SCARs – Severe Cutaneous Adverse Reactions of Drugs
A need for new recommendations

I. INTRODUCTION

The skin is among the parts of the body most commonly affected by adverse drug reactions. Eruptions are observed in 0.1–1% of patients treated with most drugs. Among the various forms of drug eruptions, some of them may cause severe life threatening consequences. These serious cutaneous drug reactions occur in approximately 0.1% of these patients, and can lead to disabling sequelae. The incidence of fatalities due to systemic and cutaneous drug reactions among inpatients is estimated at between 0.1% and 0.3%.

Severe cutaneous adverse reactions (SCARs) include 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).

II. THE ISSUES

Drug-induced adverse reactions are often classified as dose related, predictable and due to a pharmacologic effect or dose independent, unexpected and due to an allergic mechanism. Most of the rare or severe drug eruptions are mainly the result of an allergic reaction. In contrast, some of the drug eruptions related to traditional chemotherapies or targeted anticancer therapies are linked to a pharmacologic action.

II.1 About the diagnosis

The diagnosis of SCARs is still a challenge since there is currently no test from imaging, histology, biology or other biomarker evaluation that is sensitive and specific enough to ascertain that a patient develops SCARs; thus the diagnosis currently still relies on a comprehensive clinical assessment and exclusion of other causes - this last point being a source of concern for both published case reports and spontaneous reports. Skin biopsy allowing direct examination of the tissue remains the gold standard for the study of the pathophysiological steps but is not routinely used. Thus, the diagnosis of SCARs continues to be based on the morphology and pattern of skin lesions, as well as the histopathological changes of the skin lesions.

II.2 About the causality assessment

Adverse drug reaction (ADR) causality assessment is a routine procedure in pharmacovigilance but despite some attempts for creating SJS/TEN-specific causality assessment scales, such as the ALDEN score, no method has been considered as the reference for all SCARs. The use of expert opinion to identify SCARs is common practice for diagnosing these drug eruptions. There is still a need for new ADR causality assessment algorithms dedicated to the other SCARs such as DRESS, AGEP and GBFDE.

II.3 About predictive models

Prevention of SCARs is currently mainly focused on the development of new preclinical testing, with the goal of preventing potential dangerous drugs from reaching the market, and on research for more reliable biomarkers allowing early detection and monitoring for SCARs during therapy.

Recent advances in preclinical testing strategies have improved the ability to identify drugs with risk for SCARs. The construction of predictive models benefits from an integration of chemical structure, cellular end points and toxicogenomic data; data from multiple sources is probably the future.

II.4 Prevention

Prompt withdrawal of the offending medication, as for all potential drugs, is the most relevant intervention in the individual management of SCARs once detected.

Recent progress in research on SCARs has been determined by key developments in new technologies allowing the identification of genetic risk factors with improved sensitivity, specificity and efficiency.

Consequently, there is now a strong need for guidelines giving recommendations on how to prevent, detect and diagnose SCARs either during drug development or in the post-marketing phase.

III.   NEED FOR A CIOMS WORKING GROUP

III.1 Background

SCARs are an important health challenge and a limitation to the safe and effective use of medicines. Premarketing randomized clinical trials have limited power to detect SCARs and there is a lack of specific diagnostic tests for SCARS which depend on subjective causality assessment methods.

SCARs are rare, but serious adverse effects, posing substantial hurdles to drug developers, medicines regulators and health professionals / patient care.

At the pharmaceutical industry level, we can observe:
- The lack of guidance regarding SCARs in special populations, especially cancer patients, patients with pre-existing autoimmune diseases, elderly, and children;
- The need for comprehensive and systematic workflows for safety data capture and analysis;
- The lack of consensus for better clinical practice.

At the regulatory level we can observe:
- The lack of harmonized definitions on SCAR case qualification, the need for ensuring completeness of safety assessment and management in drug

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 for pharmacovigilance and practice to monitor and manage SCARs in clinical trials during the drug development and post-marketing phases;
- The lack of relevant information provided in the Summary of Product Characteristics (SmPC) regarding SCARs: the "adverse effects information" is quite similar for all drugs even if they are not having the same risk for developing SCARs.

Furthermore, the magnitude of attrition of new chemical entities during drug development accounting for up to > 80% from phase I to regulatory application has put an unsurpassable barrier for the clinical translation of new drugs. This has taken the industry to a point where a revision of existing strategy is overdue.

