predefined clinical criteria. It is used in clinical trials to manage subjective evaluations and enhance a harmonized approach.

The adjudicator refers to one or more assessors, independent from site investigators, who use information collected in the trial to assess the same outcome. In order for relevant information to be captured when there is a suspicion of SCAR in a clinical trial, AE-specific follow-up forms are developed by sponsors and submitted to investigators for completion. This allows the creation of a standardized process for the assessment of AE reports and enhanced case documentation to support appropriate diagnosis and causality assessment.

Considering the low frequency of SCAR, a panel of independent experts is rare. More often, independent dermatology experts are involved to review and assess a adverse skin event that is considered a potential SCAR.

Inclusion of a blinded independent dermatologist or allergist is considered a strength when planning for clinical trials where suspected SCAR are foreseen, as it allows for accurate monitoring and assessment of adverse skin events.[34]

5.3.2.2 Other clinical tools

In addition to an independent expert in cADRs, integration of skin biopsy results, photographs and investigator trainings and materials may allow for more accurate monitoring and evaluation of adverse skin events.[34]

5.3.3 Targeted follow-up forms

Targeted Follow-up Forms can be used to document relevant information that will allow appropriate SCAR assessment. Certain limitations and difficulties are acknowledged when collecting the information proposed on the follow-up forms, such as the paucity of biopsies typically performed on cutaneous lesions, incomplete information obtained from the reporter on the characteristics of cutaneous lesions or absence (or insufficient quality) of photographs of cutaneous lesions under standardized conditions. In addition, there is the potential for missing data entry (e.g. subjects who withdraw from studies, lack of follow-up in the postauthorization period).

Important elements to be captured on the follow-up forms may include medical history/risk factors, AE information (e.g. nature of first symptoms, type of cutaneous event, extent of a rash/distribution of cutaneous lesions, associated symptoms, evidence of internal organ involvement), evidence of viral infection, whether photosensitivity is suspected, whether photographs were taken, if the medicinal product was stopped or dosage reduced and the outcome of the event. A systematic approach for assessment of the SCAR signal is key to complement the adjudication process. This topic is further discussed in Chapter 6 ("Preauthorization Safety Data Collection and Analysis"). Scientific adjudication is required to assess the causal relationship between the suspect culprit medicinal product and SCAR.

This approach includes the following steps:

- Case definition, described in more detail in Chapter 1 "What are Severe Cutaneous Adverse Reactions",
- Pattern analysis: evaluating the number of cases with a compatible chronology, cases without a suggestive chronology, cases with no chronology available and cases where the diagnosis of SCAR was not confirmed. In addition, evaluating the number of cases with concomitant exposure to medicinal products known to induce SCAR and/or with possible underlying conditions that may provide alternative explanations (e.g. infections, systemic lupus erythematosus [SLE], T-cell lymphoma),
- Literature review: to evaluate whether there are cases of SCAR reported with the suspected culprit medicinal product or within the product class in key epidemiological studies on SJS/TEN (e.g. EuroSCAR).

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CHAPTER 6.

PRE-AUTHORIZATION SAFETY DATA COLLECTION AND ANALYSIS

Chapter summary

This chapter provides guidance to investigators about the information to be collected during the initial assessment of a potential SCAR. The chapter also addresses the risk factors associated with the development of SCAR and contains an overview of differential diagnoses that may act as confounding factors when analysing a SCAR.

Subsections contained in this chapter:

- Investigator assessment,
- Risk factors and confounding factors

Conclusions or recommendations

When appropriate assessment of a SCAR during clinical development has been conducted, communicating the SCAR to various stakeholders in the clinical trials is important. Timely awareness by stakeholders, including study participants, investigators and regulatory authorities, is necessary to allow prompt identification of these events and rapid intervention, thereby ensuring patient safety. Additionally, sponsors of a clinical trial where a SCAR has been reported may consider implementing protocol changes to allow for continued monitoring and additional characterization of a potential SCAR.

6.1 Introduction

Timely recognition of a potential SCAR case by investigators is of utmost importance for patients' safety and assessing the impact of such a reaction on the clinical programme. Initial steps in this assessment require the acquisition of detailed information about the suspected AE that could suggest and confirm a SCAR diagnosis.

6.2 Investigator assessment

SCAR needs to be promptly recognized because of the associated high morbidity and mortality as well as the potential impact on a clinical programme. A clinical trial participant presenting with a widespread rash temporally associated with a potential culprit medicinal product should trigger an evaluation of a possible SCAR case (SJS, TEN, DRESS/DIHS, AGEP or GBFDE).

Clinical trials whose patient population include high-risk patients for the occurrence of SCAR (e.g. HIV-infected patients, oncology patients, patients with SLE)[1] and/or exposure to medicinal products (either as an investigational medicinal product or concomitant medication) with a known risk of inducing SCAR (e.g. aromatic anticonvulsants, allopurinol, antiretrovirals, oxicams) should lead the sponsor and investigators to consider the occurrence of possible SCAR. Additionally, investigators overseeing clinical trials whose population is comprised of elderly patients should keep in mind that prompt diagnosis is of utmost importance, since higher mortality rates and clinical complications are more frequently observed in older patients.[2-4]

When a SCAR is suspected, the first measure should be to interrupt the treatment with the alleged culprit medicinal product. An assessment of the likelihood that the investigational medicinal product is implicated is required, taking into consideration two main points, namely the information that is available on other medicinal products within the same class and that elicit similar reactions, and time to onset of the reaction.

Additionally, all concomitant medications need to be evaluated and, once a particular SCAR diagnosis is suspected (e.g. DRESS, SJS/TEN), the typical latency period should be compared with the time elapsed since last exposure to the suspected medicinal product.(Figure 7.)

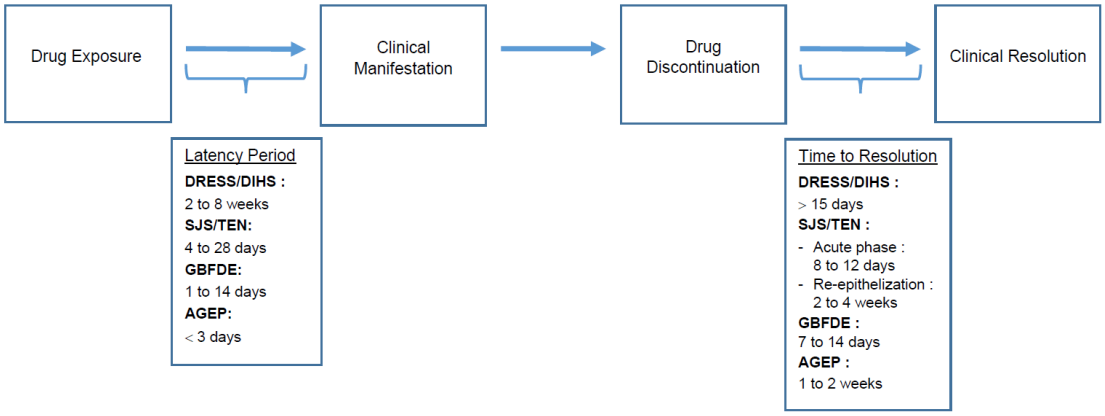

Figure 7. The SCAR timeline
References:[5-24]

The pattern of skin involvement and accompanying signs/symptoms can suggest SCAR and certain characteristics might suggest a particular diagnosis. SJS/TEN may present with blisters, skin detachment, exfoliation, positive Nikolsky's sign, oral and genital mucosa involvement, as well as eye involvement (e.g. corneal ulcers, conjunctivitis). The occurrence of a prodromal period is common with SJS/TEN, usually preceding skin manifestations by three days and presenting with fever, myalgia, arthralgia, malaise, photophobia or conjunctival itching or burning.

In DRESS/DIHS, fever, facial oedema and lymph node enlargement are typically present. In addition, a long latency period is typically observed (2-8 weeks) and the clinical resolution usually follows a protracted course (>15 days).[6,7] In a clinical trial setting, a patient with characteristic lesions and systemic symptoms should be evaluated for exposures to new medicinal products, recent dosage changes or use of known high-risk medicinal products, which occurred 2-8 weeks prior to the onset of lesions or systemic symptoms. The investigational medicinal product should also be assessed for a possible contributive role. It is noteworthy to mention that several recently developed medicinal products have been reported as DRESS/DIHS syndrome culprits, such as anti-hepatitis C virus agents (boceprevir and telaprevir), targeted therapies for oncological diseases (sorafenib, vismodegib and vemurafenib), rivaroxaban and febuxostat.[7] The diagnosis of DRESS/DIHS should be guided by a scoring system, such as RegiSCAR and J-SCAR,[6,8] to the extent that clinical and laboratory information is available.

FDE is characterized by the occurrence of erythematous macules/plaques, residual hyperpigmentation, and a history of recurring lesions in the same affected area, after exposure to various medicinal products (NSAIDs, paracetamol/acetaminophen, antibiotics). GBFDE is a rare and more severe form of FDE, presenting with blisters and is clinically similar in appearance to SJS/TEN. The absence of constitutional symptom and internal organ involvement, presence of well-demarcated blisters and erythematous patches, absence or paucity of mucosal erosions, a history of similar eruptions and onset within hours of exposure to the associated medicinal product favour a GBFDE diagnosis.[4]

In a 2013 study, Lipowicz et al. compared GBFDE cases with SJS/TEN cases and found that although the majority of patients with GBFDE had skin detachment of less than 10% of BSA (30/58 patients), the mortality rate was significant and comparable to SJS/TEN (22% versus 28%).

The most characteristic feature of AGEP is the presence of widespread sterile pustules, with an initial predilection for flexural areas and subsequent spread to trunk and limbs. Systemic manifestations and laboratory abnormalities can also occur, such as fever, leukocytosis, neutrophilia and eosinophilia,[9] as well as mucous membrane involvement in about 20% of the cases (typically limited to oral mucosa).[10] A rapid onset (hours to a few days) after medicinal product exposure is also observed and can help differentiate from other SCAR.

In all potential SCAR, because appropriate diagnosis considers clinical, histopathologic and laboratory features, a specialist in the management of medicinal product-induced cutaneous lesions should be consulted, such as a dermatologist, allergist or other subject matter expert. A skin biopsy for histopathologic examination may provide useful information for the assessment of the event as well as key information to help distinguish between different SCAR entities (e.g. SJS/TEN versus GBFDE) and other conditions in the SCAR differential (e.g. autoimmune blistering diseases).[11]

Table 7 provides recommended information to be collected by the investigator in case a SCAR diagnosis is suspected. This information may help to confirm the diagnosis and inform causality assessment.

