Drug exposure and risk of acute liver failure leading to registration for liver transplantation (ALFT): Results of the SALT-III study in adults in France

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Abstract

Background: Acute Liver Failure (ALF) leading to liver Transplantation (ALFT) is largely related to drugs: drug induced liver injury (DILI), as shown by SALT-I (2005-2007) and SALT-II (2008-2013) studies and the American DILI network. **Objectives**: To estimate the evolution of the risk of DILI-induced ALFT in France in 2015-2016 .

Methods: Multicentre, prospective and retrospective case-population study focused on adults patients registered on transplant list for ALF over 2 years (2015-2016). Data were collected in 17 liver transplant centres. Cases were classified into 2 groups: 1) ALFT "with identified non-DILI cause" (viral, autoimmune hepatitis), and 2) ALFT with well-identified DILI cause, cases with drug exposed ALFT and undetermined ALFT. Drug exposure within 30 days prior to index date (initial symptoms of liver disease) was investigated for all cases whatever the cause of ALFT. The risk of drug-exposed ALFT, expressed as rate per million treatment-years (tt-yrs), will be calculated using reimbursement data of EGB (permanent random sample of the national healthcare insurance system database). This incidence rate will be compared to that of ALFT "with identified non-DILI cause" in order to identify drugs increasing the risk of ALF. **Results:** To date, 119 of 148 cases ALFT cases have been adjudicated by a hepatologist group in the 17 liver transplant participating centres. Among them: 53 cases (44.5% of ALFT) have been classified as ALFT with non-DILI cause (autoimmune hepatitis n=17 (14.3%); vascular liver injury n=10 (8.4%); hepatitis B n=8 (6.7%); other viruses n=4 (3.4%); alcoholic ALF n=6 (5.0%); mushroom intoxication n=4 (3.4%); other causes n=4 (3.4%) and 50 cases (42% of ALFT) related to paracetamol including 30 cases (25%) with voluntary overdosage and 21 cases (17.6%) of accidental paracetamol-DILI; 10 cases (8.4%) exposed to drugs 30 days prior to liver injury including 4 DILI with probable causality: amoxicillin (1 case), antituberculous (1 case), antiepileptics (1 case) chemotherapy (1 case) and 6 cases with possible other DILI (several concomitant drugs) and 5 cases (4.2%) not exposed to drugs 30 days prior to liver injury. **Conclusions:** In France, over the years 2015-2016, the role of paracetamol in ALFT is further increasing, with a significant proportion of accidental counterpart. Other drugs account for 8.4% of ALFT. Non identified causes is significantly reduced. The results for the whole 143 patients will be available for April 2018.

Background

- Acute liver injury has been reported with most drugs, and is one of the most common reasons for drug withdrawal from market or interruption of development. Most severe cases result in Acute Liver Failure leading to registration for Transplantation (ALFT).
- Non-steroidal anti-inflammatory drugs (NSAIDs) and paracetamol have often been involved in liver injury.
- Because of a suspected greater risk of hepatotoxicity with an NSAIDs, the SALT-I study, required by the CHMP (Committee for Medicinal Products for Human Use), has been realised to assess the risk of ALFT in patients exposed to NSAIDs over the years 2005-2007. This retrospective study was conducted in 7 countries (France, Greece, Ireland, Italy, the Netherlands, Portugal and the United Kingdom) with the participation of 55 transplantation centres in Europe, including 20/21 centres in France. The SALT-I study demonstrated the feasibility of this type of multicentre study.
- The SALT-I study was completed by the SALT-II study, covering the years 2008-2013, that was conducted in France. The methodology was similar to SALT-I but the objective was to assess all drug exposures, not only NSAIDs.
- The SALT-III study was realised in France and took advantage of this network of French liver transplantation centres.

Objectives

- To develop the network of liver transplant centres for the prospective identification of drug-related ALFT
- To evaluate the risk of drug-exposed ALFT in adults in the 30 days prior to index date (ID, date of first symptoms) according to the drug dispensing in France over 2015-2016, estimated and extrapolated from data provided by the national healthcare insurance system (Echantillon Généraliste de Bénéficiaires: EGB).

