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

Dominique Larrey[1,2], Lucy Meunier[1], Georges-Philippe Pageaux[1], Séverine Lignot-Maleyran[3], Sophie Micon[3], Simon Lorrain[3], Régis Lassalle[3], Cécile Droz-Perroteau[3], Nicholas Moore[3]

[1] Hôpital Saint Eloi, Liver Unit, Montpellier (France)
[2] IRB INSERM 1183
[3] Bordeaux PharmacoEpi, INSERM CIC1401, Université de Bordeaux - Bordeaux (France)

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INTRODUCTION

Acute Liver Failure leading to liver Transplantation (ALFT) indication is largely related to drugs (DILI), as shown by our previous SALT-I (2005-2007) and SALT-II (2008-2013) retrospective multicentre studies and the American DILI network. The main objective of SALT-I concerned only the risks associated with NSAIDs. SALT-II, extended the study period to 2008-2013, thus increasing its power and extended the risk calculation to all drugs. SALT-III, takes advantage of this network of liver transplantation centers to allow for better and more systematic ascertainment of drug exposures.

AIM

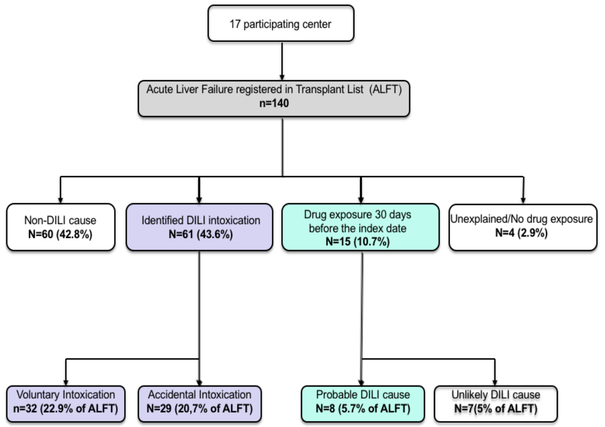
SALT-III study is aimed to estimate the evolution of the risk of DILI-induced ALFT in France in 2015-2016 : to compute event rates for drugs of interest from the exposure data provided by the national healthcare insurance system.

METHOD

- Multicentre, case-population study focused on adults patients registered on transplant list for ALF over 2 years (2015-2016) in France.
- Data are collected in 17 liver transplant centers.
- Cases are classified in 2 groups: ALFT "with identified non-DILI cause" (viral, autoimmune hepatitis) and 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) is investigated for all cases, whatever the cause of ALFT.
- The risk of drug-exposed ALFT, expressed as rate per million treatment-years, will be calculated using reimbursement data of EGB (permanent random sample of the national healthcare insurance system database). The results will be available in April 2018.
- The role of drug has been assessed according to recent causality international assessment method : Roussell Uclaf Causality Assessment Method (RUCAM) and the DILIN expert method.

RESULTS

Result 1: Patient disposition in the SALT III study



17 centers included 140 patients. All cases were reviewed by a group of hepatologists to determine the cause of ALFT.

Result 2: Indication of liver transplantation for acute liver failure in the 140 included patients

Non drug-related causes	**60 (42.8%)**
- Autoimmune hepatitis	15 (10.7%)
- Hepatitis B	12 (8.6%)
- Other virus	4 (2.8%)
- Alcoholic hepatitis	7 (5.0%)
- Mushrooms	4 (2.8%)
- Vascular liver injury	13 (9.3%)
- Other causes	5 (3.6%)
Drug exposures *(Intoxication/probable-DILI cause)*	**69 (49.3%)**
Paracetamol	59 (42.1%)
- Voluntary intoxication	32 (22.8%)
- Accidental intoxication	27 (19.3%)
Others drugs	8 (5.7%)
Illegal compounds	2 (1.4%)
Unexplained causes *(No drug/unlikely-DILI cause)*	**11 (7.8%)**

The cause of liver injury leading to the indication of liver transplantation was analyzed and classified into 3 groups: drug-induced, non drug-induced and unexplained. This last category including cases without any drug exposure and cases with drug exposure where causality assessment « unlikely ».

