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ORIGINAL RESEARCH ARTICLE

Causality of Drugs Involved in Acute Liver Failure Leading to Transplantation: Results from the Study of Acute Liver Transplant (SALT)

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Abstract

Background Several methods have been proposed to assess causality in drug-induced liver injury but none have been tested in the specific context of acute liver failure leading to transplantation (ALFT).

Objective We took advantage of the Study of Acute Liver Transplant (SALT), a European case-population study of ALFT, to test different causality scales.

Methods Causality was assessed by experts in SALT, a 7-country case-population study from 2005 to 2007 of adult otherwise unexplained ALFT, for all drugs found within 30 days prior to the date of initial symptoms of liver disease (index date), using information content, causality scales, and data circuit determined from a pilot study, Salome.

Results The consensus points from Salome were to provide full data on drugs including international non-proprietary name (INN) and doses except for non-steroidal anti-inflammatory drugs (NSAIDs) and to use the World Health Organization (WHO) causality scale. In SALT, among the 9,479 identified patients, 600 (6.3 %) were cases of ALFT, of which 187 had been exposed to drugs within 30 days, without overdose. In 130 (69.5 %) of these the causality score was possible, probable, or highly probable.

Conclusion In ALFT cases, once other clinical causes have been excluded and drug exposure established within 30 days, the main discriminant characteristic for causality will be previous knowledge of possible hepatotoxicity.

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1 Background

Assessment of causality in drug-induced liver disease is a challenge. Several methods have been developed for causality assessment, such as Morges 9 points of consideration, the European ABO systems, probability calculation (Bayes' theorem) [1], French imputation systems [2, 3], the Naranjo ADR probability scale [4], and the World Health Organization (WHO) causality categories (http://who-umc.org/Graphics/24734.pdf, accessed 15 May 2012). Most are non-specific [1, 5, 6]. Others, such as the Roussel Uclaf Causality Assessment Method (RUCAM), have criteria that are specifically adapted to hepatotoxicity [2, 7]. Causality relies on the duration of drug exposure, the effect of dechallenge and possibly rechallenge, on the existence of specific biological or clinical markers, and the exclusion or not of other potential causes, as well as previous knowledge of potential hepatotoxicity of the suspect drug(s). In the case of severe acute liver failure leading to transplantation (ALFT), a number of these elements will be missing, mostly dechallenge and rechallenge (or re-exposure). Furthermore, if causes other than drugs are excluded, in fact the cases become cases of otherwise unexplained ALF exposed to medication before the onset of the liver disease, and knowledge of prior hepatotoxicity may be acquired before other elements. Causality methods have not been formally tested in ALFT, and we therefore sought to explore the performance and usefulness of different causality methods under these circumstances, taking advantage of the Study of Acute Liver Transplant (SALT) [8–10]. The main study was preceded by a pilot study, Salome, testing different data presentation options for drugs and choice of methods to be applied to the main SALT study.

2 Methods

2.1 SALT

The methodology and the principal results of the main SALT are described elsewhere [8–11]. Briefly, the SALT was a multicenter case-population study conducted in seven European countries, namely France, Greece, Ireland, Italy, Netherlands, Portugal, and the UK. For ALFT cases, symptoms and dates, laboratory results, drug exposure history, and concomitant factors and diseases were anonymized and extracted. ALFT cases were classified as with or without an identified clinical cause (i.e., viral, ischemic, or autoimmune hepatitis). Cases without identified clinical cause were divided into exposed or not exposed to drugs within 30 days prior to index date (ID, date of onset of liver disease, clinical or laboratory). This exposure window included the last alleged ingestion of the drug of interest. Sensitivity analyses also tested other exposure windows from 7 to 90 days. Drug-exposed cases were further classified into (1) acute drug overdose (with or without suicidal intent); (2) exposed to NSAIDs; (3) exposed to drugs other than NSAIDs. Cases were reviewed and validated by a national case classification hepatologist, who defined the ID and wrote a case abstract for all drug-exposed ALFTs.