Medicinal product characteristics	- Published evidence including notoriety for the known medicinal product: e.g. aromatic anticonvulsants, sulfonamides, oxicam NSAIDs - For medicinal products under investigation, potential pharmacodynamic interactions such as chemical structure, metabolites or mechanisms of action should be considered
Patient characteristics	- Demographics: age, gender, genetic background - Patients with HIV infection, malignancies, SLE or other autoimmune diseases, transplant patients. - Genetic risk factors: presence of medicinal product-specific HLA risk alleles and known exposure to certain agents (e.g. DIHS/DRESS/SJS/TEN induced by dapsone and *HLA-B*13:01*[12], SJS/TEN induced by carbamazepine and *HLA-B*15:02*[12], DIHS/DRESS/SJS/TEN induced by allopurinol and *HLA-B*58:01*[12]
Skin involvement characteristics	- Time to onset of cutaneous lesion - Time to resolution of the event, if reaction is resolved - Description of rash, distribution, location and morphology of cutaneous lesions (e.g. presence of papules, macular papules, exanthema, pustules, urticaria, blisters, bullae, exfoliation, oedematous plaques, hyperpigmentation, target-like lesions, positive Nikolsky's sign) - Approximate body surface area affected: <10%, 10-30%, >30% - History of recurring skin lesions at the same site (GBFDE) - Biopsy and immunofluorescence results, if available - Patch testing, prick testing, lymphocyte stimulation testing, immunophenotyping or HLA genotyping, if available

Presence of accompanying and/or preceding signs and symptoms	- Presence of oral or genital mucosa involvement - Fever (body temperature >38 °C) - Other constitutional signs/symptoms: fatigue, arthralgia - Enlarged lymph nodes (DRESS/DHS) - Facial oedema (DRESS/DIHS) - Eye involvement (conjunctivitis, corneal ulcer), (SJS/TEN)
Presence of Accompanying Laboratory Abnormalities	- Leukocytosis - Lymphocytosis - Lymphopenia - Presence of atypical lymphocytes (DRESS/DIHS) - Eosinophilia - Thrombocytopenia (DRESS/DIHS) - Evidence of internal organ involvement (DRESS/DIHS): AST and/or ALT increase, creatinine increase, proteinuria, haematuria, decreased creatinine clearance, cardiac enzymes elevation, amylase and/or lipase increase. - Evidence of reactivation of herpes viruses (HHV6 - DRESS/DIHS)

Table 7. Potential SCAR initial assessment in the clinical trial setting

6.3 Risk factors and confounding factors

6.3.1 Risk factors

The process for monitoring and identifying potential SCAR cases during preauthorization clinical development and postauthorization depends on the predilection of the medicinal product association with SCAR. The following paragraphs will briefly cover several risk factors that should be considered: patient population (age, comorbidities, genetic background), pharmacology (class and target) of the medicinal product, and pharmacogenomics, when assessing the risk for SCAR in a clinical programme.

Patient population

Patient population characteristics including age, comorbidities and genetic background must be considered when determining SCAR risk for the patient and/or patient population. It is uncommon for SJS/TEN to occur in children less than two years of age[13]. Singh et al. published a retrospective study[14] evaluating EHRs of a tertiary hospital in Northern India, in which the majority of SCAR occurred in the older age group (41-65 years old).

Replotting the data (Table 6) shows that approximately 50% (42-59%) of each SCAR (SJS/TEN, DRESS and AGEP) and exfoliative dermatitis (ExDerm) occurred in the 41–65 year old age group and that the youngest age group (0-18 years old) consistently represented the lowest proportion for each SCAR.

In addition to the age of the individual, comorbidities are important risk factors for SCAR. SCAR tend to be more common in immunocompromised patients such as individuals with HIV infection, as well as individuals with malignancy or hepatic disease.[15,16] To understand the comorbidity impact on SCAR risk, Table 7 replots the data from Singh et al. Acute infections were found to be the most common comorbidities for SJS/TEN and DRESS, while seizure disorder and diabetes were the most common comorbidities for AGEP and ExDerm.

Specific genetic associations and HLA alleles may be over or under expressed in different patient populations (Table 8).[9] The linkage between abacavir hypersensitivity and *HLA B*57:01* is an example that illustrates how over assignment of the clinical syndrome and low allele frequency in certain population groups can wrongly lead to the assumption that a HLA association to a particular drug hypersensitivity is restricted to race.[9,17] A case-control study was able to demonstrate the 100% sensitivity of *HLA-B*57:01* as a marker for immunologically confirmed abacavir hypersensitivity, in both US white and black patients, demonstrating the clinical utility of allele screening that is generalizable across races.[18]

Pharmacology

The most common compound classes that induce SCAR include antibiotics, anticonvulsants, analgesics, antituberculosis agents, antiretroviral and herbal agents.[19,20] In addition to the compound classes listed above, immune-modulatory targets and/or modalities may induce SCAR.[21,22]

Pharmacogenomics

Associations between SCAR and specific class I and class II HLA alleles are medicinal product-specific and can vary across different populations.(Table 8)[9-25] A comprehensive review of pharmacogenomic markers in SCAR has recently been published.[24] Currently, there is no specific pharmacogenomic marker or panel that will indicate a higher risk of SCAR for an investigational new medicinal product or recently authorized product, but the literature highlights[25,26,27] the importance of pharmacogenomics in determining SCAR risk factors in the postauthorization phase.

age	Percentage of SCAR condition (modified from Singh et al.) SJS-TEN	DReSS	ExDerm	AGEP
0 - 18	17	14	15	23
19 - 40	32	36	26	35
41 - 65	51	50	59	42
Total	100	100	100	100

Table 8. Age distribution for SCAR
Adapted from Singh et al.[14]
Permission obtained from John Wiley & Sons

Comorbidities	Percentage per SCAR (modified from Singh et al.) SJS-TEN	DRESS	ExDerm	AGEP
Seizure disorder	23	8	28	30
Diabtes mellitus	9	8	22	30
Connective tissue disorder	8	13	17	20
Malignancy	8	8	0	0
Cardiac disease	6	4	0	10
Acute infection	37	50	22	0
HIV	8	8	6	0
TB	2	0	6	10

Table 9. Comorbid medical conditions at the time of SCAR diagnosis
Adapted from Singh et al.[14]
Permission obtained from John Wiley & Sons

Drug and Clinical Presentation	HLA Allele	Population
Abacavir Hypersensitivity Syndrome	*B*57:01*	5-8% White <1% African <1% Asian
Allopurinol SJS/TEN and DRESS/DIHS	*B*58:01*	9-11% Han Chinese 1-6% White
Carbamazepine SJS/TEN	*B*15:02*	10-15% Han Chinese <0.1% White
Carbamazepine DRESS	*A*31:01*	Chinese Europeans Japanese

Table 10. Key HLA associations with SCAR
Adapted from Peter et al.[9]
Permission obtained from Elsevier

6.3.2 Confounding factors

Clinical entities that mimic SCAR manifestations and are considered differential diagnoses include infections, autoimmune disorders and haematologic malignancies. Cutaneous eruptions that are due to an underlying disease (e.g. haematologic malignancies presenting with skin changes, autoimmune disease flares) may initially manifest with extensive skin involvement. Such eruptions need to be considered and ruled out as required.

On an individual level, there may be additional confounding factors and one must be aware that in clinical trials these factors might impact the study outcome if not addressed properly. To illustrate the importance of excluding possible confounding factors, RegiSCAR, a scoring system for the diagnosis of DRESS, has a criterion for the evaluation of other potential causes (Chapter 1.4.2.3 Clinical characteristics). If three of the following tests are performed and negative, one additional point is added to the patient's total score, in favour of DRESS: hepatitis A virus, hepatitis B virus, hepatitis C virus, mycoplasma, chlamydia, antinuclear antibody, blood culture.

6.3.2.1 Skin manifestations of the underlying disease

Paraneoplastic erythroderma (PE) is described in association with haematologic malignancies, such as acute myeloid lymphoma and solid tumours (e.g. lung, prostate, thyroid, liver, ovaries, breast). Hence, an acute onset of erythroderma in oncology patients might be solely related to the underlying disease. PE can manifest as generalized erythema (>90% of BSA), scaling, with or without lymphadenopathy. According to Curth's postulates, which are criteria used to identify a relationship between an internal malignancy and a cutaneous disorder, the malignancy and the skin disease run a parallel course. Successful treatment of the tumour leads to regression of the skin disease and, conversely, recurrence of the tumour leads to the return of cutaneous signs and symptoms.[28]

Leukaemia cutis is characterized by the infiltration of leukaemic cells into the epidermis, dermis or subcutaneous tissue. It may precede, follow, or occur concomitantly with systemic leukaemia in 2.1- 30% of patients.[29] Typical manifestations include macules, papules, plaques, nodules, ulcers and blisters, but an erythrodermic form has been described in a patient with newly diagnosed acute myeloid leukaemia shortly after induction chemotherapy.[30]

Patients with HIV infection are prone to syndromes manifesting with fever and rash due to the disease itself, infections or ADRs. Importantly, immune reconstitution inflammatory syndrome (IRIS) is an entity linked to the introduction of antiretroviral therapy (ART). IRIS occurs in 10- 25% of patients who start highly active ART and is dependent on factors such as low baseline CD4 cell count.[31] A study with 423 ART-naive patients with HIV infection found a median IRIS onset of 48 days.[32] IRIS-related cutaneous manifestations might have several presentations, depending on the eliciting agent and whether it is linked to an opportunistic infection. One example of a dermatological manifestation of IRIS is eosinophilic folliculitis, which can present with pruritic, erythematous papules or pustules, leukocytosis, eosinophilia and mimic AGEP.[33,34] Cutaneous leishmaniasis has also been described in the context of IRIS, with disseminated erythematous papules, oral and genital mucosa ulcers.[35]

6.3.2.2 Infections

Numerous infectious entities can present with clinical manifestations undistinguishable from SCAR and this can lead to a delayed interruption of the offending agent and possible introduction of ineffective treatments. For DRESS/DIHS, due to concomitant fever and lymphadenopathy, viral diseases such as infectious mononucleosis, parvovirus B19 infection, Coxsackie infection, measles, dengue and viral hepatitis,[7,8] belong to the list of differential diagnoses to be considered. A retrospective analysis conducted in 2013 found that half of the patients with DRESS were initially diagnosed with infection (13/26 patients), which resulted in unnecessary treatment with antibiotics. It is worth mentioning that a rash occurring in the setting of infectious mononucleosis and concomitant treatment with a penicillin-derived agent (e.g. ampicillin, amoxicillin) is not uncommon and may represent a transient virus-mediated immune alteration.[36]

AGEP presents with a combination of fever, leukocytosis and pustules, which can be easily confused with an acute infectious event. Pustulosis acuta generalisata is a differential diagnosis to be considered, usually occurring in children (although reported in adults as well) following a streptococcal infection.[10,37] Similarly, Staphylococcal scalded skin syndrome (SSSS) or Ritter disease is another possible differential diagnosis of infectious etiology for SJS/TEN and AGEP, more frequently seen in children and in adults with immunosuppression. It results from an infection with exotoxin-producing strains of Staphylococcal aureus (possible primary sources: impetigo, conjunctivitis, pharyngitis, otitis, wound infection) and presents with desquamation, blistering and constitutional symptoms, in the absence of mucosal involvement.[38]

