REGISCAR

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

study protocol

written by
Maja Mockenhaupt, Dokumentationszentrum schwerer Hautreaktionen (dZh), Freiburg University, Germany and Jean-Claude Roujeau, Paris XII University, France
for the RegiSCAR study group

March 2010

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/DRESS) 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/DRESS 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.

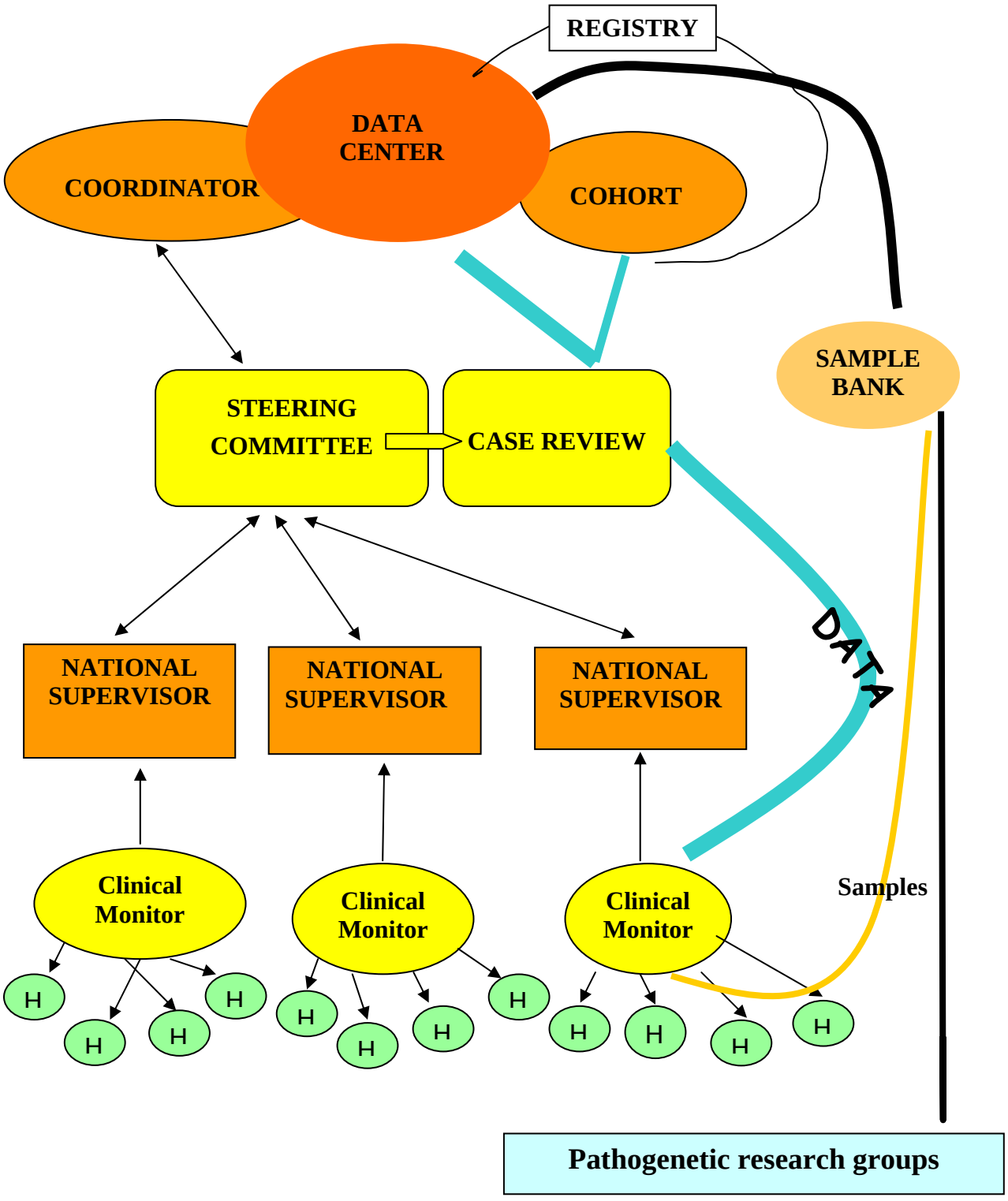
The ongoing discovery of susceptible genes for SCAR is a major advance in the promising field of pharmaco-genetics. It would not only prove the validity of the concept that in the next future the prescription of medications will integrate information on the genetic background of individual patients but 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 pre-paid envelopes. (See Appendix for detailed information).