2.2 Salome Pilot Study

The aim of the Salome pilot study was to understand the variability in the causality classification depending on the level of blinded/disclosed case information. Six of the eight members of the independent international case adjudication committee (CAC), composed of hepatologists and pharmacoepidemiologists, participated in Salome; the French coordinator was excluded as he validated the cases, and one CAC member did not participate. The first 30 drug-exposed cases of ALFT identified from the French arm of the SALT were chosen and validated by the French coordinator. These 30 cases were then submitted to the six participating CAC members. A case adjudication form (CAF) was used, which included chronological and clinical criteria. Chronological criteria were the interval between start of treatment and onset of liver disease as defined by the national coordinator, regression of liver abnormalities after the withdrawal of the treatment, and relapse of abnormalities after re-challenge. Clinical criteria included viral status, if age greater than 50 years old, intake of many drugs, intake of a hepatotoxic agent, analyses of autoantibodies, drug analysis in blood, and liver biopsy.

The CAF included three causality scales: the WHO-UMC causality assessment system [1, 5], the RUCAM [2, 3, 7], and the Venulet scale [6].

Each case was sequentially assessed three times with increasing levels of details: At level 1, all drug names were blinded as A, B, C…; doses were stated as "therapeutic", "overdose", or "not known". At level 2, information from assessment 1 was provided together with therapeutic classes of the drugs [12]. Finally at level 3, information from assessment 2 was provided with full drug data except for NSAIDs, which were always kept blinded as "NSAID".

After all these assessments were completed, the data flow among the CAC members who participated to Salome was simulated in accordance with the SALT protocol: Four of the experts were randomly selected. For each of the 30 cases, the concordance of the four experts was evaluated. If three or four were convergent, the causality assessment of the drug was retained. If more than two gave diverging assessments, then this case was evaluated by the remaining experts. If the other experts' opinions diverged, a meeting of all experts would be called to reach a consensual

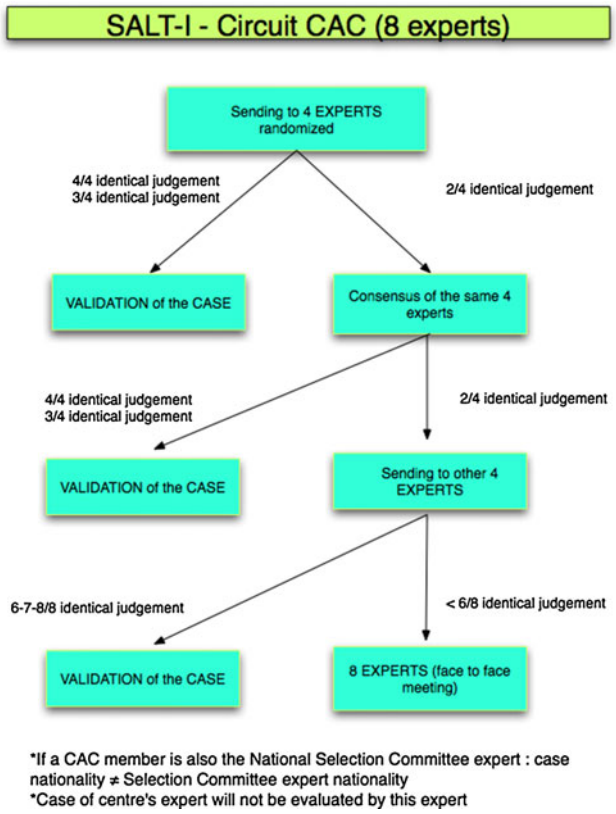

Fig. 1 Case circuit among the case adjudication committee experts

causality assessment. Figure 1 shows the case circuit among the eight experts of the CAC for the main SALT study.

2.2.1 *Statistical Analysis*

The total number of assessments for all drugs assessed in all three steps by all experts was summed. The concordance between the scales was tested.

