Pharmacologie médicale

Bordeaux PharmacoEpi
CIC Bordeaux CIC1401

EURO-SALT

Study of Acute Liver Transplant

A study of drug-exposed acute liver failure in European transplant centres

"10 years in 10 countries"

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Conflict of interest

Nothing to declare.

A feasibility Study of EURO-SALT (EURO-SALT(f)) is being conducted. Financing is obtained through a public grant by ANSM (*Appel à candidatures pour financer des projets de recherche sur thématiques ciblées – 1, 2015*).

EURO-SALT and EURO-SALT(f) are conducted and analysed independently by Bordeaux PharmacoEpi Platform, CIC Bordeaux CIC1401, Department of Medical Pharmacology, University of Bordeaux.

Funding options for EURO-SALT is being sought…

Flow

- Context
  - SALT-I study
  - SALT-II study
  - SALT-III study
- EURO-SALT project
  - EURO-SALT(f): Feasibility study of EURO-SALT
- Help and assistance requests from ENCePP

Context (1): SALT-I

- At the request of the CHMP
- Multicentre, multinational 7-countries (France, Greece, Ireland, Italy, Portugal, Netherlands, UK)
- Risk of ALFT in cases without identified clinical cause exposed to NSAIDs & paracetamol
- Case-population
- Retrospective, evaluation period 3-years (2005 – 2007)

- ✓ Similar per-user risk of ALFT between different NSAIDs,
- ✓ 3-fold higher rate of ALFT in users of paracetamol at therapeutic doses,
- ✓ ALFT had a pattern suggestive of type B (genetic or allergic) reactions,
- ✓ Publications:

  6 full-text articles, 2 Letters-to-the-Editor (BMJ 2013 & Epidemiology 2013), 1 Editorial (Journal of Hepatology 2014).

Context (2): SALT-II

- Funding is obtained through a public grant by Bordeaux University Foundation,
- Follows the same case-population methodology as in SALT-I
  - except the causality assessments,
  - extending retrospective part another 7-year period (2008-2014),
  - focuses on all drugs including herbal medicines.
- Ongoing in France with participation of all liver transplant centres,
  - Validation of all drug-exposed ALFT cases without identified clinical cause from 2008 – 2013 terminated by Prof GP Pageaux,
  - Data collection for the year 2014 ongoing.

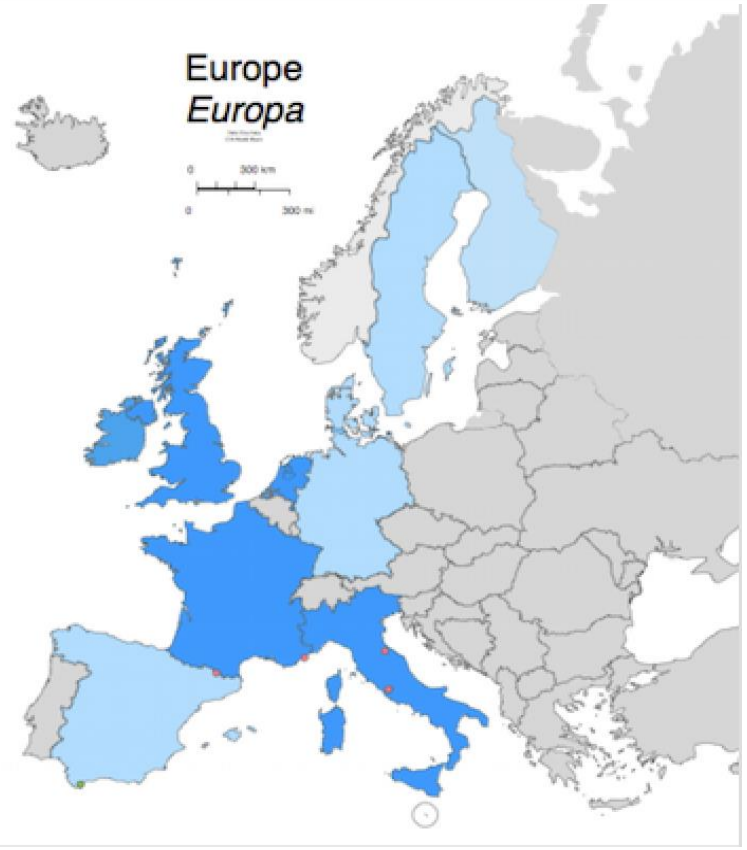
Context (3): SALT-III

- Funding is obtained through a public grant by ANSM (AAP-2013-029),
- Prospective case-population surveillance of ALFT
  - focus on all drugs including herbal medicines,
  - inclusion period is two years, retrospective data collection to have all ALFT cases will be performed,
  - ALFT cases will be examined if with/without identified clinical cause,
  - drug exposure will be investigated for all ALFT cases using all available data,
  - blood samples are drawn and kept for further genetic analyses,
    - ✧SALT-III*gene*: a sub-study of SALT-III to develop the methodology for the pharmacogenetic analyses of SALT-III. It is currently under development and in search of funding options...
- Ongoing in France with participation of all liver transplant centres,
  - case inclusion (will terminate 31 December 2016)

Objectives of EURO-SALT

- to extend SALT-II and SALT-III in Europe,
- evaluate drug-associated risk of ALFT with/without identified clinical cause, both retrospectively and prospectively.