6.3.2.3 Autoimmunity

Acute cutaneous lupus erythematosus (ACLE) may manifest as an acute onset of generalized rash in sun-exposed areas and since it is frequently associated with SLE, systemic manifestations and laboratory abnormalities can also be found. A severe subtype of ACLE, TEN-like ACLE, has been described, presenting with bullous lesions and epidermal detachment.[39,40] Characteristic histopathologic features and presence of elevated antinuclear antibody titres and positive anti-dsDNA antibodies can help distinguishing ACLE from SCAR.[41-43]

A specific form of subacute cutaneous lupus erythematosus (SCLE), drug-induced (DI-SCLE), may also have a clinical presentation that can mimic SCAR. It can arise within weeks to years of medicinal product exposure, with a median latency of six weeks.[41] The most commonly implied drugs are thiazides, terbinafine, calcium channel blockers, angiotensin-converting enzyme inhibitors and TNF-inhibitors.[41] DI-SCLE has also been reported to occur in patients with prior diagnosis of SLE[44] and can be associated with Ro/SSA autoantibodies in > 80% of patients. Histopathology shows lupus erythematosus-specific changes and the SCLE lesions may last for weeks to months.[41]

Another autoimmune entity worth highlighting in this section is a subtype of pustular psoriasis: acute generalized pustular psoriasis (AGPP), also known as generalized pustular psoriasis of von Zumbusch. Medicinal product administration (e.g. lithium, progesterone, phenylbutazone, antimalarials, fluoxetine, ustekinumab, infliximab, adalimumab and apremilast), medicinal product withdrawal (e.g. systemic corticosteroids) and infections (e.g. upper respiratory tract infection) can be precipitating factors for AGPP.[45]

Its clinical presentation resembles AGEP, with a sudden appearance of widespread sterile pustules on painful plaques/erythema and systemic symptoms (fever, malaise, arthralgia). Similar to AGEP, mucosal involvement can occur, but factors such as history of prior episodes, personal or family history of psoriasis and presence of arthritis contribute to an AGEP diagnosis.

6.3.2.4 Peripheral T-cell lymphomas

Angio-immunoblastic T-cell lymphoma, a mature peripheral T-cell lymphoma, can exhibit a similar clinical presentation to DRESS, with widespread rash, lymphadenopathy, peripheral eosinophilia, atypical lymphocytosis and other internal organ involvement.[46] The occurrence of B-symptoms (fever, malaise and weight loss)[47] prior to the onset of rash can be a clue for the diagnosis and is present in 55-77% of patients, as well as hepatosplenomegaly.[48] Histolopathogical examination of the skin might not be conclusive for the diagnosis and a lymph node biopsy might be required. Sézary syndrome, an aggressive type of cutaneous T-cell lymphoma, typically presents with erythroderma, pruritus and generalized lymphadenopathy, and can resemble DRESS. Peripheral blood findings such as circulating leukaemic “Sézary cells” (atypical mononuclear cells) and skin biopsy findings can help in the distinction. A patient diagnosed with DRESS with persistent cutaneous alterations and/or constitutional symptoms beyond the expected time for clinical resolution, should prompt the investigator to consider peripheral T-cell lymphomas as possible diagnoses.

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CHAPTER 7.

POSTAUTHORIZATION SAFETY DATA COLLECTION AND ASSESSMENT

Chapter summary

Sources for postauthorization surveillance include spontaneous AE reporting systems, EHRs and registries. Analysis of individual case safety reports (ICSRs) and aggregate safety reports are central to the identification of patterns that are suggestive of SCAR.

Conclusions or recommendations

- Postauthorization data sources provide valuable insight into the real-world occurrence of rare AEs such as SCAR.
- EHRs, designed for patient care and follow-up, may be used to confirm or reject true reports of SCAR and establish causality.
- SCAR-–specific registries and networks bring together comprehensive elements and expertise needed to identify true SCAR and establish a causal relationship.

7.1 Introduction

cADRs are amongst the most common AEs (2-3% of all AEs) reported throughout the lifecycle of medicinal products.[1,2] Since approximately 0.2-29.3% of patients with cADRs become severe and require hospitalization[3-7] it is essential to detect symptoms indicative of severity early during the process. While clinical trials offer precise data on the incidence (in the study population during the observation period of the trial) and severity of common AEs, the reports collected after authorization offer insights into the occurrence and nature of cADRs in the real-world setting. A close evaluation of preauthorization factors has shown that approximately 20% of safety issues leading to marketing withdrawals of a medicinal product or the addition of a boxed warning in its product labelling in the postauthorization phase were related to rare AEs such as serious skin and hypersensitivity reactions that are difficult to detect in preauthorization clinical trials.[8]

7.2 Sources of data

International guidelines, in particular those issued by CIOMS and ICH, outline the sources and analytical approaches for data on AEs arising from the use of medicinal products in the general population.[9,10] Data sources for postauthorization surveillance include spontaneous reports, electronic health records (EHRs), registries, along with clinical trial data and preclinical data.

7.2.1 Spontaneous Adverse Event reporting systems

Spontaneous reporting of AEs suspected to be an adverse reaction to a medicinal product is at the heart of postauthorization safety surveillance. Healthcare professionals and consumers spontaneously report AEs associated with an intervention, i.e. use of a medicinal product in an individual patient or consumer. The resulting ICSRs are designed to capture information that is relevant to the understanding of the AEs. ICSRs are submitted to the pharmaceutical company that is responsible for the medicinal product, and/or the applicable authority, in accordance with the spontaneous reporting system in that jurisdiction. Pharmaceutical companies are required to submit ICSRs to the regulatory authorities as per local regulation.

In ICSRs, cADRs reported as serious, i.e. leading to or prolonging hospitalization or disability/incapacity, or are of a life-threatening nature and/or associated with a fatal outcome, or are otherwise medically serious[11], are specifically of interest in the detection and confirmation of serious SCAR. Medical history, concurrent medication along with start and stop dates, and the potential for skin/mucosal reactions (e.g. included in the label) are routinely used for assessment of a potential causal relationship to the medicinal products.

Key information for appropriate causality assessment include the percentage of BSA, laboratory tests, timing and dose of suspected and/or concurrent medication as well as personal and family medical history. Furthermore, follow-up with the reporter of the ICSRs may be challenging and the source medical documents are rarely available. Often the AEs are not reported in real time[12] and underreporting is a well-recognized phenomenon of spontaneous reporting.[13] The aggregate data in large spontaneous reporting datasets are monitored and analysed for early identification of safety signals, especially for rare AEs.[14,15]

The WHO's Vigibase (over 20 million ICSRs[16], the EMA's EudraVigilance data analysis system (EVDAS – 14.5 million ICSRs[17] and the US FDA MedWatch program (US FDA AE Reporting System – 2 million ICSRs/year[18] are monitored for events that are disproportionately reported for a medicinal product.[12-20] Medicinal product-event pairs of disproportionate reporting are reviewed to determine if there is a potential safety signal for further investigation of causality and potential need for regulatory action.[21] Patterns of spontaneous reporting in large datasets can be used to generate hypotheses on associations with specific or class of medicinal products[21-25] and build models to predict factors such as chemical structure[26] and/or molecular targets[27] linked to SCAR.

7.2.2 EHRs

EHRs contain detailed patient-level information collected by healthcare professionals for a variety of reasons, e.g. billing and reimbursement, laboratory parameters or medications prescribed for a specific event. In EHRs, the standard International Classification of Diseases Clinical Modification (ICD-CM) coding systems is used to structure the relevant information.[28] EHRs enable the study of common diseases, medicinal product response (efficacy or adverse) phenotypes and the genetic profile for several diseases.[29,30]

The ICD-CM-based phenotyping algorithms applied to large insurance claims datasets such as US Kaiser Permanente and US FDA Sentinel Initiative and Medical Information Database Network can also inform the clinical course of the disease through longitudinal records[28,31], detection of rare AEs[32-37] and evaluation of safety signals with characterization of emerging safety topics following medicinal product authorization.[38,39]

The correct diagnosis of SCAR is clinically challenging and routinely hindered by the circumstance of non-medicinal product related diseases such as EMM, being mistaken with SJS/TEN particularly in children.[40] Algorithms that combine clinical expertise, specific ICD codes, clinical course (including the duration of hospitalization) and number of medical encounters together with biomedical analytics have been used to explore patients with a high likelihood of rare AEs such as SJS/TEN.[41-45]

In one study, the ICD-9 codes identified approximately 57 000 cases of potential SJS/TEN among approximately 60 million patients in 12 US research units and managed care organizations. The potential cases were further adjudicated by board-certified dermatologists. Multivariate models were used to detect factors independently associated with validated SJS/TEN case status.

Length of hospitalization and application of new ICD codes specific to SJS/TEN increased the likelihood of SJS/TEN case status. The positive predictive value (PPV) of ICD-9 codes 695.12-695.15 was 50% among hospitalized cases and of those hospitalized for three or more days, the PPV ranged from 57-92%. These results provide some support via a combination of search codes and search terms for identifying cases using EHR data.[41]

A separate study demonstrated that the PPV for ICD codes specific to SJS/TEN was 29%. The addition of medicinal product-specific ICD codes with SJS/TEN-specific or erythema multiforme codes increased the PPV to 38% and maintained a 99.8% NPV for phenytoin-related SJS/TEN.[46]

These exploratory and mining algorithms along with their performance metrics (e.g. PPV and NPV) rely on predetermined algorithm definition and selection criteria and need to adapt to the evolving clinical definitions of SCAR.[47] Because SJS/TEN is a rare and severe reaction, EHR-based algorithms should favour sensitivity over specificity (i.e. high NPV) with reasonable PPV. Innovative methodology and technology such as Boolean logic, natural language processing, and machine learning can be shown to produce reliable algorithms.[47]

Furthermore, innovative technological solutions can be used to leverage the unstructured data (e.g. pictures, pathology records, clinical records including percentage of BSA and/or mucosal involvements) included in EHRs. Natural language processing and artificial intelligence offer the opportunity to automatically recognize and translate the unstructured data into specific data points accessible by automated search algorithms. The technology can also identify patterns to ascertain medicinal product causality particularly if multiple medicinal products were initiated within a short time period.[46]

7.2.3 Registries and Networks

In general, registries refer to both programmes that collect and store data and the records that are so created.[48] The National Committee on Vital and Health Statistics describes registries as “an organized system for the collection, storage, retrieval, analysis, and dissemination of information on individual persons who have either a particular disease, a condition (e.g. a risk factor) that predisposes [them] to the occurrence of a health-related event, or prior exposure to substances (or circumstances) known or suspected to cause adverse health effects.”[49] Additionally, EMA describes patient registries as “organised systems that use observational methods to collect uniform data on a population defined by a particular disease, condition or exposure, and that is followed over time” that can help monitor the safety of medicines.[50]

The term patient registry is generally used to distinguish registries focused on health information from other record sets. Other terms also used to refer to patient registries include clinical registries, clinical data registries, disease registries and outcomes registries.[51,52] Coordination between registries to create a network may aid in data collection harmonization across different disease areas and interoperability between registries.[53] Registries include extensive records of healthcare knowledge beyond specific effects of a medicinal product of interest. The historical or contemporaneous control data included in the registries are increasingly used to gain insight into the “real world” data.[54]

Registries or registry studies may be required as part of marketing authorization for several reasons:

1) If the benefits, but more specifically the risks, are not completely understood at the time of authorization,
2) Address a specific concern about safety or efficacy,
3) Generate postauthorization data in more extensive patient populations while providing access in a restricted population.[55]

Regulatory authorities may require “new registries” to be developed as well as the use of existing disease registries to perform “registry studies”.[54] FDA and EMA have developed detailed guidance for industry to address identified and potential safety concerns and how to deal with missing data.[56,57]

A retrospective review identified a total of 73 registries for the 116 new drugs – 46 disease registries and 27 (exposure to a single) drug registries – approved by the Committee for Medicinal Products for Human Use (CHMP) in the EU between January 1, 2007 and December 31, 2010. For nine drugs, the registry was a specific obligation imposed by the regulators. The level of innovation and the orphan status of the drugs were determinants positively predicting postauthorization registries (OR 10.3 [95% CI 1.0-103.9] and OR 2.8 [95% CI 1.0-7.5], respectively).[58]

Effective coordination of medical, surgical, behavioural and basic scientific disciplines is required to efficiently reduce SCAR-related short- and long-term morbidity and mortality, and advance clinical care and research. Professional networks bring together SJS/TEN phenotype adjudication committees, centralized biological sample collection and repositories in platforms to study the pathogenesis and predictors of SCAR. These networks are leveraged to rigorously define criteria for clinical diagnosis, causality assessment, estimation of risk factors and centralized sample collection to aid the study of the mechanisms and search for treatment options.[46] Examples of registries and networks follow.