2.3 Causality Analysis in SALT

All cases of drug-exposed ALFT in the SALT, irrespective of NSAID exposure, were assessed for causality by the CAC members (Fig. 1) in accordance with the consensus results of the Salome pilot study. The CAF used for the SALT included chronological and clinical criteria and only the WHO scale (Annex 1 in the Electronic Supplementary Material, ESM). In addition to the causality scales, the CAC experts were requested to assess the causality for individual drugs using a visual analogue scale (VAS) that ranged from "0—not at all involved in ALF" to "100—totally causal in the occurrence of the case". The CAC assessed the quality of documentation by another VAS that ranged from "0—no relevant data in the report" to "100—all data present and complete" [13–16]. Visual scales were used because they are a standard metric for global introspection and expert opinion.

2.3.1 *Statistical Analysis*

Demographic characteristics were sorted out for drug-exposed cases of ALFT (NSAID-exposed, paracetamol-exposed [acetaminophen-exposed], and non-overdose [NSAID-exposed or non-NSAID-exposed]) with causality scores from "possible" to "highly probable". The total number of assessments for all drugs assessed in all three steps by all experts was summed. Mean VAS scores were calculated both for causality assessment of drugs and quality of documentation.

3 Results

3.1 Salome Pilot Study

Overall, there were 429 assessments for 30 drug-exposed cases of ALFT completed at all three information levels. The WHO causality scale was completed for 97.4 % of these, RUCAM for 32.6 %, and the Venulet scale for 96.3 %. The RUCAM scale could not be completed in two-thirds of the cases (67.4 %) and the final scores could not be calculated. The experts judged that in most cases, the data elements necessary to complete the RUCAM were not present or not relevant, especially concerning outcomes, so that in effect the RUCAM was found to be not applicable to ALFT cases.

The completion rate reached 96.3 % for Venulet's scale. However, only the final causality decision part was fully completed, not the scores, so that the conclusions based on the Venulet scale were used only as a global scale.

WHO causality classifications by level of assessment and the WHO causality classification by level for all drugs evaluated at all three levels of drug information are presented in Table 1. As the amount of drug information increased, the certainty of the causality assessment increased. From the first information level to the second, there were 161 (37.5 %) changes. For 70 (43.5 %) the causality level decreased, whereas for 91 (56.5 %) it increased. From the second level to the third, there were 179 (41.7 %) changes; for 70 (39.1 %) the causality level decreased, whereas for 109 (60.9 %) increased. Mean VAS for each level was calculated as 5.2/10, 6.0/10, and 6.7/10 for information levels 1, 2, and 3, respectively. The concordance of causality assessments by two scales, WHO and Venulet, was compared at each information level (Table 2). However, only the final causality decision part of the Venulet scores was compared, as most experts did not complete the whole scale.

Table 1 WHO causality classifications by level of assessment in Salome pilot study

WHO classification	Level 1 ($n = 489$) *n* (%)	Level 2 ($n = 488$) *n* (%)	Level 3 ($n = 441$) *n* (%)
Non-assessable	118 (24.1)	86 (17.7)	35 (8.0)
Unrelated	15 (3.1)	28 (5.7)	50 (11.3)
Unlikely	89 (18.2)	131 (26.8)	142 (32.2)
Possible	251 (51.3)	200 (41.0)	154 (34.9)
Probable/likely	16 (3.3)	42 (8.6)	46 (10.4)
Highly probable/certain	0 (0.0)	1 (0.2)	14 (3.2)

Level 1 drug name blinded, dose as therapeutic, overdose, unknown; *Level 2* level 1 + therapeutic class; *Level 3* level 2 + full drug information; *WHO* World Health Organization

Table 2 Concordance between the WHO and Venulet scales in Salome pilot study

	Level 1 *n* (%)	Level 2 *n* (%)	Level 3 *n* (%)
Concordance	389 (90.7)	400 (93.2)	392 (91.4)
No concordance	5 (1.2)	11 (2.6)	14 (3.3)

The results of the Salome pilot study were evaluated and discussed during a face-to-face meeting of all CAC experts. The consensus points applied to the SALT were (1) having full data on drugs including international non-proprietary name (INN) and doses except for NSAIDs (level 3), (2) using the WHO causality scale, (3) applying the case circuit among the experts simulated in Salome. The CAC experts also agreed to merge WHO causality levels for the final causality score analyses for SALT—unrelated with unlikely, and probable with highly probable—thus leaving three levels of causality: unrelated/unlikely, possible, and probable/highly probable, in addition to not assessable.