Methods (1): Countries

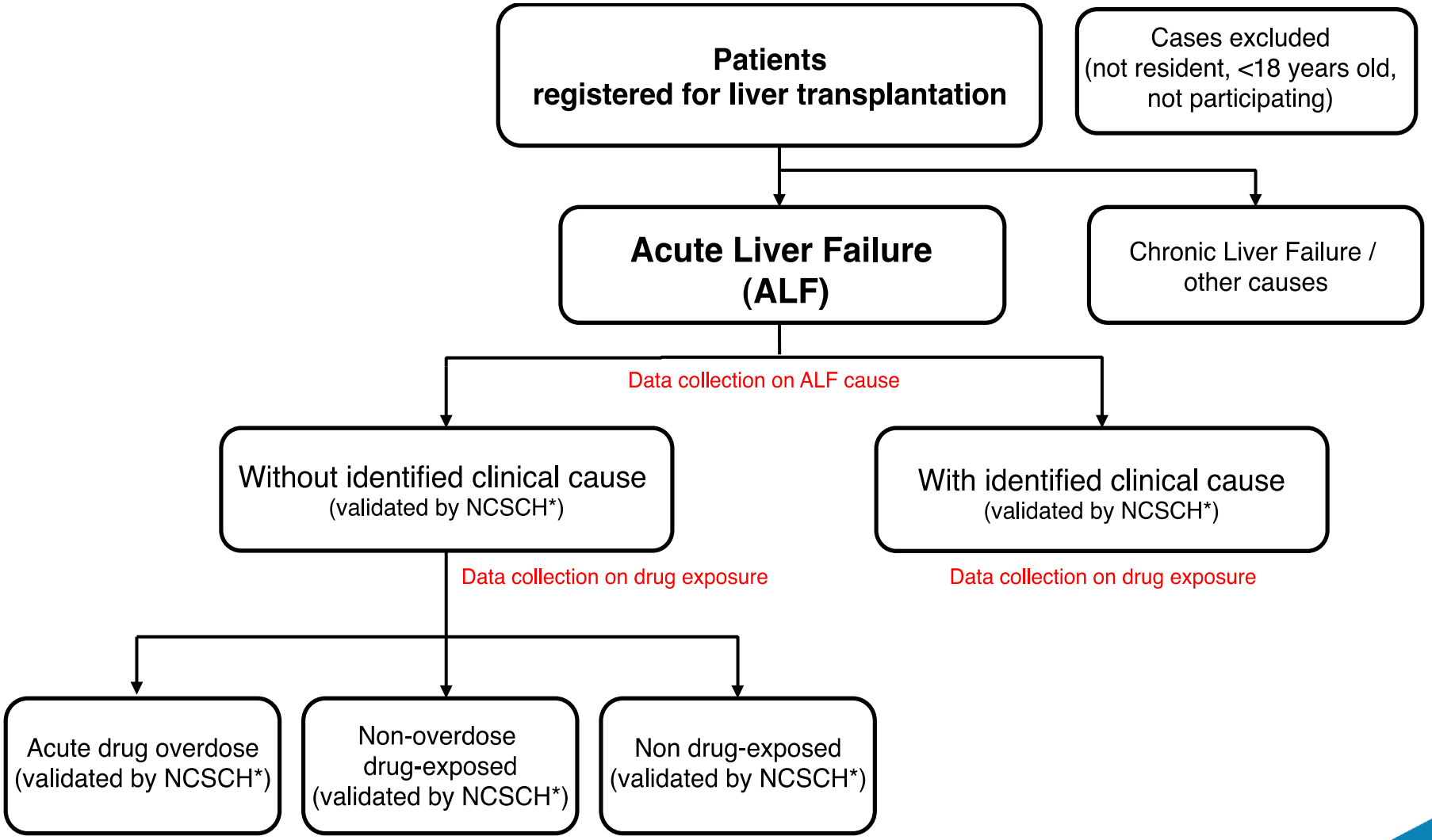


- The EURO-SALT is envisaged to be conducted in 10 countries:
  - five from the original SALT: France, Ireland, Italy, Netherlands, UK
  - five new countries: Denmark, Finland, Germany, Spain, Sweden

Methods (2): General study design

- Multicentre, multinational case-population study of drug-exposed ALFT without identified clinical cause in liver transplant centres.
- Anticipated project duration: 5 years (or more)
- Index date (ID): date of registration on transplant list (whether the transplantation is actually performed or not)
- Exposure window: 30 days before ID
- Cases will be identified at participating liver transplant centres, using national or local transplant registries.

