REGISCAR

INTERNATIONAL REGISTRY OF SEVERE CUTANEOUS ADVERSE REACTIONS (SCAR) TO DRUGS AND COLLECTION OF BIOLOGICAL SAMPLES

study protocol

written by
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SUMMARY

Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), acute generalised exanthematous pustulosis (AGEP) and hypersensitivity syndrome/drug reaction with eosinophilia and systemic symptoms (HSS/DR ESS) are rare but very severe cutaneous adverse reactions (SCAR) to drugs with high morbidity and mortality.

Objectives

The aim of the consortium is to reduce the medical and economic burden of severe cutaneous adverse reactions (SCAR) on public health and to improve the safety of medication use. The practical objectives of this study are:

1) to build an International Registry of SCAR for continuous surveillance of new drugs with adequate pharmaco-epidemiologic methodology and for providing reference information on SCAR.
2) to organise a standardized collection of biological samples (plasma, lymphocytes, DNA and skin) to allow high quality studies on pharmaco-genetics and investigations of the mechanisms of these reactions,
3) to 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.

Description of the work

All validated cases of SJS/TEN, AGEP and HSS/DR ESS requiring admission in one of the hospitals participating in the network will be included in the study. Active case finding will be used through regular contact with all relevant facilities. In each country a trained investigator will interview each case patient and collect information on medication use in the 8 weeks preceding the onset of the disease, recent infections, demographic information and relevant medical history. A standardised case record form will be used to collect prospective clinical information up to the date of discharge and later if indicated. As done in previous studies an international group of experts will ascertain all cases using a strict process of validation.

With informed consent, samples of skin biopsies and of blood will be directed to a specialised bank for separation and conservation of plasma, lymphocytes and DNA.

The clinical database will provide estimates of the risks of medications. It will also provide information on the outcome, allow the validation of prognosis indexes, and give insights on the effect of treatments.
Biological samples will be used for the following investigations: determination of the phenotype, functions and antigenic specificity of lymphocytes isolated at the time of the reaction from the blood and skin of patients; study of susceptibility genes by an association study directed first at candidate genes and second at the full genome by using state of the art technology such as for example single nucleotide polymorphisms (SNPs), microarrays, determination of the serum level of a variety of cytokines that may have a prognostic value. Duplicates of biological samples and of the clinical database will be accessible to scientists who have a project validated by an independent scientific board and by the steering committee of our project.
1. INTRODUCTION

Severe Cutaneous Adverse Reactions (SCAR) include Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), acute generalised exanthematous pustulosis (AGEP) and hypersensitivity syndrome/drug reaction with eosinophilia and systemic symptoms (HSS/DRESS). These diseases are rare (1.5 to 3 cases/million population/year) but very severe with an overall mortality of 10-20 and frequent disability in survivors.

The rarity of these reactions explains why the risk cannot be quantified during pre-marketing clinical studies of new medications. Their severity largely affects the evaluation of the benefit/risk ratio of medicines. It is, therefore, essential for the safety of medications to maintain a continuous surveillance of SCAR using epidemiological methods with a good standard of quality.

An international network has quantified the risks of SCAR in several European countries, by performing two case-control studies in the past 20 years. In Germany these prior studies were done in conjunction with a national registry for severe skin reactions.

RegiSCAR will extend this registry on SCAR to the international level, constitute a large international cohort of patients with these rare diseases, and organise a standardized bank of biological samples. This will allow the collection of data on risk factors, mechanisms of the reactions, outcome, and impact of specific treatments.

2. OBJECTIVES

The general objective of the RegiSCAR-project is to increase the knowledge on severe cutaneous adverse reactions (SCAR) in terms of their risk factors as well as their pathogenesis and pathophysiology. In particular, the specific objectives of RegiSCAR are:

1. to establish the international Registry of SCAR by extending the European registry already existing to an international one. This registry will collect all cases occurring in a network of hospitals covering all the participating countries. The risks will be quantified by using simultaneously different new methodologies.

2. to organise the standardized collection of biological samples from these patients by a “professional” bank for allowing present and future in-vitro investigations to study the underlying mechanisms of SCAR and to develop predictive tests.