At 8±2weeks 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:	**YES**	**NO**
- clinical experimentation on human beings	I_I	IXI
- clinical experimentation on persons unable to give a valid consent	I_I	IXI
- collection of data on persons unable to give a valid consent	IXI	I_I

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

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 data bases. 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

German team/Coordination Maja MOCKENHAUPT	Dermatologist	Dokumentationszentrum schwerer Hautreaktionen (dZh), Department of Dermatology, University Medical Center Hauptstrasse 7 79104 Freiburg, GERMANY tel: +49 761 270-6723 fax: +49 761 270-6834 e-mail:dzh@uniklinik-freiburg.de
Data Center Martin SCHUMACHER	Director of IMBI/ Statistician	Institute of Medical Biometry and Medical Informatics (IMBI), University Medical Center Stefan-Meier-Str. 26 79104 Freiburg, GERMANY tel: +49 761 203 6662 fax: +49 761 2003 6680 e-mail: ms@imbi.uni-freiburg.de
Peggy Sekula	Statistician	e-mail: ps@imbi.uni-freiburg.de
French team Jean-Claude ROUJEAU	Dermatologist	Departement de Dermatologie Hôpital Henri Mondor 94010 Créteil cedex, FRANCE tel: +33 1 49 81 25 12 fax: +33 1 49 81 25 02 e-mail: jean-claude.roujeau@hmn.ap-hop-paris.fr
Ariane AUQUIER-DUNANT	Statistician/ Epidemiologist	e-mail: adunant@igr.fr

Dutch team Sylivia Kardaun	Dermatologist	Universitair Medisch Centrum Groningen (UMCG) Afd. Dermatologie De Brug 2 de verdieping K 2.063 9700 RB Groningen, NETHERLANDS tel: +31 50 36 12 520 fax: +31 50 36 12 624 e-mail: s.h.kardaun@derm.umcg.nl
Biological Sample Bank Bijan Ghaleh		Biothèque du Centre d'Investigation Clinique Plateforme de Ressources Biologiques Hôpital Henri Mondor 51, Avenue du Maréchal de Lattre de Tassigny 94010 Créteil, FRANCE tel: +33 1 49 81 37 86 fax: +33 1 49 81 47 97 e-mail: bijan.ghaleh@inserm.fr
Genetics team Alain HOVNANIAN	Genetician	Service de Génétique Médicale CHU Purpan – BP 3028 Unité Inserm U563 Pavillion Lefevre 31024 Toulouse cedex 03, FRANCE tel : +33 5 61 15 84 31 fax : +33 5 61 49 90 36 e-Mail : Alain.Hovnanian@toulouse.inserm.fr
Italian team Luigi NALDI	Dermatologist/ Epidemiologist	Centro Studi GISED – FROM Padiglione Mazzoleni – Presidio Spedaliero Matteo rota Via Garibaldi 13/15 24122 Bergamo, ITALY tel. +39 035 22 78 719, +39 035 22 78 720 fax +39 035 22 78 673 e-mail: luigi.naldi@gised.it

Austrian team Alexis SIDOROFF	Dermatologist	Department of Dermatology University of Innsbruck Anichstr, 35 6020 Innsbruck, AUSTRIA tel: +43 512 504 2971 fax: +43 512 504 3010 e-mail: alexis.sidoroff@uibk.ac.at
Taiwan Chia-Yu Chu	Dermatologist	Department of Dermatology National Taiwan University Hospital 7 Chung-Shan South Road Taipei 100, TAIWAN tel: +886 2 23 56 2141 fax: +886 2 23 93 4177 e-mail: chiayu.chu@gmail.com, chiayuchu@ntu.edu.tw
Taiwan Wen-Hung Chung	Dermatologist	Department of Dermatology, Chang Gung Memorial Hospital, Chang Gung University College of Medicine, Taipei, Taiwan 199. Tung Hwa North Road Taipei, TAIWAN tel: +886 2 27 13 5211 fax: +886 2 27 19 5114 e-mail: wenhungchung@yahoo.com
South Africa Gail Todd	Dermatologist	Division of Dermatology University of Cape Town Groote Schuur Hospital, Ward G23, Observatory, 7925 Cape Town, SOUTH AFRICA tel: +21 404 3376 fax: +21 447 8232 e-mail: gtodd@uct.ac.za