Methods (3): Case selection flow chart



*National Case Selection Committee Hepatologist

Methods (4): Retrospective part

- The retrospective part will follow the SALT-II methodology:
  - Data collection will be performed for the 90-day exposure window. Main data analyses will be performed for 30-day exposure window period.
  - Will evaluate a 10-year period (2005-2015). Different retrospective data collection periods are anticipated for different countries; more specifically:
    - ✓ **Denmark, Finland, Germany, Spain, Sweden** (not participated to SALT-I): Patient registered on the transplantation list between 1st January 2005 and 31st December 2015,
    - ✓ **Italy, Ireland, Netherlands, and the UK** (participated to SALT-I): Patient registered on the transplantation list between 1st January 2008 and 31st December 2015,
    - ✓ **France** (where SALT-II will be finalised): Patient registered on the transplantation list between 1st January 2014 and 31st December 2015.

Methods (5): Prospective part

- The prospective part will follow the SALT-III methodology:
  - The start of prospective case inclusion may be anticipated from 2017 (or 2018) to 2020 (or 2021) in 10 countries, depending on the start year of the EURO-SALT.
  - Methodology of the pharmacogenetic data analyses of EURO-SALT prospective part will be further developed with regards to that of SALT-IIIF*gene* sub-study.

EURO-SALT(f)

- Funding is obtained through a public grant by ANSM (AAP-2013-029),
- Final report to be sent to the ANSM by June 2017.
- Objectives of this feasibility study:
  - to determine the final participating European countries,
  - to list the liver transplant centres participating to EURO-SALT,
  - to estimate the number of liver failure cases (ALF is the main diagnosis),
  - to determine regulatory aspects in each participating country, including regulatory steps for blood and genetic material collection from patients included in the study,
  - to determine data source(s) for population drug exposure data, the existence of a national database (*i.e.* healthcare insurance system, reimbursement database, general practitioners database, prescriptions database etc.); clarification of processes on data request, data extraction, transfer of extracted data etc.,
  - to write the final study protocol of EURO-SALT.

EURO-SALT(f): Status (1)

- All liver transplant centres in the 10 countries (Denmark, Finland, France, Germany, Ireland, Italy, Netherlands, Spain, Sweden, UK) are identified and listed.
- Centres are currently being contacted with a Pre-study Site Evaluation Questionnaire in order to determine:
  - the responsible (or other relevant) person of the centre,
  - the contact details of the centre,
  - registered / transplanted patient population (only adult, only paediatric, both adult and paediatric),
  - the availability of electronic database for registered or transplanted cases at national or local level(s),
  - the approximate total number of patients registered for liver transplantation/year,
  - the approximate total number of patients transplanted/year,
  - the approximate total number of CLF and ALF cases registered in the transplant list/year,
  - regulatory aspects in each country for the conduct of the project:
    - ✓ From the experience of SALT-I, it is obvious that there is no harmonised regulations to obtain authorisation for the conduct of a pharmacoepidemiological study,
    - ✓ determining regulatory steps for blood and genetic material collection from patients included in the study.
- The contacts and all replies are being documented.

EURO-SALT(f): Status (2)

- Build up a Scientific Consortium with public and private partners
- Identification of a national hepatologist in each country
  - be the contact person,
  - be responsible for case selection and case validation
- Visits/teleconferences will be organised for each country as per need in order to present the EURO-SALT project to the participating centres, and eventually to start the project set-up.

EURO-SALT(f): Status (3)

- Participating liver transplant centres in anticipated countries:
  - Denmark 1 / 1
  - Finland 1 / 1
  - France 21 / 21
  - Germany 1 / 26*
  - Ireland 1 / 1
  - Italy 7 / 23
  - Netherlands 2 / 3
  - Spain 0 / 26*
  - Sweden 0 / 2*
  - UK 6 / 7

* Identification source of liver transplant centres: European Liver Transplant Registry - ELTR

EURO-SALT: Congress presentations

- SFPT 2016, Nancy. Poster presentation
- ICPE 2016, Dublin. Poster presentation.

Perspectives and Conclusion

- Proven feasible by SALT-I study, even on a wider scale.
- EURO-SALT will evaluate the risk of drug-associated ALFT with/without identified clinical cause for a “10 year-period in 10 countries”.
- The prospective nature will allow for real-time assessment of emerging risks related to drugs newly introduced to the market, thus earlier signal identification of a major drug-related public health issue.
- Determining genetic risk factors will help clarifying underlying conditions.
- The new methods to be developed are
  - use of hospital information systems to store and extract case data,
  - systematic retrieval of blood samples for pharmacokinetic, toxicological and pharmacogenetic evaluation of drug hepatotoxicity,
  - identifying possible cofactors or drugs that might worsen the prognosis or outcome of the initial liver injury.
- Linking to claims databases could provide more exposure information. This is a novel issue that has not been yet studied systematically.

ENCePP help & assistance requested

- Italy, Germany, Spain, Sweden
  - Identification of national hepatologist
  - Identification and participation of liver transplant centres
- Funding options
  - Public
  - Private