3. to constitute a cohort of patients with SCAR, who will be followed if indicated for the evaluation of the outcome and impact of specific treatments.
**Expected achievements**

The constitution of an international registry will contribute to better organisation of a multidisciplinary network that already functions in several countries. The registry will allow to quantify the risks of SCAR associated with medications, especially newly released ones. This is of obvious importance for patients and physicians, but also for drug companies and for regulatory agencies.

The standardized collection of biological samples established in connection with the international registry will provide access to samples of serum, lymphocytes and DNA and skin samples from patients. The international registry will permit for the first time systematic large scale in-vitro investigations on these dramatic reactions.

Studies are planned in the fields of genetic, immunology and pharmaco-genetics. Further projects will be possible due to the continuity and progressive increase of the collection.

The ongoing discovery of susceptible genes for SCAR is a major advance in the promising field of pharmaco-genetics. It would not only prove the validity of the concept that in the next future the prescription of medications will integrate information on the genetic background of individual patients but also provide insights on the mechanisms of SCAR and open opportunities for the prevention and treatment of other less severe but more frequent drug reactions.

A better understanding of the immunological mechanisms by which a drug reaction leads to widespread destruction of the epidermis could facilitate the development of biological tests for predicting elevated risks in pre-clinical development of new drugs and/or for determining the culprit drug in patients who develop SCAR when taking several drugs.

A clinical cohort will provide clinical information on diagnosis and prognosis, prevalence of sequelae, effect of current treatments, and evaluation of existing prognosis indices in the participating countries.
3. STUDY PROTOCOL

3.1 Diagram of study organisation

H = Local Hospitals where patients are included.
3.2 Cases

3.2.1 Definitions

**Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN)**

The incidence of SJS/TEN is about 1.5 cases/million/year in Europe. Disease definitions elaborated during the former studies of SCAR, EuroSCAR and RegiSCAR will be used. Documentation of cases with clinical photographs and skin biopsies will be required. The index day, i.e. the day of the onset of the skin reaction is usually easy to determine. Drug information will be collected within the 8 weeks preceding the onset of the reaction.

**Acute generalised exanthematous pustulosis (AGEP)**

The incidence is equal to that of SJS and TEN. The prior EuroSCAR-study has provided an improved case definition.

**Hypersensitivity syndrome/drug reaction with eosinophilia and systemic symptoms (HSS/DRESS)**

HSS/DRESS is another type of SCAR, sometimes confused with SJS or AGEP. The study will contribute to a better case definition and evaluation of outcome and culprit drugs.

3.2.2 Detection of cases

All cases of TEN, SJS, AGEP and DRESS requiring hospital admission will be included. Active case findings rather than voluntary reporting will be used in order to avoid bias from enrolment conditional to drug exposure. This will involve regular contact with all relevant facilities where patients with SCAR are treated.

3.2.3 Inclusion criteria

**Potential cases**

SJS/TEN: 1) hospitalisation, 2) widespread exanthema with 1% or more of skin detachment; more than one blister, not only acral involvement, with or without mucous membrane erosions, 3) signed informed consent

AGEP: 1) hospitalisation, 2) acute pustular eruption (many pustules within a few days; except relapse of pustular psoriasis, localized or palmoplantar exanthema, exanthema with a clear infectious trigger (e.g. candida), localized pustular contact dermatitis), 3) signed informed consent
HSS/DRESS: 1) hospitalisation, 2) acute onset of exanthema with fever >38°C, 3) enlarged lymph nodes, 4) involvement of at least one internal organ, 5) eosinophilia >10% or >700/μl, atypical lymphocytes, lymphopenia <4000, lymphocytosis, thrombopenia, 6) signed informed consent

Age, gender, associated diseases (in particular HIV infection) will not be exclusion criteria. Patients unable to answer because of severe illness will be included if the consent can be obtained from a legal guardian. This legal guardian and/or the patient may decide later whether his/her data can be included in the study or not.

Validation

All potential cases will be reviewed by an expert group for final inclusion in the study (see 3.2.8).