Methods

- **Design:** multicentre and **case-population** study focused on drug-exposure of patients with ALFT **over 2 years** (2015-2016).
- **Identification and inclusion** of adult patients with ALFT and resident in French liver transplantation centres.
- **Data collection** through an electronic CRF completed by the Research Clinical Assistants using **hospital medical files** (all drug exposures collected, including herbal medicines).
- **Classification of ALFT cases** by a Case Selection Committee:
  - ALFT with identified cause (viral hepatitis, auto-immune, etc.)
  - ALFT without identified clinical cause
    - acute drug overdose (with or without suicidal intent)
    - exposure to drugs without overdose
    - no drug exposure
- **Primary endpoint:** incidence rate (IR) of ALFT for cases without identified clinical cause exposed to drugs of interest within the 30 days before ID.
- Drug exposures preceding the ALFT were compared with **the population exposure after extrapolation of EGB data**. The IR for all ALFT without identified clinical cause exposed to drugs were computed for each drug of interest and expressed per billion dispensed defined daily doses (DDD), per million exposed patients, and per million exposed patients-years.

Declaration of interest

The study was performed with the collaboration of the team of CHU of Montpellier and received funding from ANSM (Appel à projet 2013).

Results

Study populations

- **140 ALFT cases** were included by the 17 participating centres: **80 (57.1 %) "without identified clinical cause"** and 60 (42.9 %) "with identified clinical cause" (*figure 1*).
- The number of ALFT "without identified clinical cause" was relatively constant since the SALT-I/II studies (33.6 *vs* 41.0 *vs* 40.0 cases/year, respectively for SALT-I, SALT-II, SALT-III). As for SALT-II, the number of non-overdose drug-exposed ALFTs decreased (21.6 *vs* 13.6 *vs* 7.5 cases/year, respectively for SALT-I, SALT-II, SALT-III) whereas the number of acute drug overdose ALFTs continued to increase (10.6 *vs* 22.0 *vs* 30.5 cases/year respectively for SALT-I, SALT-II, SALT-III).