3.2 SALT

The consensus points of Salome listed above were applied to the causality assessments of drugs identified in the main SALT.

Fifty-two liver transplant centers contributed 9,479 patients; 600 (6.3 %) were cases of ALFT of which 301 had been exposed to drugs, with no other identifiable clinical cause. A total of 187 had been exposed to drugs within 30 days without overdose, and 114 were acute drug overdose (Fig. 2). Demographics of these cases with causality scores possible, probable, or highly probable were not different from the demographics of the whole population [10].

Forty ALFT cases were identified as exposed to at least one NSAID within 30 days prior to ID, resulting in a total of 43 NSAID exposures. Thirty-three of these exposures were judged possible, probable, or highly probable. The causality score was possible in 32 of 33 exposures; in only one case, involving etodolac, was the causality found to be probable (Table 3). Sixteen of the 31 cases exposed to NSAIDs were also exposed to paracetamol, 13 of which had paracetamol causality scores possible, probable, or highly probable.

Among the 187 non-overdose, drug-exposed cases (including those exposed to NSAIDs), in 130 (69.5 %) the causality score was possible, probable, or highly probable. Of these, 53 (40.7 %) were with non-overdose paracetamol. Among the 164 paracetamol-exposed cases of ALF with causality score possible, probable, or highly probable, 111 (97.3 %) were paracetamol overdoses.

All 111 overdoses with causality scores possible, probable, or highly probable (out of 114 cases of acute drug overdose) were attributed to paracetamol.

Mean VAS values for causality for the 33 exposures to NSAIDs (corresponding to 31 ALFT cases) with causality score possible, probable, or highly probable are presented in Table 3. Mean VAS values for the non-NSAID-exposed cases (114 cases, 213 non-NSAID drugs) are shown in Table 4. They ranged from 50 to 70 for the same final WHO causality score possible. Mean VAS values for completeness of documentation for non-NSAID-exposed ALFT cases ranged from 37.3 to 77.

Individual causality for all non-NSAID drugs found in the SALT is also provided as Annex 2 in the ESM.

4 Discussion

Case causality assessment evaluates the relationship between drug use and the event, to find out particularly whether a drug seems likely to have caused the event and the strength of the possible relationship between the drug and the event. Causality assessments classify uncertainty, mark individual case reports, and improve the scientific basis of assessment. On the other hand, they neither eliminate nor quantify uncertainty. They cannot give quantitative measurement of the likelihood of a relationship or distinguish valid from invalid cases or quantify the contribution of a drug to the development of an adverse event or change the uncertainty to certainty. Causality assessments can seldom prove that a specific drug caused a specific reaction.

In the case of severe hepatotoxicity leading to transplantation, especially dechallenge and rechallenge (or re-exposure) will be missing and therefore causality is