UK Daniel Creamer	Dermatologist	Consultant Dermatologist King's College Hospital Denmark Hill London SE5 9RS, GREAT BRITAIN tel. +44 20 7346 3258 fax + 44 20 3299 3616 e-mail: Daniel.creamer@kingsch.nhs.uk

7. REFERENCES

Arevalo JM, Lorente JA, Gonzalez-Herrada C, Jimenez-Reyes J. Treatment of toxic epidermal necrolysis with cyclosporin A. J Trauma 2000;48(3):473-8

Bastuji-Garin S, Rzany B, Stern RS, Shear NH, Naldi L, Roujeau J-C. A clinical classification of cases of toxic epidermal necrolysis, Stevens-Johnson syndrome and erythema multiforme. Arch Dermatol 1993;129:92-96.

Bastuji-Garin S, Fouchard N, Bertocchi M, Roujeau JC, Revuz J, Wolkenstein P. SCORTEN: a severity-of-illness score for toxic epidermal necrolysis. J Invest Dermatol 2000 ; 115:149-53

Beylot C, Bioulac P, Doutre MS. Pustuloses exanthématiques aigües généralisées. A propos de 4 cas. Ann Dermatol Venereol 1980;107:37-48.

Bocquet H, Bagot M, Roujeau J-C. Drug-induced pseudolymphoma and drug hypersensitivity syndrome (Drug rash with eosinophilia and systemic symptoms-DRESS). Semin Cut Med Surg 1996;15:250-7.

Choquet-Kastylevsky G, Intrator L, Chenal C, Bocquet H, Revuz J, Roujeau J-C : Increased levels of interleukin 5 are associated with the generation of eosinophilia in drug-induced hypersensitivity syndrome, Br J Dermatol, 139:1026-32,1998.

Correia O, Delgado L, Ramos JP, Resende C, Fleming Torrinha JA. Cutaneous T-cell recruitment in toxic epidermal necrolysis, further evidence of CD8+ lymphocyte involvement. Arch Dermatol 1993;129:466-8.

Craven NM . Management of toxic epidermal necrolysis. Hosp Med 2000 Nov;61(11):778-81.

Dietrich A, Kawakubo Y, Rzany B, Mockenhaupt M, Simon JC, Schopf E . Low N-acetylating capacity in patients with Stevens-Johnson syndrome and toxic epidermal necrolysis. Exp Dermatol 1995;4:313-6.

French LE, Tschopp J. Fas-mediated cell death in toxic epidermal necrolysis and graft-versus-host-disease: potential for therapeutic inhibition. Schweiz Med Wochenschr 2000; 130: 1656-61.

Fritsch PO, Ruiz-Maldonado R. Erythema multiforme, Stevens-Johnson Syndrome-Toxic Epidermal Necrolysis. Pp 636-54. In Fitzpatrick TB et al. Dermatology in general medicine. McGraw-Hill, New York, 1998.

Garcia-Doval I, LeCleach L, Bocquet H, Otero XL, Roujeau JC. Toxic epidermal necrolysis and Stevens-Johnson syndrome: does early withdrawal of causative drugs decrease the risk of death? Arch Dermatol. 2000;136:323-7.

Halebian PH, Corder VJ, Madden MR, et al. Improved burn center survival of patients with toxic epidermal necrolysis managed without corticosteroids. Ann Surg 1986; 204: 503-12.

Haus C. Paquet P, Marechal-Courtois C. Long-term corneal involvement following drug-induced toxic epidermal necrolysis (Lyell's disease). Ophthalmologica. 1993;206:115-8.