3.2.4 Exclusion criteria

1) The following diagnoses are excluded: pemphigus, erythema multiforme, bullous pemphigoid, staphylococcal scalded skin syndrome, mechanobullous eruption (heat, cold, friction, pressure), acute pustular psoriasis, Kawasaki’s disease, toxic shock syndrome, graft-versus-host disease, vasculitis, and epidermolysis bullosa,

2) SCAR occurring in recipients of a bone marrow transplant,

3) absence of signed informed consents

3.2.5 Length of participation/timing of the study

For cases included in the registry the interview of the patient (or of a parent or relative or legal guardian) will last for about 30 minutes. This interview will be done only once within 30 days after admission.

Patients participating in the cohort will be asked their consent and to provide biological samples before the 5th day after admission. They will be interviewed for about 30 minutes within 30 days after admission. Follow-up examinations, if indicated, will be performed at day 30 and one year later.

3.2.6 Data collected

In hospitals, specially trained health care professionals (physician, pharmacist, research nurse) will perform a standardised interview with the patient (or parents and/or legal guardians), as soon as possible after admission. The data collection forms are already designed to obtain information concerning drug use within 8 weeks preceding hospital admission or the onset of the disease, demographic information and relevant medical history (see Annex). To optimise data collection on drug use, patients will be interviewed with the help of a list of indications (e.g. pain, headache, cough...
and a list of drugs (trade-names of the main "suspect" drugs). This information will be collected for the inclusion of all patients in the Registry.

3.2.7 Collection of biological samples

Only for patients included in the cohort with written informed consent blood and blister fluid (in cases with blisters) will be collected within 5 days after admission.

This sampling will consist in

- 2 x 7 ml of blood on EDTA for preparation of DNA (children: 1 x 7 ml)
- 2 x 7 ml of blood on heparin or ACD for separation of lymphocytes (3 tubes for HSS/DRESS)
- 1 x 7 ml of blood without anticoagulant for separation of serum (children 1 x 5 ml)
- all available fluid collected by puncture of blisters
- 3-4 mm fragment of the skin biopsy needed for the diagnosis

Blood samples will be sent to the collection center by express delivery using safety boxes and prepaid envelopes. (See Appendix for detailed information).

At 8±2 weeks another blood sample will be drawn (2 x 7 ml on heparin or ACD for separation of lymphocytes, 1 x 5 - 7 ml blood sample without anticoagulant for separation of serum).

3.2.8 Validation of cases for final inclusion

Detailed clinical histories, photographs and biopsies obtained for all potential cases will be reviewed by an international committee of dermatologists twice a year in order to confirm and classify the diagnosis (without any knowledge of exposure to etiologic factors). The same group of experts will also determine (without information on exposures) the date of onset of the reaction (probable index-day). The process of validation is standardized, combining a scoring system and expert consensus. Potential cases are classified as “excluded”, “possible”, “probable” or “definite” cases. Analyses are usually restricted to “probable” and “definite” cases.

3.3 Ethical considerations

The project involves:

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- use of human embryonic or foetal tissue
- use of other human tissue
- animal experimentation
- other (use of personal data, genetic information, etc.)

Because it is only based on interviews of cases, the registry does not raise important ethical considerations. Confidentiality of data will be ensured by collecting and transmitting no piece of information permitting identification of cases.

Because it comprises the collection of blood samples of cases for studies including genetic analyses, the cohort requires written informed consents from patients and the approval of the study by appropriate ethical committees in each participating country. Project of information letter, and consents are provided in annex. Different forms will be used for patients able to understand, parents of children, and patients unable to understand, who may afterwards agree to their inclusion into the study or withdraw from participation.

Actually about 10-15% of cases occur in children and we consider that children should be included for two reasons: 1) the spectrum of causative drugs is different than for adults, 2) the prognosis and the incidence of sequelae also differ.

About 20% of patients may be too acutely ill to provide an informed consent. One may suspect that these patients with the most severe forms of the disease could have a different background than those with milder forms (e.g. having two copies of a susceptibility gene). Therefore, we consider that these patients should also be included.

4. ANALYSES

4.1 Data management/analysis/quality control

Data entry will be done either in each national team under the responsibility of the national coordinator or in the data center at Freiburg, Germany. Data will be centralized by the data center, according to the European requirements on confidentiality on medical records.