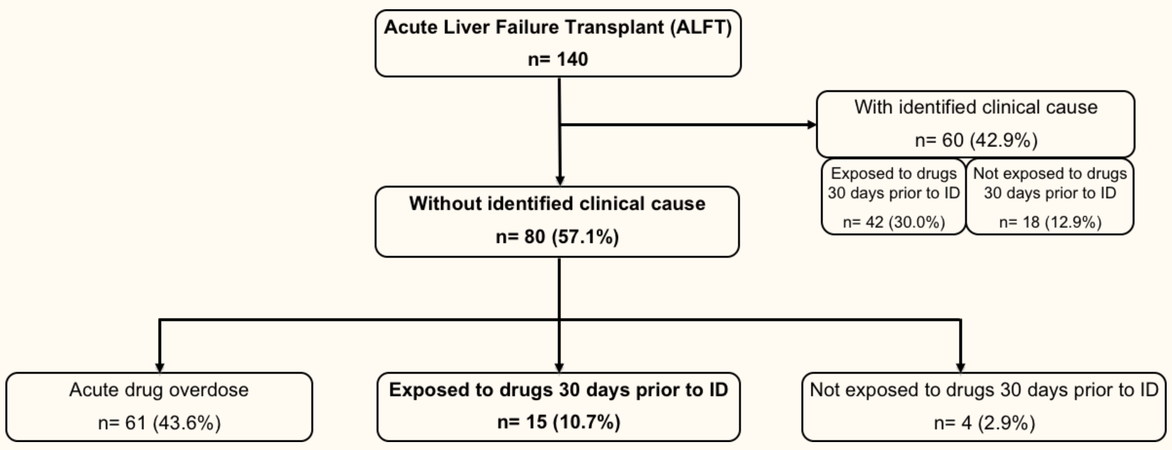

Figure 1 : Inclusion and selection of ALFT cases over the period 2015-2016

ALFT without identified clinical cause: demographics and exposure

- Almost 61% of the 80 ALFTs "without identified clinical cause" were female and had a mean age of 40.6 (±11.5) years. Liver transplantation was performed for 51.3% of cases.
- Among the 80 ALFTs "without identified clinical cause":
  - **61 acute drug overdoses**: **96.7% were exposed to paracetamol** and overdose was attributed to paracetamol for 95.1% (44.3% non-intentional *vs* 50.8% intentional) (*Table 1*). The other most frequently found drug exposures were: **anxiolytics (45.9%), antidepressants (23%), opioids (19.7%), antiepileptics (18%), antipsychotics (14.8%), hypnotics et sedatives (14.8%) and NSAIDs (11.5%)** (*Table 2*).
  - 15 non-overdose drug exposures: **5 cases were exposed to paracetamol**, 2 cases to anxiolytics and 2 cases to NSAIDs.
- Because of the small number of non-overdose drug exposed ALFTs (n=15), drug exposures could not be compared with acute drug overdose ALFTs (n=61). The drug exposure preceding the overall ALFT "without identified clinical cause" seemed to be consistent with drug exposure observed in SALT-II.

Table 1 : Paracetamol exposure (within 30 days before ID) of ALFT cases without identified clinical cause

	Acute drug overdose n = 61		Exposed to drugs n = 15	
At least one exposure to paracetamol, n (%)				
Paracetamol (plain and combinations)	**59**	**(96.7)**	**5**	**(33.3)**
Paracetamol	57	(93.4)	5	(33.3)
Paracetamol combinations	7	(11.5)	0	(0.0)
Paracetamol, combinations excl. psycholeptics	*2*	*(3.3)*	*0*	*(0.0)*
Paracetamol, combinations with psycholeptics	*0*	*(0.0)*	*0*	*(0.0)*
Codeine, combinations	*5*	*(8.2)*	*0*	*(0.0)*
Tramadol, combinations	*0*	*(0.0)*	*0*	*(0.0)*
Pseudoephedrine, combinations	*1*	*(1.6)*	*0*	*(0.0)*
At least one overdose with paracetamol (plain and combinations), n (%)	**58**	**(95.1)**	**0**	**(0.0)**
At least one non-intentional overdose	27	(44.3)	0	(0.0)
At least one intentional overdose	31	(50.8)	0	(0.0)

Table 2 : Other most frequent drug exposures (within 30 days before ID) of ALFT cases without identified clinical cause

	Acute drug overdose n = 61		Exposed to drugs n = 15	
At least one exposure, n (%)				
Anxiolytics	28	(45.9)	2	(13.3)
Antidepressants	14	(23.0)	1	(6.7)
Opioids	12	(19.7)	0	(0.0)
Antiepileptics	11	(18.0)	1	(6.7)
Antipsychotics	9	(14.8)	0	(0.0)
Hypnotics and sedatives	9	(14.8)	0	(0.0)
NSAID	7	(11.5)	2	(13.3)
Ketoprofen	*6*	*(9.8)*	*0*	*(0.0)*
Ibuprofen	*1*	*(1.6)*	*1*	*(6.7)*
Diclofenac, combinations	*0*	*(0.0)*	*1*	*(6.7)*
Muscle relaxants, centrally acting agents	***2***	***(3.3)***	***0***	***(0.0)***
Tetrazepam	*2*	*(3.3)*	*0*	*(0.0)*

ALFT without identified clinical cause: incidence rates (IR)

- The IR of ALFT [95% CI] for non-overdose paracetamol (at therapeutic dose) was 0.09 [0.03; 0.21] case per million patient-years, 0.57 [0.39; 0.81] when non-intentional paracetamol overdoses were included and **1.13 [0.87; 1.45] cases per million patient-years when all paracetamol exposures were considered** (therapeutic doses, intentional and non-intentional overdoses) (*Table 3*).
- High IR of ALFT were observed for tuberculosis treatment, direct acting antivirals and acetylsalicylic acid (15.5 [0.47; 86.6], 0.81 [0.10; 2.94] and 0.77 [0.02; 4.32] cases per million patients-years, resp.).