Heng MCY, Allen SG. Efficacy of cyclophosphamide in toxic epidermal necrolysis, clinical and pathophysiologic aspects. J Am Acad Dermatol 1991;25:778-86.

Hering O, Mockenhaupt M, Rzany B, Schroder W, Schopf E. The dermal type of erythema multiforme: a rare variant of Stevens-Johnson syndrome or cases of clinical misclassification? Acta Derm Venereol 1997;7:217-8.

Herndon DN. Toxic epidermal necrolysis, a systemic and dermatologic disorder best treated with standard treatment protocols in burn intensive care units without the prolonged use of corticosteroids. J Am Coll Surg. 1995;180:340-2.

Hertl M, Bohlen H, Merk HF. Efficacy of cyclophosphamide in toxic epidermal necrolysis. J Am Acad Dermatol 1993;28:511.

Hewitt J, Ormerod AD.Toxic epidermal necrolysis treated with cyclosporin. Clin Exp Dermatol 1992;17:264-5.

Knowles SR, Uetrecht J, Shear NH :Idiosyndratic drug reactions : the reactive metabolite syndromes. Lancet 2000 ;356 :1587-91

Le Cleach L, Delaire S, Boumsell L et al. Blister fluid T lymphocytes during toxic epidermal necrolysis are functional cytotoxic cells which express human natural killer (NK) inhibitory receptors. Clin Exp Immunol 2000;119:225-30

Leyva L, Torres MJ, Posadas S, et al : Anticonvulsant-induced toxic epidermal necrolysis :Monitoring the immunologic response. J. Allergy Clin Immunol 2000 , 105 :157-65

Lyell A. Drug-induced toxic epidermal necrolysis. An overview. Clin Dermatol 1993;11:491-2.

Magina S, Lisboa C, Goncalves E, Conceicao F, Leal V, Mesquita-Guimaraes J.A case of toxic epidermal necrolysis treated with intravenous immunoglobin.Br J Dermatol. 2000;142:191-2.

Mockenhaupt M, Schopf E. Epidemiology of drug-induced severe skin reactions. Semin Cutan Med Surg 1996;15:236-43

Moudgil A, Porat S, Brunnel P, Jordan SC. Treatment of Stevens-Johnson syndrome with pooled human intravenous immune globulin. Clin Pediatrics 1995;34:47-51.

Naldi L, Locati F, Marchesi L, Cainelli T. Incidence of toxic epidermal necrolysis in Italy. Arch Dermatol 1990;126:1103-4.

Paquet P, Paquet F, Al Saleh W, Reper P, Vanderkelen A, Pierard GE. Immunoregulatory effector cells in drug-induced toxic epidermal necrolysis. Am J Dermatopathol 2000 Oct;22(5):413-7.

Paul C, Wolkenstein P, Adle H, Wechsler J, Revuz J, Roujeau J-C. Apoptosis as a mechanism of keratinocyte death in toxic epidermal necrolysis and Stevens-Johnson syndrome. Br J Dermatol 1996;134:710-14.

Penso D, Roujeau J-C, Guillaume J-C, et al. Toxic epidermal necrolysis after oxicam use. J Am Acad Dermatol 1986;14:275-6.

Renfro L, Grant-Krebs JM, Daman LA. Drug-induced toxic epidermal necrolysis treated with cyclosporin. Int J Dermatol 1989;28:441-4.

Romero-Rangel T, Stavrou P, Cotter J, Rosenthal P, Baltatzis S, Foster CS. Gas-permeable scleral contact lens therapy in ocular surface disease. Am J Ophthalmol 2000 Jul;130(1):25-32

Roujeau J-C, Guillaume J-C, Fabre J-P, Penso D, Fléchet M-L, Girre J-P. Toxic epidermal necrolysis (Lyell syndrome) incidence and drug etiology in France, 1981-1985. Arch Dermatol 1990;126:37-42.

Roujeau J-C, Huyn NT, Bracq C, et al. Genetic susceptibility to toxic epidermal necrolysis. Arch Dermatol 1987;123:1171-3.