RegiSCAR

RegiSCAR is a multinational SCAR registry which includes medicinal product and biological samples aimed to reduce the medical and economic burden of SCAR on public health and to improve the safety of medication use. The objectives of RegiSCAR are:

1) build a European Registry of SCAR for continuous surveillance of new medicinal products with adequate pharmaco-epidemiologic methodology and for providing reference information on SCAR
2) organize a centralized collection of biological samples (plasma, lymphocytes, DNA and skin) to allow high quality studies on pharmacogenetics and investigations of the mechanisms of these reactions
3) constitute a cohort of patients in order to study the outcome, prognosis factors, sequelae and impact on quality of life of these severe side effects of medicine.

The RegiSCAR study includes all reports of SJS/TEN, AGEP and DRESS in patients hospitalized in one of the institutions participating in the network in six countries. In each country, a trained investigator interviews each case patient and collects information on medication use in the eight weeks prior to disease onset, recent infections, demographic information and relevant medical history in a standardized case record form. Each case record is ascertained by an international group of experts by means of a strict validation process.

Skin biopsies (patients) and blood samples (patients and controls) are sent to a specialized tissue bank for separation and conservation of plasma, lymphocytes and DNA. The data registry provides estimates of the risks of medicinal products using case-control and case cross-over analyses as well as linkage to databases on medicinal product utilization. RegiSCAR also provides information on the outcome, allows the validation of prognosis indexes and gives insights on the effect of treatments.

Biological samples are used to determine the phenotype, functions and antigenic specificity of lymphocytes isolated at the time of the reaction from the blood and skin of patients. In addition the samples are used to study the susceptibility genes by an association study directed first at candidate genes and second at the full genome by using 1000 single nucleotide polymorphisms and determine the serum level of a variety of cytokines that may have a prognostic value.[59]

Australian Registry of Severe Cutaneous Adverse Reactions

The Australian Registry of Severe Cutaneous Adverse Reactions (AUS-SCAR) is a multidisciplinary collaboration utilizing a range of clinical, health services and translational research methodologies to address the significant knowledge gaps in SCAR causality, prevention, diagnosis and treatment. AUS-SCAR collects prospective clinical data (medicinal product causality, treatments and outcomes) and bio-banked samples (DNA, blood and skin) from patients at 15 participating Australian sites. The data is subsequently used to examine SCAR epidemiology, causality, pharmacogenomic predictors and explore novel ex vivo/in vitro diagnostics.[60]

International Registry for Toxic Epidermal Necrolysis

The International Registry for Toxic Epidermal Necrolysis (IRTEN) is an international, observational web-based registry for prospective anonymized collection of clinical data and biological samples in individuals suffering of SJS/TEN. The IRTEN data is used to enhance the understanding of SJS/TEN including its epidemiology, clinical characteristics including outcome, short- and long-term complications, real-time data concerning causative medicinal products and therapy, with the ultimate aim of fostering improved patient care.[61]

U.S. FDA Sentinel Initiative

The Sentinel Initiative was launched in May 2008[62] in response to the FDA Amendments Act of 2007. The Initiative is the largest multisite distributed database in the world dedicated to marketed medical product safety. The Sentinel Operation Center leverages organizational partnerships in the areas of epidemiology, clinical medicine, pharmacy, statistics, health informatics, data sciences and network operations to support postauthorization safety analyses.[62] An important aspect of Sentinel's active surveillance is to develop and understand the validity of algorithms for identifying health outcomes of interest.[62]

Society of Dermatology Hospitalists SJS/TEN Study Group

The Society of Dermatology Hospitalists (SDH) is a collaborative research effort of 18 tertiary care centres. Retrospectively, SDH member institutions collected information on SJS/TEN patients related to disease course, management and outcomes. The SDH database includes 405 SJS/TEN cases in the United States between 2000 and 2015, with most treated after 2010. In this cohort, 66% of patients met the definition criteria for TEN (>30% BSA denuded) or SJS/TEN overlap (10–30% BSA denuded) at the time of admission.

At the time of admission, the severity of illness score for TEN (SCORTEN)[63] predicted mortality for the cohort to be 20%. Actual mortality of patients in the cohort was 13.7%, yielding a standardized mortality ratio of 0.69 (95% confidence intervals 0.57, 0.78). Medications accounted for 91.3% of cases, predominantly implicating trimethoprim/sulfamethoxazole (26%).[46]

Canadian Pharmacogenomics Network for Drug Safety

The Canadian Pharmacogenomics Network for Drug Safety (CPNDS) is pan-Canadian active surveillance network that compiles the detailed information collected by trained active surveillance clinicians. The CPNDS database includes detailed clinical information with 93 974 reports of medication use, including 10 475 reports of ADRs[64], which can be used to identify novel predictive genomic markers of severe ADRs in children and adults. The CPNDS was the first group to confirm the role of HLA markers for carbamazepine-related skin reactions in children.[65]

The CPNDS actively investigates both previously identified pharmacogenomic biomarkers and novel genomic variations associated with severe reactions. Collaboration with the EpiPGX Consortium has led to the identification of over 80 SCAR cases related to anticonvulsants. Additionally, the CPNDS has published clinical practice guidelines for carbamazepine-related ADRs[66] and collaborates with several consortia to update guidelines and develop pharmacogenomic panels for commercial use that include ADR pharmacogenomic markers.

International Consortium on Drug Hypersensitivity Network

The International Consortium on Drug Hypersensitivity (ITCH) network was established to recruit patients with SCAR and includes approximately 1500 phenotyped cases from 12 countries with associated genetic data.[67] The ITCH cohort has been used to identify medicinal product-specific genetic predisposing factors and genetic factors predisposing to SJS/TEN regardless of medicinal product etiology. GWASs conducted on 1260 SCAR cases in the cohort included quality control procedures (i.e. controlling for population stratification, imputation using the latest releases of genomic data and validation of imputed genetic variants).

The ITCH database includes 177 SJS/TEN cases from Caucasian patients from three ethnic groups: Spanish, Italian and Northern European. Evaluation of the 177 SJS/TEN cases identified an HLA-B allele that is associated with SJS/TEN irrespective of drug. This HLA-B allele is present at 0.02% of the general Caucasian population (n = 9237 not exposed to drug) but is found at 100-fold higher frequency among SJS/TEN cases.[68] Medicinal product-specific analysis of cases in the ITCH cohort have replicated HLA allele associations previously identified in other populations. In 13 European patients with allopurinol-related SCAR of whom nine had SJS, *HLA-B*58:01* was identified at a genome-wide significance level with an odds ratio of 36.[68] While the association of *HLA-B*58:01* with SJS was just below genome-wide significance in this population, the odds ratio was higher at 45,[68] which is consistent with previous data suggesting that *HLA-B*58:01* is present in approximately 60% of allopurinol-related SJS/TEN patients of European ancestry.

Moreover, the ITCH network includes African recruitment sites. Evaluation of the African cohort has identified the association of *HLA-C*04:01* with SJS/TEN secondary to nevirapine. Additional analysis of the interaction of *HLA-C*04:01* with the endoplasmic reticulum aminopeptidase genes, which influence peptide processing, demonstrated that endoplasmic reticulum aminopeptidase 2 may have a protective effect.[69]

7.3 Assessing causality with postauthorization information

The causality assessment of a suspected ADR is an essential approach in pharmacovigilance, as an attempt to investigate the association between the suspected ADR and the use of a certain medicinal product. Safety information collected during the postauthorization phase is one of the main sources for identifying SCAR because these reactions are usually rare and therefore may only be recognized after a medicinal product has been approved and used by a large number of patients.[70]

7.3.1 Causality assessment for ICSRs

Given the rare occurrence but high risk of adverse sequelae including fatal outcomes of SCAR, spontaneous reporting of suspected SCAR by healthcare professionals is key for the assessment and management of SCAR risk in the postauthorization phase. Additionally, applicable reporting systems including relevant case details permit a meaningful assessment of SCAR subsequent to treatment with a particular medicinal product. (See also Appendix 2 Examples of Targeted Follow Up Forms). The determination of causality for ICSRs, in pre- and postauthorization phases alike, refers mainly to medical assessment as well as the use of defined algorithms (e.g. ALDEN score for SJS/TEN) (Chapter 5.2.2.1 Algorithm of drug causality for epidermal necrolysis).

There are different causality classifications available (e.g. WHO-UMC scale, Naranjo scale) [71,72], but preferably it is simplified to a binary yes/no causality[73], also in line with regulatory reporting requirements. However, to date there is no universally-accepted causality assessment scale. When assessing medicinal product causality in a patient with SCAR, several factors should be taken into consideration including SCAR type, day of symptom onset (“index day”), medicinal product notoriety, time since medicinal product intake and onset of reported event, dechallenge/rechallenge information, comorbidities, concomitant medications, and plausible or biologic or pharmacologic explanation. In general, for assessment of temporal relationship of medicinal product intake to event onset, i.e. five times the elimination half-life (“rule of five”) can be used. However, since elimination of a medicinal product varies from person to person due to factors like age, weight, other medications taken, as well as kidney function and/or liver function, the use of the elimination half-life can only be an estimate of how long it may take for the medicinal product to be removed from the body. Challenges for causality assessment especially in postauthorization reporting are incomplete case information, use of multiple medicinal products and inter-current or chronic underlying illness.

7.3.2 Risk management planning and pharmacovigilance strategies

With the potential for severe and life-threatening outcomes, additional risk management measures, in addition to routine risk minimization measures such as product labelling, may need to be implemented to prevent or reduce the severity of outcomes from SCAR. These risk minimization measures are discussed in Chapter 8.

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CHAPTER 8.