In clinical practice, there is a mounting concern in relation to the ongoing burden of SCARs and the emergence of SCARs related to novel biologics as well as the increasing cost of diagnosis and management.

III.2 Aim of the working group

To establish a balanced, efficient, global perspective on SCAR detection, susceptibility factors, severity, outcome and probability through causality assessment tools, monitoring and management during the drug development and post-marketing phases.

III.3 Composition of the group

The panel of experts should encompass wide participation, preferably members from all six WHO regions (European, Eastern Mediterranean, African, South-East Asian and Western Pacific, and American), coming from Academia, the Pharmaceutical Industry and Regulatory Authorities, to ensure synergies and prevent redundant studies.

III.4 Gaps to fill in

1. Interpretation and management of SCAR safety signals, considering that SCAR assessments differ between clinical practice and clinical trials. We need to build safety into drug development.

2. Guidance on data analysis from patients with SCARs included in clinical trials to reach a consensus on terminology and level of evidences needed to assess clinical safety, data standards, and data acquisition.

3. Data capture and analysis of signals during premarketing clinical trials: to adopt standards for data and biospecimen acquisition and management, to allow future biomarkers development and validation.

4. Defining the best causality assessment process in clinical trials to reflect the degrees of uncertainty in causal link.

5. Guidance to assess SCAR safety from data for special populations with abnormal immune status, such as cancer patients, patients with autoimmune diseases, elderly, and paediatric patients.

6.   Validating traditional and new biomarkers: combining large SCAR safety datasets across many clinical trials in different patient populations to generate sufficient number of SCAR events.

People able to capitalize on this guidance: drug developers, regulatory authorities, physicians and scientists involved in clinical trials, academics and patients alike.

The CIOMS guideline would create a reference worldwide for regulators and clinicians involved in post- and pre- marketing authorization, as well as pharmaceutical and biotechnology companies involved in product development and marketing.

III.5 Deliverables

We have listed below some possible deliverables and some are probably still missing. It will be the first task of the group to agree a final list.

 - Scenario and burden of SCARs worldwide

- Chemical hazards and susceptible hosts and its interactions

- Identification of SCAR signals in clinical trials and during post-marketing monitoring

- Clinical SCAR assessment

- Harmonization of nomenclature, clinical measurements, definitions, classification, patterns and outcomes
- Diagnostic approach to SCARS
    - SCAR recognition
    - Best practice use of the current standard tests for SCAR diagnosis
    - SCARs related to novel biologics modulating inflammation and immune responses
    - Performing proper characterization of a SCAR case: information required
    - Work up for exclusion of alternative clinical/pharmacological causes
    - Stop rules
    - Decision on when to break the blind in a clinical trial
- In-depth analysis of existing re-challenge data to provide recommendations
- Standardization of the case report form for prospective multicentre data collection
- Standard operating procedures (SOPs) for the collection and storage of all biological samples (skin biopsy, serum, plasma, DNA, RNA, urine and stool) related to phenotypic data in clinical trials, clinical research and prospective SCAR registries.

- Analysis, interpretation and quantification of SCAR signals
    - Assessment of the SCAR potential and the benefit of a drug—risk balance
    - Assessment of the social acceptability of the risk

- Causality assessment methods for SCARs
    - According to type of SCARs.
    - Taking into account all available information of the suspected culprit drug
    - Minimum criteria required for SCAR assessment

- SCARs in special populations: oncology, rheumatology/immunology, geriatrics and paediatrics.

- SCAR Risk Management:
  - SCAR monitoring, for regulators, drug developers and drug users
  - Information to include in SmPCs regarding SCARs
  - SCAR risk communication

- Risk minimization strategies, also considering support through personalized medicine approaches.

IV.   CONCLUSION

Indeed, there is a strong need to launch the Working Group to address the present knowledge and practice gaps related to SCARs in order to formulate pragmatic consensus-based recommendations to address the outstanding issues listed above. Furthermore, the collaborative efforts brought together to accomplish this task could create the environment to hold an annual monothematic conference on SCARs jointly with industry, academia, scientists, clinicians and regulatory authorities to advance our understanding of SCARs, helping to identify the bottlenecks and gaps in this field further, foster hypothesis-driven research and stimulate the shift of SCAR healthcare strategies from a reactive to proactive preventive practice. These efforts would ultimately enable approaching patient's risk stratification and the development of a safe personalized medicine.