All the data exchanges will be written in English language. Full names or surnames will not be recorded on the databases. The data center will acknowledge all data received. When needed, automated reminder will be addressed from the data center to the investigators and/or to the national coordinator.
Data quality checks will be performed automatically by the software, regarding inconsistencies, limit values, mandatory fields. Each patient file will be manually checked by a clinical study monitor, verifying the completeness and apparent appropriateness of data entries. E-mail, fax or telephone will be used in case of doubt regarding any of the entries. One out of each 10 cases will be audited in depth according to a random procedure, allowing the clinical study monitor to visit the investigator site, after investigator agreement, for source data verification. Visits may be gathered at particular study end-points for minimising the travel costs induced by such a procedure. Each investigator will be asked to accept the principle of source data in depth audit, providing the source data will not move from the local site, and patient confidentiality will be strictly protected.

4.2 Statistical analyses

4.2.1 Analysed variables

For the cohort study the main endpoints will be

- risk factors of mortality
- prevalence of sequelae after one year
- quality of life after one year

Secondary endpoints will be

- duration of hospitalisation

4.2.2 Population studied

All patients included in the cohort with a validated diagnosis and follow-up information.

All cases notified to the registry with a validated diagnosis and a defined day of onset of SCAR (index-day).

4.2.3 Methods

The data from the cohort will be analysed using standard methods. Relative risks of death, occurrence of sequelae and alteration of the quality of life will be estimated for various risk factors and treatments. Confounding will be controlled by stratified (Mantel-Haenszel) and multivariate (conditional and unconditional logistic regression) techniques.

Data analysis will be performed using the SAS Institute Software from data stored on ORACLE files on UNIX operating system based in the data center.
The data from the registry will be used for pharmaco-epidemiologic analyses using two different methods:

1) Utilisation of private external population based database(s) (prescription database or adequate cohort(s) of controls) to perform a case-control analysis with cases of SCAR included in the registry.

2) Applying case-crossover methodology. Exposures are compared between a risk period (e.g. week 1 before onset of the reaction) and control periods (e.g. week 4 and week 7 before onset) for each case.

3) Using improved algorithms to determine drug causality in individual cases. One was elaborated by the RegiSCAR group for SJS/TEN and provided good agreement with the results of case-control analysis of EuroSCAR data.

Intermediate analyses

Twice a year the data included in the Registry will be analysed in terms of number of with various types of SCAR and risks linked to medications. This will begin with the issue of a raw list of all medications used by the case patients in the 8 weeks period preceding hospital admission for SCAR. A formal evaluation of risks will be performed for drugs emerging from this list as possible suspects. The results will be presented to the members of the Steering Committee and a public alert will be issued if necessary.

5. PROPERTY OF THE STUDY

The results obtained in each country are the property of each national team. The results of the international study are the common property of all participants and cannot be used by anybody without the formal authorisation of the group. All decisions on management of the study and release of results orally, by publications or in many other way are taken by the “Steering Committee” of the RegiSCAR study.

The steering committee consists of the following members:

Maja Mockenhaupt  (from the German team)
Sylvia Kardaun    (from the Dutch team)
Luigi Naldi       (from the Italian team)
Jean-Claude Roujeau (from the French team)
Martin Schumacher  (from the Data center)
Alexis Sidoroff  (from the Austrian team)

In case of non-participation of some team the corresponding leader will quit the steering committee.

For authorship of the main publication of the results from the RegiSCAR study the four “useful” ranks (1, 2, 3, last) will be shared by 3 clinicians (according to the number of cases included in the study) and 1 methodologist. If (as expected) several publications result from the study, all members of the steering committee will be authors in a useful rank for at least one paper.

Concerning studies performed in collaboration with “external” teams and based on biological samples and/or data collected by RegiSCAR, the authorship will be shared (normally on a 50/50 basis) between the RegiSCAR group and the team performing the specific study.
## 6. PARTICIPANTS

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7. REFERENCES


8. LIST OF APPENDICES

Appendix 1
Questionnaire of Cases (Registry and Cohort)

Appendix 2
Drug list

Appendix 3
Information Sheet and Consent forms for patients

Appendix 4
Quality of Life Questionnaire (SF 36)