Result 3: List of drugs with causality classified from probable to definite (n=69 cases)

Drugs	Cases (n)
Paracetamol	59
Ecstasy/Cocaine	2
Atorvastatin	1
Amoxicillin/clavulanic acid	2
Amoxicillin/josamycin	1
Cefotaxim	1
Anti-tuberculous	1
Antiepileptics	1
Chemotherapy	1

Result 4: Characteristics of the 80 ALFT cases according to drug exposure in the 30 days prior to index date for the years 2015 to 2016

	Acute drug intoxication n = 61	Exposed to drugs n = 15	Not exposed to drugs n = 4	Total n = 80
Gender, n (%)				
Male	26 (42.6)	3 (20.0)	2 (50.0)	31 (38.8)
Female	35 (57.4)	12 (80.0)	2 (50.0)	49 (61.3)
Age at registration in transplant list (in years)				
Size (missing)	61 (0)	15 (0)	4 (0)	80 (0)
Mean (± SD)	39.1 (10.7)	46.8 (12.5)	40.0 (13.6)	40.6 (11.5)
Median	37.0	46.0	35.0	38.5
[p25% - p75%]	[31.0;46.0]	[38.0;52.0]	[31.5;48.5]	[32.0;48.0]
[Min - Max]	[21.0;66.0]	[25.0;70.0]	[30.0;60.0]	[21.0;70.0]
Age at registration on transplant list (in categories), n (%)				
[18 - 30[years	12 (19.7)	1 (6.7)	0 (0.0)	13 (16.3)
[30 - 40[years	21 (34.4)	4 (26.7)	3 (75.0)	28 (35.0)
[40 - 50[years	18 (29.5)	4 (26.7)	0 (0.0)	22 (27.5)
[50 - 60[years	7 (11.5)	4 (26.7)	0 (0.0)	11 (13.8)
[60 - 70[years	3 (4.9)	0 (0.0)	1 (25.0)	4 (5.0)
[70 - 80[years	0 (0.0)	2 (13.3)	0 (0.0)	2 (2.5)
Transplanted, n (%)	28 (45.9)	10 (66.7)	3 (75.0)	41 (51.3)
Year of registration in transplant list, n (%)				
2015	33 (54.1)	8 (53.3)	0 (0.0)	41 (51.3)
2016	28 (45.9)	7 (46.7)	4 (100.0)	39 (48.8)

CONCLUSIONS

- In France, over the years 2015-2016, paracetamol is the first cause of ALFT. It's role is increasing compared to previous SALT I and II studies with a significant proportion of accidental counterpart.
- Idiosyncratic DILI account for 5.7 % of ALFT.
- Unexplained cause accounted for 7.8 % of ALFT.

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REFERENCES

1. Danan G, Benichou C. Causality assessment of adverse reactions to drugs--I. A novel method based on the conclusions of international consensus meetings: application to drug-induced liver injuries. J Clin Epidemiol. 1993 Nov;46(11):1323–30.
2. Fontana RJ, Watkins PB, Bonkovsky HL, Chalasani N, Davern T, Serrano J, et al. Drug-Induced Liver Injury Network (DILIN) prospective study: rationale, design and conduct. Drug Saf. 2009;32(1):55–68
3. Gulmez SE, Moore N, Pageaux G-P, Lignot S, Horsmans Y, Stricker B, Bernuau J, Bissoli F, Thorburn D, Montastruc JL, Micon S, Hamoud F, Lassalle R, Jové J, Blin P, Larrey D. Causality of Drugs Involved in Acute Liver Failure Leading to Transplantation: Results from the Study of Acute Liver Transplant (SALT). Drug Saf. 2013; 36:757–64.

CONTACT INFORMATION

dom-larrey@chu-montpellier.fr