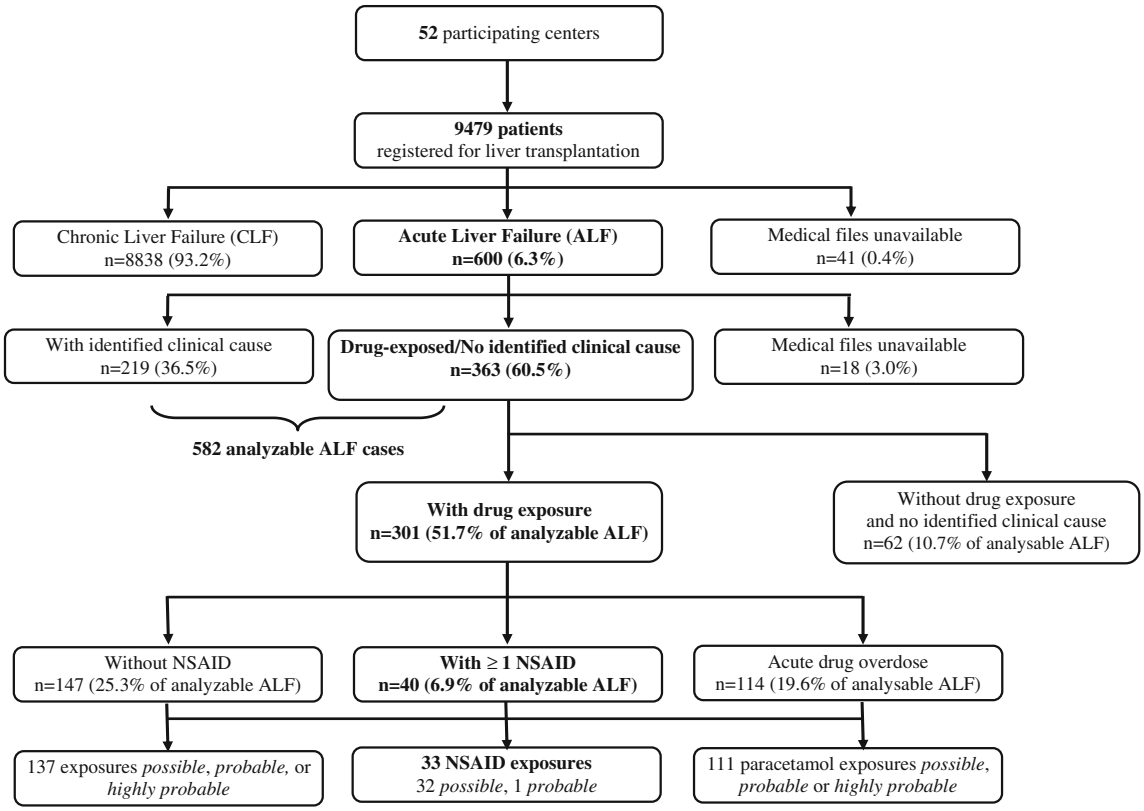

Fig. 2 Final case inclusion in seven participating countries over a 3-year period [adapted from the previous publication (Drug Saf. 2013 Feb;36(2):135–44. doi:10.1007/s40264-012-0013-7)]

difficult to assess. There has been no systematic evaluation of causality methods in these circumstances.

The US Food and Drug Administration (FDA) has provided a guideline about causality assessment with correlation of likelihood (e.g., probable, greater than 50 %; possible, 25–50 %; and unlikely, less than 25 %) [17]. This is consistent with our VAS findings. All cases classified as possible had a VAS value above 25, and the vast majority above 50 out of a maximum 100.

The Salome pilot study was done to define the level of information blinding for causality assessment and the causality scale to be used, to define the effect of drug name blinding on causality assessment at different levels, and to define the case circuit between the CAC experts for the SALT. Following Salome, the CAC experts wished to have full data on drugs including INN and doses, except for NSAIDs. The WHO causality scale was agreed to be the most appropriate scale for causality assessment considering a pragmatic approach of cases with unavailable data, related to the nature of the cases.

These consensus points were applied to causality assessments of the cases in the main SALT. There were no significant differences between decisions of the assessments at Salome level 2 and 3 for causality scores unlikely, possible, or probable/likely. However, at level 2 paracetamol was not kept blinded, which probably changed the certainty for causality scores non-assessable and highly probable/certain.

The three causality methods or scales used in Salome have different characteristics, which explain their performances in this context. These are cases where essentially all non-drug causes have been excluded, and for which there is no assessable dechallenge, because the target organ has been replaced in most cases. In addition the challenge is represented by the presence of the drug within 30 days before the first symptoms of the liver disease, which is a compatible time sequence in all methods. The main differentiation criterion will therefore be related to the pre-existing knowledge about the drug's hepatotoxicity from the literature. This allowed us to highlight the different philosophies between the methods: the WHO approach is based on global assessment of combined criteria, whereas the Venulet and RUCAM methods are based on the identification and scoring of individual information items. In both this results in a numeric score, which is then translated to a lexical appreciation. The Venulet scale uses the same terminology as the WHO method for this global final appreciation, whereas RUCAM tends to keep the numeric

Table 3 Mean values of visual analogue scale values based on the causality for the 33 exposures to NSAIDs within 30 days prior to the index date (31 ALFT cases) with causality score possible, probable, or highly probable