Roujeau J-C, Kelly JP, Naldi L et al. Medication use and the risk of Stevens-Johnson syndrome or toxic epidermal necrolysis. N Engl J Med 1995;333:1600-7.

Roujeau J-C, Stern RS. Severe adverse cutaneous reactions to drugs. N Engl J Med 1994;331:1272-85.

Rzany B, Hering O, Mockenhaupt M, Schroder W, Goerttler E, Ring J, Schopf E. Histopathological and epidemiological characteristics of patients with erythema exudativum multiforme major, Stevens-Johnson syndrome and toxic epidermal necrolysis. Br J Dermatol 1996;135:6-11

Rzany B, Mockenhaupt M, Baur S, Schroder W, Stocker U, Mueller J, Hollander N, Bruppacher R, Schopf E. Epidemiology of erythema exsudativum multiforme majus, Stevens-Johnson syndrome, and toxic epidermal necrolysis in Germany (1990-1992): structure and results of a population-based registry. J Clin Epidemiol 1996;49:769-73

Rzany B, Mockenhaupt M, Stocker U, Hamouda O, Schopf E. Incidence of Stevens-Johnson syndrome and toxic epidermal necrolysis in patients with the acquired immunodeficiency syndrome in Germany. Arch Dermatol 1993;129:1059.

Rzany B, Schmitt H, Schöpf E. Toxic epidermal necrolysis in patients receiving glucocorticosteroids. Acta Derm Venereol (Stockh) 1991;71:171-2.

Scheuerman O, Nofech-Moses Y, Rachmel A, Ashkenazi S. Successful treatment of antiepileptic drug hypersensitivity syndrome with intravenous immune globulin. Pediatrics 2001 Jan;107(1):E14

Schnyder B, Burkhart C, Schnyder-Frutig K et al : Recognition of Sulfomethoxazole and Its Reactive Metabolites by Drug-Specific $CD4^+$ T cells from allergic Individuals. J Immunol. 2000, 6647-54

Schulz JT, Sheridan RL, Ryan CM, MacKool B, Tompkins RG A 10-year experience with toxic epidermal necrolysis. J Burn Care Rehabil 2000;21:199-204

Shear NH, Spielberg SP, Grant DM, Tang BK, Kalow W. Differences in metabolism of sulfonamides predisposing to idiosyncratic toxicity. Ann Intern Med 1986;105:179-84.

Shöpf E, Stühmer A, Rzany B, Victor N, Zentgraf R, Kapp JF. Toxic epidermal necrolysis and Stevens-Johnson syndrome, an epidemiologic study from West Germany. Arch Dermatol 1991;127:839-42.

Sidoroff A, Halevy S, Bavinck JN, Vaillant L, Roujeau JC. Acute generalized exanthematous pustulosis (AGEP) - A clinical reaction pattern. J Cutan Pathol. 2001;28:113-9

Stern RS, Albengres E, Carlson J, Chen D, Kreft C, Dai W, Joseph M, Tilson H, Wiholm BE, Kreft C. An international comparison of case definition of severe adverse cutaneous reactions to medicines. Drug Saf 1993;8:69-77.

Tegelberg-Stassen MJ, van Vloten WA, Baart de la Faille H. Management of nonstaphylococcal toxic epidermal necrolysis: follow-up study of 16 case histories. Dermatologica 1990;180:124-9.

Viard I, Wehrli P, Bullani R et al. Inhibition of toxic epidermal necrolysis by blockade of CD95 with human intravenous immunoglobulin. Science 1998;282:490-3.

Wolkenstein P, Latarjet J, Roujeau J-C et al. Randomised comparison of thalidomide versus placebo in toxic epidermal necrolysis. Lancet 1998;352:1586-9.

Yawalkar N, Egli F, Hari Yet al : Infiltration of cytotoxic T cells in drug-induced cutaneous eruptions. Clin Exp Allergy, 2000, 30 :847-55

Yawalkar N, Shrikhande M, Hari Yet al : J. Evidence for a role for IL-5 and eotaxin in activating and recruiting eosinophils in drug-induced cutaneous eruptions. Allergy Clin Immunol 2000, 106 : 1171-76

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)