Table 3 : ALFT incidence rates in drug-exposed patients "without identified clinical cause" (30-day exposure window) over 2015-2016

Drug	Nb of cases exposed to drugs	Nb of DDD of drug (extrapolation)	Nb of patients exposed to drug (extrapolation)	Nb of patient-years exposed to drugs (extrapolation)	Case per billion DDD (for 2 years) [95% CI] [1]	Case per million patients (for 2 years) [95% CI] [1]	Case per million patient-years [95% CI] [1]
Paracetamol (plain and combinations) (at therapeutic dose)	5	2 498 282 411	36 137 433	55 752 141	2.00 [0.65; 4.67]	0.14 [0.04; 0.32]	0.09 [0.03; 0.21]
Paracetamol (plain and combinations) * (with non-intentional overdoses)	32	2 498 282 411	36 137 433	55 752 141	12.81 [8.76; 18.08]	0.89 [0.61; 1.25]	0.57 [0.39; 0.81]
Paracetamol (plain and combinations) * (with intentional or non-intentional overdoses)	63	2 498 282 411	36 137 433	55 752 141	25.22 [19.38; 32.26]	1.74 [1.34; 2.23]	1.13 [0.87; 1.45]
Paracetamol alone	5	1 780 302 000	34 050 488	51 194 175	2.81 [0.91; 6.56]	0.15 [0.05; 0.34]	0.10 [0.03; 0.23]
Acetylsalicylic acid	1	16 838 099	1 149 345	1 290 668	59.39 [1.78; 330.80]	0.87 [0.03; 4.85]	0.77 [0.02; 4.32]
Beta-lactam antibacterials, penicillins	3	663 654 391	19 222 656	23 777 700	4.52 [0.93; 13.21]	0.16 [0.03; 0.46]	0.13 [0.03; 0.37]
Drugs for peptic ulcer and gastro-oesophageal reflux disease	2	3 006 081 268	19 517 382	27 895 428	0.67 [0.08; 2.41]	0.10 [0.01; 0.37]	0.07 [0.00; 0.26]
Lipid modifying agents, plain	2	3 587 223 326	7 322 942	12 951 303	0.56 [0.07; 2.02]	0.27 [0.03; 0.99]	0.15 [0.02; 0.56]
Direct acting antivirals	2	135 871 579	2 029 869	2 463 344	14.72 [1.77; 53.21]	0.99 [0.12; 3.56]	0.81 [0.10; 2.94]
NSAID	2	1 186 037 176	25 753 376	35 278 647	1.69 [0.20; 6.10]	0.08 [0.00; 0.28]	0.06 [0.00; 0.20]
Anxiolytics	2	1 807 931 443	10 905 287	15 239 767	1.11 [0.13; 4.00]	0.18 [0.02; 0.66]	0.13 [0.00; 0.47]
Treatment for tuberculosis	1	6 293 300	60 148	64 268	158.90 [4.77; 885.07]	16.63 [0.50; 92.60]	15.56 [0.47; 86.67]
Antiepileptics	1	610 895 943	2 536 825	3 684 374	1.64 [0.05; 9.12]	0.39 [0.01; 2.20]	0.27 [0.00; 1.51]
Antidepressants	1	1 989 367 566	6 136 744	9 329 569	0.50 [0.02; 2.80]	0.16 [0.00; 0.91]	0.11 [0.00; 0.60]

* Plain and combinations (N02BE01+N02BE51+N02BE71+N02AA59+N02AX52+R01BA52)
[1] Poisson 95% CI

Conclusion

- The SALT-III study confirmed ALFT in drug-exposed patients is a rare but important event.
- **Paracetamol exposure at therapeutic doses or at overdose** is still the **almost exclusive drug cause for liver transplantation.** It has increased in France since SALT-I/SALT-II studies (periods 2005-2007; 2008-2013).
- The **high IR of ALFT** for cases exposed to **treatment for tuberculosis** and **direct acting antivirals** observed in SALT-III were also found in SALT-II and need to be evaluated in complementary data analyses (pooled analysis of SALTI/SALT/II/ SALTIII studies).

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