RISK MINIMIZATION

Chapter summary

Prompt evaluation and discontinuation of the potentially offending medicinal product(s) are the most appropriate immediate interventions in the management of SCAR once detected, based on the benefit-risk balance of the medicinal product for the given patient.

Key developments in SCAR research include new technologies allowing the identification of genetic risk factors with improved sensitivity, specificity and efficiency.

Routine risk minimization measures and additional risk minimization measures for SCAR are presented with examples.

Conclusions or recommendations

The recognition and diagnosis of SCAR can be challenging. Awareness of patients, caregivers, and HCPs of the risk of SCAR with medicinal products is paramount to ensure timely discontinuation of the medicinal product and administration of appropriate treatment, given their potential for severe and life-threatening outcomes. Hence, risk management, comprised of routine and additional risk minimization measures, is essential to ensure the safe use of these medications.

The selection of risk minimization tools to inform patients and HCPs of a medication's benefits and risks is vital for patients to make informed treatment decisions. Risk minimization for SCAR ensures awareness of recommendations for screening to identify patients at risk, characterization of the risk for timely recognition and recommended actions to monitor, manage and mitigate these risks to prevent or improve potential clinical adverse outcomes.

8.1 Introduction

Risk is defined as "[t]he probability of developing an undesirable outcome relating to the quality, safety or efficacy of the medicinal product".[1] Risks are characterized by the following ADR attributes: severity (intensity), frequency, potential for prevention or early detection, extent of reversibility and range of outcomes. The regulatory categorization of AEs relevant to risks as "serious" or "non-serious" had been primarily used to provide guidelines for pharmaceutical companies for AE report submission to regulatory authorities. Seriousness should be distinguished from the severity of an event, which is the intensity of the event. Severity of an event, in addition to other attributes and patient risk factors, could lead to patient clinical outcomes that may need a particular type of intervention to mitigate. Grading of severity (i.e. mild, moderate, severe) may be dependent on medical judgement and patient perspective; however, grading systems for AEs and laboratory abnormalities are currently being utilized (e.g. CTCAE, Drug-Induced Liver Injury Network). The assessment of the severity of an adverse reaction or risk, its frequency, and other attributes and risk factors, are necessary to understand the impact of the adverse reaction on the benefit-risk profile of a product.

Categorical definitions of risks are utilized in regulatory risk management documents. The ICH Pharmacovigilance Guidance has provided the following categories of risks:[1]

- Identified Risk: an untoward occurrence for which there is adequate evidence of an association with the medicinal product of interest,
- Potential Risk: an untoward occurrence for which there is some basis for suspicion of an association with the medicinal product of interest but where this association has not been confirmed,
- Important identified risk and important potential risk: an identified or potential risk that can impact the benefit-risk profile of the product or have implications for public health. What constitutes an important risk will depend on several factors, including the seriousness of the risk, and the impact on the individual and public health. Typically, any risk that is likely to be included in the Contraindications or Warnings and Precautions section of the product information should be considered important.

An additional concept that could constitute a form of risk for a medication and is therefore part of risk management activities and documents pertains to missing Information, which are gaps in knowledge about the safety of a medicinal product for a certain anticipated use or for use in particular patient populations.[2]

8.2 Risk management

Risk management entails the following reiterative cycle: identification, assessment/characterization, prevention/mitigation and measurement of the effectiveness of the risk minimization measures.[1,3] Once risks have been identified and assessed for clinical relevance, potential patient outcomes and overall impact, risk management strategies are then planned and developed. Risk management occurs throughout the medicinal product lifecycle.

The primary objective of risk management strategies is to have better patient outcomes. To do this, pharmacovigilance activities for data collection and assessment are instituted to understand and characterize the risk. Additionally, risk minimization measures to reduce the frequency that the risk will occur (termed “risk prevention”) or/and reduce the severity when it does occur (termed “risk mitigation”) and reduce undesirable outcomes, may be implemented.[1] Although many risks cannot be eliminated, their frequency and/or severity may be substantially reduced by putting an appropriate risk minimization plan in place.

Given that SCAR could occur, albeit infrequently, during clinical development, additional safety data may be needed either to provide additional evidence to further support the causal association between SCAR and an implicated medication or further characterize this risk in the postauthorization setting, where increased utilization by the indicated population is expected. Beyond routine standardized surveillance for SCAR, additional pharmacovigilance activities may also be required.

These additional pharmacovigilance activities may include active and targeted surveillance in collaboration with key dermatology stakeholders or organizations that collect safety data relevant to SCAR, such as registries, networks and tertiary referral medical centres. Importantly, additional pharmacovigilance activities in the form of Postmarketing Requirements/Commitments and Post-Authorization Safety Studies may be required as a condition of authorization to further characterize the risk of SCAR from a medicinal product in the indicated population. The types of safety studies conducted to further characterize risks in the postauthorization setting include postauthorization observational studies, non-interventional safety studies, postauthorization surveillance safety studies[4] and pharmaco-epidemiologic studies utilizing real-world data.

At authorization, risk management activities are described in detail in documents such as the Risk Management Plan (RMP) in the EU and the Pharmacovigilance Plan (PV Plan) and Approval Letters in the US. These risk management documents describe the activities and studies that will be conducted in the postauthorization setting to identify and/or further characterize the safety profile of the authorized medicinal product and the measures to prevent or minimize the risks associated with the medicinal product.[5]

There are two types of risk minimization measures, routine and additional, which are further discussed below.

8.3 Routine risk minimization measures

Risk minimization measures that relate to standard activities and provide routine information on the benefits and risks of a medicinal product to the patient and HCP for all medicinal products are classified as routine risk minimization measures.

These include product information, which is proposed by marketing authorization holders and agreed by regulatory authorities providing patients and HCPs on the appropriate and safe use of a medicinal product[1] (e.g. US Prescribing Information and for specific products, the Medication Guide, EU SmPC, the Canadian Product Monograph, the Japanese Product Information; patient information brochures; information on medicinal product packaging) as well as packaging size appropriate to the typical treatment duration and a risk-appropriate legal status of the product (i.e. prescription-only medication).[6]

The information and recommendations outlined in the product information[1] should therefore support the optimal and safe use of a medicinal product in clinical practice with the goal of providing the appropriate medicine at the correct dose and timing, with an awareness of the benefits and risks of the product.

Especially for medicinal products for which a causal association with a severe or potentially life-threating outcome of an ADR has been identified, adequate information and recommendations for monitoring and treatment are needed in the medicinal product's patient brochure to ensure awareness and the actions that should be taken to manage the risk, including reporting specific signs and symptoms to HCPs[1] (e.g. US Patient Package Insert and Medication Guide or EU package leaflet).

Information relevant to risks and severe and/or serious ADRs are usually included in specific sections of the label, such as "Warnings and Precautions" and "Undesirable Effects/Adverse Reactions," and are reflected in the patient brochure.

In addition to information regarding the character, severity, outcome(s) of the risk or ADR, an estimate of the frequency should be provided and expressed in a standard category of frequency.[7] If the frequency cannot be estimated from the clinical trials or postauthorization study data, the term 'not known' may be used. This may be applicable when the ADR has been identified from spontaneous reporting without knowledge of the exposure at population level.

In general, the language used to describe the risks in the product information should be clear and concise. Detailed recommendations from regulatory authorities regarding the description and characterization of the risks, together with actions that may prevent and/or mitigate such risks can be found in regulatory guidance documents, including the EU Guideline on the Summary of Product Characteristics[8] and the U.S. FDA Guidance for Industry for product information.[9,10]

Examples of language used to describe and/or characterize the risk of SCAR in product information of authorized medications can be found in Appendix 1.

For some medicinal products, additional risk minimization measures may be required as part of the marketing authorization terms in addition to the product information, patient brochure, and product container/package information

8.3.1. Routine risk minimization measures for SCAR

SCAR, as described in Chapter 1 of this Report, are diverse cADRs that range from common, mild and self-limited cutaneous reactions with an estimated incidence of 0.3% to 8%, to uncommon potentially life-threatening forms of delayed systemic hypersensitivity. Cutaneous clinical manifestations range from maculopapular exanthema, urticaria, FDE, phototoxic and photo-allergic eruptions to erythema-multiforme-like reactions.

At baseline, routine risk minimization measures are necessary to provide prescribers and patients with information relevant to cADRs and SCAR. These include product information, the patient brochure and container/package information, as previously stated. (See examples: Medicinal Product A, Medicinal Product B, Medicinal Product C, Medicinal Product D)

Of note, terminologies used in the product information should be considered carefully to ensure standardization and consistency. Terminologies should be standardized based on Medical Dictionary for Regulatory Activities (MedDRA)[11], as agreed in the ICH framework.

For SCAR, the following MedDRA Preferred Terms (PTs) are available under the MedDRA version 26.1 Preferred Terms: 'Stevens-Johnson syndrome', 'Toxic epidermal necrolysis', 'Acute generalized exanthematous pustulosis', 'Drug reaction with eosinophilia and systemic symptoms', 'Generalized bullous fixed drug eruption', 'SJS-TEN overlap' and 'AGEP-DRESS'.

Because SCAR may potentially be severe and/or serious and possibly life-threatening, risk management of SCAR may necessitate strategies beyond these routine risk minimization measures. These will be addressed in the following sub-section (Additional risk minimization measures).

8.4 Additional risk minimization measures

In addition to routine measures adopted to address medicinal product risk, additional risk minimization measures are "interventions intended to prevent or reduce the probability of an undesirable outcome or reduce its severity should it occur".[3] Additional risk minimization measures should be proposed when deemed essential for the safe and effective use of the medicinal product.

These measures aim to ensure the following:

- Guide appropriate patient selection with the exclusion of patients where use is contraindicated,
- Support on-treatment monitoring of important risks and/or
- Early identification and management of an adverse reaction to limit its severity/seriousness and mitigate adverse outcomes.[12]

8.4.1 Additional risk minimization measures for SCAR

In addition to routine risk minimization (e.g. product information), further risk minimization measures have been developed and implemented to expound on information found in the product information regarding risks, outcomes, screening, identification of patients at risk, monitoring and management. In the context of SCAR, these may include the following activities/programmes:

- Educational tools/training programmes, used to provide targeted information regarding risks to HCPs or patients (e.g. patient alert card), to supplement product information,
- Risk Evaluation and Mitigation Strategies (REMS), a medicinal product safety program implemented in the U.S. and required for certain medications to inform, educate and reinforce actions to reduce the frequency and/or severity of a safety outcome, such as a SCAR.[13] Elements to assure safe use (ETASU) may be a component of a REMS programme, in addition to materials distributed to HCPs, pharmacists, and nurses and handouts for patients, such as Medication Guides[14]
- Other risk minimization measures, such as Direct Healthcare Professional Communication (DHPC) or Dear Health Care Provider Letter (DHCP).

An example of an additional risk minimization measure implemented for a SCAR associated with a medicinal product (Medicinal Product E) is provided below. Details can be found in Appendix 1.

8.4.2. Educational tools for healthcare professionals

Educational tools for HCPs provide specific recommendations on the use (what to do), the contra-indications (who the product should not be prescribed to), and/or warnings (e.g. how to prevent or manage the described risk or adverse reaction) associated with the medicinal product and the key risks that require additional minimization measures.[12] These educational tools may include guidance on prescribing (including selection of patients, testing, monitoring), special administration procedures and details of information to be given to patients and other information on managing risk.

The type and format of a particular tool is dependent on the target audience, message and modalities of use of the medicinal product. Tools can include HCP training programmes featuring websites, brochures, posters and check lists (e.g. if certain actions need to be performed prior to prescribing a medication).

For the example in Appendix 1 (Medicinal Product E), HCP educational programmes were developed to increase HCP awareness and understanding of the risk and expand on information that is included in the medicinal product information. These were published on a website aimed at HCPs. In addition, a slide presentation was included and provides guidance on HLA-B screening, information about diagnosis of hypersensitivity reaction, management and avoidance of rechallenge.

8.4.3. Educational tools for patients and/or caregivers

Educational tools targeting patients and caretakers aim to increase their awareness of risks associated with a medicinal product to inform their decision to initiate treatment, awareness of signs and symptoms of adverse reactions and/or risks for early recognition and awareness of the course of action to take should any of these sign or symptoms occur.[12] A patient alert card is a tool designed to inform patients of a particular risk.[1] It is used when patients are required to carry on them essential information about their current therapy and the main risks associated with this therapy The purpose is to alert HCPs of the risks and if needed, ensure medical intervention. In the US, some medicinal products are dispensed to patients with a Medication Guide, as part of authorized product information.

The information contained in the patient alert card should be succinct and be kept to the minimum necessary to convey the key minimization messages and required action.[13] For the example of Medicinal Product E above, the patient alert card contains information about the clinical presentation of the hypersensitivity reaction and guides patients to call their HCPs immediately for guidance in case two or more of the following signs or symptoms occur: fever, skin rash (redness and/or itching), nausea, vomiting, diarrhoea, abdominal pain, severe tiredness, achiness or general ill feeling.

8.4.4. Other examples of additional risk minimization measures

Other examples of additional risk minimization measures are the DHPC in the EU, and the DHCP Letters and Medication Guide (as part of a REMS programme) in the U.S.

DHPC are communications by which important information is delivered directly to individual HCPs by a marketing authorization holder or by a competent authority, to inform them of the need to take certain actions or adapt their practices in relation to a medicinal product.[15]

DHCP Letters are correspondences to HCPs that are often in the form of a mass mailing from the manufacturer or distributor of a human medicinal product or from the US FDA. DHCP letters alert HCPs about new or updated information regarding a human medicinal product.[16] In the context of SCAR, DHPCs should be considered when there is a need to inform HCPs to take immediate action or change current practice in relation to a medicinal product. These situations include:

- a new warning or precaution of a SCAR risk in the product information,
- identification of a new risk of SCAR or change in the frequency or severity of a known SCAR risk,
- new recommendations for preventing or treating SCAR,
- an ongoing assessment of an important potential risk of SCAR, for which the data that is available at a particular point in time are insufficient to take regulatory action (in this case, the DHPC should encourage close monitoring of the safety concern in clinical practice as well as reporting and possibly provide information on how to minimize the potential risk).

The content of the proposed DHPC should be agreed between the marketing authorization holder and the regulatory authority. An example of a DHPC issued in response to the risk of SCAR associated with a medicinal product (Medicinal Product F) is described in Appendix 1.

8.5. Evaluating the effectiveness of risk minimization

When an additional risk minimization measure is developed to prevent or mitigate a risk such as SCAR, planning is required on evaluating the effectiveness of the risk minimization tools, interventions or programmes. This is an integral and critical component of risk management to ensure that risk minimization measures change the behaviour of patients and HCPs and leads to improved patient outcomes.

Studies have been conducted in which a number of approaches have been applied to evaluate the effectiveness of the risk minimization measures, interventions or programmes. The objectives of these studies are to identify factors that lead to a desired outcome and understand how the proposed tools, interventions or programmes impact these factors and outcomes when used in a 'real-world' setting.

The initial step is to develop a study protocol prior to the implementation of the tool/intervention/programme that is being evaluated. The study should measure the effectiveness of a programme in several different aspects (i.e. domains or dimensions): programme coverage, efficacy/effectiveness, adoption, implementation and maintenance.

Next, the study should evaluate the degree to which a proposed risk minimization programme is implemented in 'real-world' conditions as intended (implementation fidelity) in key areas (exposure, content, frequency, duration). Lastly, to appropriately evaluate the effectiveness of a risk minimization tool/intervention/programme, the study should provide a detailed analysis plan with prespecified outcome indicators that use clinically-relevant risk prevention or mitigation endpoints and thresholds which, in turn, must be met to determine success. Considerations include the use of appropriate comparators, performance measures and time points for analysis.[1]

Details of the various approaches to consider when developing studies to evaluate the effectiveness of risk minimization measures are found in the Report of CIOMS Working Group IX: Practical Approaches to Risk Minimisation for Medicinal Products. Given the evolving landscape of risk management, the framework and methodologies that guide the development of effectiveness studies will continue to change to ensure that evaluations remain pragmatic and robust.[1]

References

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15 FDA https://www.fda.gov/drugs/drug-safety-and-availability/risk-evaluation-and-mitigation-strategies-rems
16 FDA Guidance on Dear Health Care Provider Letter: Improving Communication of Important Safety Information

APPENDIX 1

PRODUCT LABEL EXAMPLES

Medicinal Product A

Product Label

4.4 Special warnings and precautions for use

Hypersensitivity syndrome, SJS and TEN

Medicinal Product A should be withdrawn immediately when a skin rash or other evidence of sensitivity occurs as this could result in more serious hypersensitivity reactions, which can manifest in many different ways, including maculopapular exanthema, hypersensitivity syndrome (also known as DRESS) and SJS/TEN.

These reactions are clinical diagnoses, and their clinical presentations remain the basis for decision making. If such reactions occur at any time during treatment, Medicinal Product A should be withdrawn immediately. Rechallenge should not be undertaken in patients with DRESS and SJS/TEN. Corticosteroids may be beneficial in overcoming hypersensitivity skin reactions. Please see "Undesirable effects" table below.

4.8 Undesirable effects

System Organ Class	Frequency	Adverse Reaction
Immune system disorders	Uncommon	Hypersensitivity reactions
Skin and subcutaneous tissue disorders	Common	Rash
	Rare	Stevens-Johnson Syndrome, Toxic Epidermal Necrolysis
	Very rare	Fixed Drug Eruption

2. Serious hypersensitivity reactions, including skin reactions associated with exfoliation, fever, lymphadenopathy, arthralgia and/or eosinophilia including SJS and TEN occur rarely (see above table). Associated vasculitis and tissue response may be manifested in various ways including hepato-splenomegaly, hepatitis, vanishing bile duct syndrome (destruction and disappearance of the intrahepatic bile ducts), renal impairment and, very rarely, seizures. Other organs may also be affected (e.g. liver, lungs, kidneys, pancreas, myocardium, and colon).Very rarely acute anaphylactic shock has been reported. Such reactions may occur at any time during treatment. Medicinal Product A should be withdrawn immediately and permanently.

Rechallenge should not be undertaken in patients with hypersensitivity syndrome and SJS/TEN. Corticosteroids may be beneficial in overcoming hypersensitivity skin reactions. When generalized hypersensitivity reactions have occurred, renal and/or hepatic disorder has usually been present particularly when the outcome has been fatal. Corticosteroids may be beneficial in overcoming hypersensitivity skin reactions.

6. Skin reactions are the most common reactions and may occur at any time during treatment. They may be pruritic, maculopapular, sometimes scaly, sometimes purpuric and rarely exfoliative, such as SJS/TEN. The highest risk for SJS and TEN, or other serious hypersensitivity reactions, is within the first weeks of treatment.

The best results in managing such reactions come from early diagnosis and immediate discontinuation of any suspect medicinal product. Medicinal Product A should be withdrawn immediately should such reactions occur. After recovery from mild reactions, allopurinol may, if desired, be re-introduced at a small dose (e.g. 50 mg/day) and gradually increased. If the rash recurs, Medicinal Product A should be permanently withdrawn as more severe hypersensitivity may occur.

If SJS/TEN, or other serious hypersensitivity reactions cannot be ruled out, DO NOT re-introduce Medicinal Product A due to the potential for a severe or even fatal reaction. The clinical diagnosis of SJS/TEN remains the basis for decision making. If such reactions occur at any time during treatment, Medicinal Product A should be withdrawn immediately and permanently.

Medicinal Product B

Product Label

4.4 Special warnings and precautions for use

Warnings

[…]

Patients and their relatives should be made aware of early toxic signs and symptoms indicative of a potential haematological problem, as well as symptoms of dermatological or hepatic reactions. If reactions such as fever, sore throat, rash, ulcers in the mouth, easy bruising, petechial or purpuric haemorrhage appear, the patient should be advised to consult the physician immediately.

Serious dermatological reactions, including toxic epidermal necrolysis (TEN: also known as Lyell's syndrome) and SJS have been reported very rarely with Medicinal Product B. Patients with serious dermatological reactions may require hospitalization, as these conditions may be life-threatening and fatal. Most SJS/TEN cases appear in the first few months of treatment with Medicinal Product B. These reactions are estimated to occur in 1 to 6 per 10,000 new users in countries with mainly Caucasian populations. If signs and symptoms suggestive of severe skin reactions (e.g. SJS, Lyell's syndrome/TEN) appear, Medicinal Product B should be withdrawn at once and alternative therapy should be considered.

[…]

Cutaneous reactions

Serious and sometimes fatal cutaneous reactions including TEN and SJS have been reported during treatment with Medicinal Product B. These reactions are estimated to occur in 1-6 per 10 000 new users in countries with mainly Caucasian populations, but the risk in some Asian countries is estimated to be about 10 times higher.

There is growing evidence of the role of different HLA alleles in predisposing patients to immune-mediated adverse reactions.

The *HLA-B*1502* allele has not been found to predict risk of less severe adverse cutaneous reactions from Medicinal Product B, such as anticonvulsant hypersensitivity syndrome or non-serious rash (maculopapular eruption).

Hypersensitivity

Medicinal Product B may trigger hypersensitivity reactions, including Drug Rash with Eosinophilia and Systemic Symptoms (DRESS), reactivation of HHV6 associated with DRESS, a delayed multi-organ hypersensitivity disorder with fever, rash, vasculitis, lymphadenopathy, pseudo lymphoma, arthralgia, leukopenia, eosinophilia, hepato-splenomegaly, abnormal liver function tests and vanishing bile duct syndrome (destruction and disappearance of the intrahepatic bile ducts), that may occur in various combinations. Other organs may also be affected (e.g. lungs, kidneys, pancreas, myocardium, colon).

In general, if signs and symptoms suggestive of hypersensitivity reactions occur, Medicinal Product B should be withdrawn immediately. Patients who have exhibited hypersensitivity reactions to Medicinal Product B should be informed that 25-30 % of these patients may experience hypersensitivity reactions with oxacarbazepine.

Cross-hypersensitivity can occur between Medicinal Product B and aromatic anti-epileptics (e.g. phenytoin, primidone and phenobarbital).

4.8 Undesirable effects

Summary of the safety profile

Particularly at the start of treatment with Medicinal Product B, or if the initial dosage is too high, or when treating elderly patients, certain types of adverse reaction occur very commonly or commonly, e.g. CNS adverse reactions (dizziness, headache, ataxia, drowsiness, fatigue, diplopia), gastrointestinal disturbances (nausea, vomiting), as well as allergic skin reactions.

Tabulated summary of ADRs compiled from clinical trials and spontaneous reports

System Organ Class	Frequency	Adverse Reaction
	Not known**	Drug Rash with Eosinophilia and Systemic Symptoms (DRESS)
	Very rare	Stevens-Johnson syndrome*, toxic epidermal necrolysis
	Not known**	Acute Generalized Exanthematous Pustulosis (AGEP)**

* In some Asian countries also reported as rare. See also section 4.4 Special warnings and precautions for use.

**Additional ADRs from spontaneous reports (frequency not known).

[…]

There is increasing evidence regarding the association of genetic markers and the occurrence of cutaneous ADRs such as SJS, TEN, DRESS, AGEP and maculopapular rash. In Japanese and European patients, these reactions have been reported to be associated with the use of Medicinal Product B and the presence of the *HLA-A*3101* allele. Another marker, *HLA-B*1502* has been shown to be strongly associated with SJS and TEN among individuals of Han Chinese, Thai and some other Asian ancestry.

Medicinal Product C

Product Label

4.4 Special warnings and precautions for use

[…]

Hypersensitivity

Hypersensitivity and allergic reactions, including anaphylaxis and anaphylactoid reactions, may occur following a single dose (see section 4.8) and may be life-threatening. If such reactions occur, Medicinal Product C should be discontinued and an adequate medical treatment is required.

[…]

4.8 Undesirable effects

System Organ Class	Common	Uncommon	Rare	Very Rare	Frequency not known
Skin and Subcutaneous Tissue Disorders				Stevens-Johnson syndrome (potentially life-threatening) Toxic epidermal necrolysis (potentially life-threatening)	Acute Generalized Exanthematous Pustulosis (AGEP) Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)

Medicinal Product D

Product Label and Patient Information Leaflet

Product Label

4.4 Special warnings and precautions for use

Life threatening adverse reactions

Fatalities, although very rare, have occurred due to severe reactions including Stevens-Johnson syndrome, toxic epidermal necrolysis, fulminant hepatic necrosis, agranulocytosis, aplastic anaemia, other blood dyscrasias and hypersensitivity of the respiratory tract.

- Life-threatening cutaneous reactions SJS, TEN and DRESS have been reported with the use of Medicinal Product D.
- Patients should be advised of the signs and symptoms and monitored closely for skin reactions. The highest risk for occurrence of SJS or TEN is within the first weeks of treatment.
- If symptoms or signs of SJS, TEN (e.g. progressive skin rash often with blisters or mucosal lesions) or DRESS (e.g. fever, eosinophilia) are present, Medicinal Product D treatment should be discontinued.
- The best results in managing SJS, TEN and DRESS come from early diagnosis and immediate discontinuation of any suspect medicinal product. Early withdrawal is associated with a better prognosis.

- If the patient has developed SJS, TEN and DRESS with the use of Medicinal Product D, Medicinal Product D must not be re-started in this patient at any time.
- At the start of treatment, the occurrence of a generalized febrile erythema associated with pustules, should raise the suspicion of acute generalized exanthematous pustulosis (AGEP); it requires cessation of treatment and contraindicates any new administration of Medicinal Product D alone or in combination with other medicinal products.

[…]

4.8 Undesirable effects

System Organ Class	Frequency	Side effects
Skin and subcutaneous tissue disorders*	Very rare	Stevens-Johnson syndrome (SJS) *, toxic epidermal necrolysis (TEN) *. Acute generalised exanthematous pustulosis (AGEP).
	Not known	Acute febrile neutrophilic dermatosis (Sweet's syndrome), Drug reaction with eosinophilia and systemic symptoms (DRESS)*

Description of selected adverse reactions

Severe cutaneous adverse reactions (SCAR)

Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) and drug reaction with eosinophilia and systemic symptoms (DRESS) have been reported to be life-threatening.

As with any other medicinal product, allergic reactions such as an itchy rash and hives may occur in patients with hypersensitivity to the components of the medicinal product. Very rare cases of AGEP have been observed.

Patient Information Leaflet (PIL):

2. What you need to know before you take Medicinal Product D

Warnings and precautions

Talk to your doctor or pharmacist before taking Medicinal Product D:

- If you have severe allergies or asthma.
- Potentially life-threatening skin rashes (SJS, TEN and DRESS) have been reported with the use of Medicinal Product D appearing initially as reddish target-like spots or circular patches often with central blisters on the trunk.
- At the start of treatment, the occurrence of generalized skin redness with pustules, accompanied by fever, should raise the suspicion of a serious reaction called acute generalized exanthematous pustulosis (AGEP) (see section 4).
- Additional signs to look for include ulcers in the mouth, throat, nose, genitals and conjunctivitis (red and swollen eyes).
- These potentially life-threatening skin rashes are often accompanied by flu-like symptoms. The rash may progress to widespread blistering or peeling of the skin.
- The highest risk for occurrence of serious skin reactions is within the first weeks of treatment.
- If you have developed Stevens-Johnson syndrome, toxic epidermal necrolysis or drug reaction with eosinophilia and systemic symptoms with the use of Medicinal Product D, you must not be re-started on Medicinal Product D at any time.

- If you develop a rash or these skin symptoms, stop taking Medicinal Product D, seek urgent advice from a doctor and tell him that you are taking this medicine.

4. Possible side effects

Like all medicines, Medicinal Product D can cause side effects, although not everybody gets them. You may experience the following side effects with this medicine.

Stop taking Medicinal Product D and tell your doctor immediately if you have an allergic reaction. The chances of an allergic reaction are very rare (fewer than 1 in 10,000 people are affected), signs of an allergic reaction include:

Allergic reactions

- Difficulty breathing
- Fainting
- Swelling of face
- Swelling of mouth, tongue or throat which may be red and painful and/or cause difficulty in swallowing
- Chest pain
- Red patches on the skin

Common (less than 1 in 10 people)

- Skin rashes

Very Rare (less than 1 in 10,000 people)

- Potentially life-threatening skin rashes (SJS, TEN) have been reported
- Very rare cases of redness generalizing to the whole body (AGEP)
- Mouth ulcers, cold sores and ulcers or soreness of your tongue
- Skin lumps or hives (raised, red or white, itchy patches of skin)
- Blisters on your skin or inside your mouth, nose, vagina or bottom
- Inflammation of the eye, which causes pain and redness
- The appearance of a rash or sunburn when you have been outside (even on a cloudy day)

Not known (frequency cannot be estimated from the available data)

- Drug reaction with eosinophilia and systemic symptoms (an allergic type reaction in which you may develop fever, skin rash, and abnormalities in blood and liver function tests (these may be signs of a multi-organ sensitivity disorder).

If any of the side effects get serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

Medicinal Product E

Additional Risk Minimization Measures: Healthcare Professional Guide and Patient Card

Medicinal Product E hypersensitivity reaction is a delayed hypersensitivity reaction mediated via CD8+ T lymphocytes and strongly associated with the presence of the *HLA-B*57:01* allele.[1] This reaction is multi-systemic and typically presents with fever, rash, constitutional symptoms and gastrointestinal manifestations,[2] occurring usually within the first six weeks of treatment with Medicinal Product E. Upon diagnosis, treatment discontinuation is mandatory and subsequent treatment with Medicinal Product E is contraindicated, since it can result in a more severe, rapid, and potentially life-threatening reaction.[3]

In 2002, the association between the MHC class I *HLA-B*57:01* allele and a risk for Medicinal Product E hypersensitivity was described for the first time.[1,3] The prevalence of this allele varies according to the predominant populations of the geographic location, with an estimated prevalence of 5%-8% in predominantly Caucasian populations, 2-3 % in African Americans and <1% in Sub-Saharan Africa, Chinese and Japanese populations[4,5].Based on this demonstrated association and supported by the test's comparatively high PPV for this outcome[3], *HLA-B*57:01* testing prior to initiating treatment with Medicinal Product E, was recommended in the label. Subsequently, this test became part of the regulatory terms of marketing authorization and standard of care for HIV patients before initiating treatment with Medicinal Product E.

Because of the potential severity, seriousness, outcomes and consequent impact on treatment, Medicinal Product E hypersensitivity reaction is classified as an important identified risk for the medicinal product.

Both routine risk minimization measures and additional risk minimization measures are in place to prevent the risk of Medicinal Product E hypersensitivity in patients who test positive for this allele, and subsequently reduce undue exposure. The main guidance around HLA screening is provided in the product's label (i.e., "*HLA-B*5701* status must always be documented prior to initiating therapy"), but additional risk minimization measures have also been put in place to ensure awareness of the potentially life-threatening risk, and the recommended HLA screening to identify patients who may be at risk. These measures include a Healthcare Professional Guide for healthcare providers (HCPs) and a patient card for patients in the EU. In the US, the manufacturer of Medicinal Product E was required to distribute a Medication Guide to patients, as part of a REMS program.

Medicinal Product F

Additional Risk Minimization Measure: Direct Healthcare Professional Communication

Cases of SJS and TEN were reported in patients treated with Medicinal Product F. The regulatory authority and the manufacturer agreed that a DHPC was necessary to be disseminated to for healthcare providers to ensure awareness of the newly identified risk of SCAR. The content of the DHPC included a background on the safety concern, summary of the findings, recommendations on treatment interruption ("Medicinal Product F should be withheld in patients with suspected SJS or TEN") and discontinuation ("in case SJS or TEN is confirmed, and for any grade 4 rash/SCAR, treatment with Medicinal Product F should be permanently discontinued"). Lastly, the DHPC included instructions on reporting suspected adverse reactions to the regulatory authority or the manufacturer.

References

1 Mallal S, et al. Association between presence of HLA-B*5701, HLA-DR7, and HLA-DQ3 and hypersensitivity to HIV-1 reverse-transcriptase inhibitor abacavir. The Lancet. 2002 Mar 2;359(9308):727-32. PubMed Abstract

2 Peter JG, et al. Severe Delayed Cutaneous and Systemic Reactions to Drugs: A Global Perspective on the Science and Art of Current Practice. J Allergy Clin Immunol Pract. May-Jun 2017;5(3):547-563 PubMed Abstract

3 Mallal S, et al. HLA-B*5701 Screening for hypersensitivity to abacavir. N Engl J Med. 2008 Feb 7;358(6):568-79. PubMed Abstract

4 Phillips, et al. Genetic Screening to Prevent Abacavir Hypersensitivity Reaction: Are We There Yet?. Clin Infect Dis. 2006 Jul 1;43(1):103-5. Journal Article

5 Zhang, et al. Low prevalence of human leukocyte antigen-B*5701 in HIV-1-infected Chinese subjects: a prospective epidemiological investigation. AIDS Res Ther. 2015; 12: 28. PubMed Abstract

APPENDIX 2

EXAMPLES OF TARGETED FOLLOW-UP FORMS TO BE USED FOR ALL SCAR REPORTS

Follow-up questionnaires

1. Extent of the rash:
   - ≥50% of the body surface area
   - <50% of the body surface area

2. Did the subject undergo skin biopsy?
   - Yes. If positive, select one option:
     - Result suggestive of a severe cutaneous adverse reaction (SCAR), such as Stevens Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), acute generalized exanthematous pustulosis (AGEP), drug reaction with eosinophilia and systemic symptoms (DRESS)
     - Result **not** suggestive of a severe cutaneous adverse reaction (SCAR)
     - Inconclusive result
   - No

3. Has the subject had facial swelling? (i.e., facial swelling during the event of rash)
   - Yes
   - No
   - Unknown

4. Has the subject had enlarged lymph nodes? (Presence of either localized [e.g. cervical, axillary, or inguinal lymph nodes) or generalised lymphadenopathy])
   - Yes
   - No
   - Unknown

5. Were atypical lymphocytes detected at some point during the evolution of the hypersensitivity event?
   - Yes
   - No

6. Did the subject have eosinophilia (>0.5×10^9/l or 500/µL) detected at some point during the evolution of the hypersensitivity event?
   - Yes
   - No

7. Have infectious causes been excluded? Has an infection screening been conducted due to the events of fever + rash (e.g. blood count, CRP, blood culture, chest X-ray, urinalysis + urine culture)?
   - Yes
     - Description of which tests:
   - No
   - Unknown

8. Did the subject have evidence of internal organ involvement?
   Select in case there is evidence of other organs being affected concomitantly to the event of rash, resulting in liver, renal, cardiac, or pulmonary function alteration:
   - Yes. If positive, select all that apply:
     - AST/ALT increase
     - Renal involvement (creatinine and/or BUN increase, urinalysis alteration)
     - Cardiac involvement (clinical, laboratory or echocardiographic evidence of myocarditis)
     - Lung involvement (clinical or radiological evidence of pneumonitis)
     - Other
   - No
   - Unknown

9. Concomitant medications

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Severe Cutaneous Adverse Reactions (SCARs) PRODUCT XX follow-up: Relevant information to confirm the diagnosis	1. Identification no/ Country	RELEVANT	3. Date of this report:
	4. CLINICAL TRIAL ☐no ☐ yes Protocol no: Centre no: Patient no:		5. REPORTER NAME: Address: Tel.: Dermatologist: ☐ Yes ☐ No

I. THE PATIENT

6. INITIALS (first, last): 7. SEX: 8. AGE 9. WEIGHT:
10. RELEVANT OCCUPATION: 11. COUNTRY OF ORIGIN 12. OTHER:

13. PREVIOUS RELEVANT HISTORY AND CONCURRENT DISORDERS:

	No	Yes	Specify:
Skin diseases	☐	☐	
Other diseases	☐	☐	

Allergic reactions ☐ Specify:
To what drug?

Asthma ☐ Allergic rhinitis ☐ Atopic dermatitis ☐

II. THE ADVERSE REACTION *(continue overleaf if necessary)*

14. DATE OF ONSET

16. Diagnosis – type of skin disorder

☐ Stevens-Johnson syndrome (SJS)
☐ Toxic Epidermal Necrolysis (TEN)
☐ Erythema multiforme
☐ drug reaction with eosinophilia and systemic symptoms (DRESS)
☐ Acute Generalised Exanthematous Pustulosis (AGEP)
☐ Generalized Bullous Fixed Drug Eruption (GBFDE)
☐ Other:

Type of skin disorder:
☐ Macular or maculopapular rash
☐ Scarlatiniform rash
☐ Exfoliative dermatitis
☐ Bullous or vesiculous eruption

☐ Purpura (platelet count needed)
☐ palpable purpura ☐ necrotic purpura
☐ visceral involvement:
☐ Kidney ☐ GI tract ☐ Nerves
☐ Others:

15. ASSOCIATED SYMPTOMS

☐ Pruritus
☐ Contact dermatitis or eczematiform eruption
☐ Urticaria
☐ Cutaneous angioedema
☐ Mucosal angioedema
☐ Burning or pain
☐ Oozing
☐ Edema
☐ Infection
☐ Fever
☐ Arthralgia/myalgia
☐ Nodes enlargement

Associated signs:
☐ Dyspnea
☐ Tachycardia
☐ Hypotension
☐ Anaphylactic shock

☐ Other skin disorders, *(specify)*:

Were photographs taken? ☐ No ☐ Yes

17. DISTRIBUTION OF LESIONS ☐ localized ☐ disseminated
Number of lesions ☐ < 10 ☐ 10 to 30 ☐ > 30 main location:
☐ Mucosal lesions, specify:
☐ Nail/hair lesions, specify:

18. Viral infection

☐ Viral infection, specify:

Evidence for viral infection:	No	Yes	Not done
EBV	☐	☐	☐
Hepatitis B virus	☐	☐	☐
CMV	☐	☐	☐
HSV	☐	☐	☐
HHV-6	☐	☐	☐
HHV-7	☐	☐	☐
HIV	☐	☐	☐
Other:			

19. IS PHOTOSENSITIVITY SUSPECTED? ☐ No ☐ Yes
Localization of lesion: ☐ Face ☐ Neck ☐ Hands/forearms ☐ Legs/feet ☐ Other specify?
Intensity of solar exposition: ☐ High ☐ Low

20. LABORATORY DATA
Leucocytes:
PMNs: %

SKIN BIOPSY: ☐No ☐ Yes
Result *(attach report)*

22. OUTCOME
(tick more than one box if necessary
☐ No hospitalization
☐ Death Date:
Cause:

III. SUSPECTED DRUG

23. Name

24. Indication

25. Daily dose

26. Route

27. Date beginning

28. Date end

29. Duration

30. ADMINISTRATION OF THIS DRUG AFTER THE BEGINNING OF THE REACTION
☐ Stopped
☐ Continued (same dose)
☐ Reduced dose
☐ Other:

31. IMMEDIATE RESULT
☐ Improvement ☐ No change
☐ Aggravation ☐ Uninterpretable

32. READMINISTRATION OF THE DRUG
☐ No ☐ Yes
Dose: Date:
And if yes:

33. RECURRENCE OF THE REACTION
☐ No ☐ Yes
☐ Uninterpretable

34. PREVIOUS THERAPY WITH THE SAME DRUG
☐ No ☐ Yes, date:
Safety issues:

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Eosinophils: Platelets: ESR: ALT/AST: (N- /) Alk.Ph.: (N- /) In case of more information, please add additional lab data in the below description 37/ 38	IMMUNOFLUORESCENT STAINING: ☐ No ☐ Yes Result *(attach report)* Other investigation: Result *(attach report)*	☐ Hospitalization necessary Address: ☐ Prolonged hospitalization ☐ Complete recovery ☐ Recovery with sequelae *(specify)*:	Relationship between the reaction And the death ☐ Not assessable ☐ Unlikely ☐ Likely
21. TREATMENT OF REACTION ☐ No ☐ Yes (continue overleaf)			

IV. CONCOMITANT THERAPY *(continue overleaf if necessary)*

35. DRUGS	Route	Daily dose	Duration	Dates of administration		Indications
				Beginning	End	

36. CAUSAL RELATIONSHIP Enoxaparin ☐ Not assessable ☐Unrelated ☐ Unlikely ☐ Possible ☐ Probable ☐ Highly probable

(Reporter's assessment)
Comments, including causal relationship with concomitant therapies:

37. Description of lesion(s) on the skin
type [erythematic, papules, plaques, eczema, blisters, etc.], topography [sun exposed area only, trunk and upper extremities, face, etc.], specificity [confirmation of typical morphology of skin lesions), start and stop date(s) of skin lesion(s)…

38. All new relevant information to confirm the diagnosis of SCAR:
all relevant information confirming the SCAR diagnosis, including all relevant information regarding the most suspect drug(s):

39. Final Diagnosis ☐YES ☐NO ☐UNKNOWN, specify:
Confirmed by Dermatologist? ☐YES ☐NO ☐UNKNOWN

40. Diagnostic tests
Were any of the following diagnostic tests performed?

☐ Skin Lesion Biopsy Date:
Result:

☐ Microscopic Examination of Skin Date:
Result:

☐ Other Diagnostic Test: …….. Date:
Result:

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APPENDIX 3

SCAR WORKING GROUP MEMBERS AND MEETINGS

The CIOMS Working Group on Severe Cutaneous Adverse Reactions included the following stakeholder groups: clinicians, international organizations, pharmaceutical industry, regulatory authorities.

CLINICIANS

Chia-Yu Chu	National Taiwan University Hospital, Chinese Taipei Working Group Co-Chair
Siew Eng Choon	Monash University, Malaysia
Roni P. Dodiuk-Gad	Emek Medical Center, Israel
Koji Hashimoto	Ehime Prefectural University of Health Science, Japan
Haur Yueh Lee	Singapore General Hospital, Singapore
Filippa Nyberg	Karolinska University Hospital, Sweden
Neil Shear	Sunnybrook Health Sciences Centre, University of Toronto, Canada

INTERNATIONAL ORGANIZATIONS

Matt Doogue	IUPHAR/University of Otago/Christchurch, New Zealand

PHARMACEUTICAL INDUSTRY

David Brott	Takeda, USA
Leslie Dondey-Nouvel	Sanofi, France
Alexandre Kiazand	AstraZeneca, USA
Gerd Kullak-Ublick*	Novartis, Switzerland
Ariel R. Porcalla	AbbVie, USA
Violeta Regnier Galvao	Eli Lilly, USA
Sarah Schlief	Bayer, Germany

REGULATORY AUTHORITIES

Melissa Reyes	FDA, USA Working Group Co-Chair
Priya Bahri	EMA, Netherlands
Michael A. Pacanowski	FDA, USA
Youssef Roman	FDA, USA
Sabine Straus	Medicines Evaluation Board, Netherlands
Tien M. Truong	FDA, USA
Takahiro Ueda	Pharmaceutical and Medical Devices Agency (PMDA), Japan

*Alternate: Sylvia Lesperance, Novartis

CIOMS

Hervé Le Louet	President
Lembit Rägo	Secretary General

The Working Group met in a series of virtual meetings from 2021 to 2023 as follows:

1. 2-3 February 2021
2. 13 April 2021
3. 29 June 2021
4. 7 October 2021
5. 13 December 2021
6. 9 May 2022
7. 12 September 2022
8. 12 December 2022
9. 14 March 2023
10. 20 June 2023

The SCAR Working Group Editorial Team met three times in 2023, and included the following members:

Siew Eng Choon	Monash University, Malaysia
Chia-Yu Chu	National Taiwan University Hospital, Chinese Taipei
Alexandre Kiazand	Astra Zeneca, USA
Haur Yueh Lee	Singapore General Hospital, Singapore
Sylvia Lesperance	Novartis, Switzerland
Lembit Rägo	CIOMS
Melissa Reyes	FDA, USA

APPENDIX 4

LIST OF COMMENTATORS