NSAID	Final WHO causality score	Mean VAS for causality of NSAID	Mean VAS for completeness of documentation
Celecoxib	Possible	NA	NA
Diclofenac	Possible	NA	NA
	Possible	62.50	51.00
	Possible	51.50	49.67
Etodolac	Possible	59.00	51.00
	Probable	NA	NA
Ibuprofen	Possible	61.67	49.75
	Possible	66.33	70.75
	Possible	NA	NA
	Possible	61.50	65.00
	Possible	67.00	72.67
	Possible	NA	NA
	Possible	NA	NA
	Possible	67.25	57.00
	Possible	58.67	51.33
Indometacin	Possible	67.50	64.50
Ketoprofen	Possible	60.00	45.5
	Possible	72.67	71.67
Ketorolac	Possible	58.00	50.33
	Possible	66.00	NA
Naproxen	Possible	57.67	71.50
	Possible	63.67	61.25
Niflumic acid	Possible	65.50	75.00
Nimesulide	Possible	63.50	59.75
	Possible	77.00	66.75
	Possible	75.00	61.33
	Possible	66.00	49.00
	Possible	68.50	NA
	Possible	68.00	57.00
	Possible	70.00	59.67
NSAID (unknown INN)	Possible	63.00	62.00
	Possible	NA	NA
	Possible	NA	NA

NA not available, *WHO* World Health Organization, *VAS* visual analogue scale, *NSAID* non-steroidal anti-inflammatory drug, *INN* international non-propriety name

scale. Because of the specific nature of the events, as described above, a number of the items are either trivial (e.g., other causes, because this has been excluded by the very nature of the study and the case selection process) or not available (such as dechallenge or rechallenge, neither of which can be present in this context). It is therefore not surprising that the experts opted for the preferential use of the WHO scale, just as they only used the final lexical classification of Venulet, without trying to fill the score, and they just dropped RUCAM as being useless in the context, even though it remains the reference method for less severe hepatotoxicity except in clinical trials [18]. Because the data were mostly the same for all drugs, and the experts did not know the names of the NSAIDs, they were all judged as being possible, especially because the experts knew they were NSAIDS, and all NSAIDs have been associated with cases of hepatotoxicity. For the other drugs, it is interesting to note that with the same intrinsic information, i.e., presence within 30 days before the first symptoms, no dechallenge, no rechallenge, no other non-drug cause, that can only result in a "possible" imputability, a number of drugs were judged as having an "unrelated" causality, and others a possible or probable causality. Causality in this situation can only be related to extrinsic information, i.e., the knowledge of the hepatotoxicity of one or other of the drugs in a case. As soon as one drug in a case was judged possible or probable, the others were considered unrelated or unlikely, especially if there was no prior knowledge of a hepatotoxic risk. In some way this is may be akin to Bayesian analysis, where in the absence of new information it is the prior odds (i.e., what is known of the drug's risks) that give the final result.

Such preconception of attributable risk is also known as the "Casablanca syndrome" ("round up the usual suspects"). This is why we chose to mask the names of the NSAIDs, and judge the relative risks of the different drugs using epidemiological studies, where there is no assessment of individual cases.

The WHO method was meant as a practical tool for the assessment of case reports. It is basically a global assessment taking into account the clinical and pharmacological aspects of the case history and the quality of the documentation of the observation. There are six levels of causality, namely certain, probable/likely, possible, unlikely, conditional/unclassified/unrelated, non-assessable/unclassifiable, but our experts reduced this to three levels, namely probable, possible, and unlikely, underlining the difficulty of actually judging fine differences in causality, though this may be specific to the event judged here.

Because causality assessment in adverse drug reactions is always retrospective, one of the major issues is the quality and completeness of the available data used for causality assessment. Despite the usual thoroughness of the investigations in these patients, there were 18 ALFT cases out of 600 (3 %) ALFT for which information was not sufficient to determine whether or not they had been exposed to drugs and therefore were not considered by the CAC.

Table 4 Mean values of visual analogue scale based on final WHO causality scores for non-NSAID drugs exposed within 30 days prior to index date (213 non-NSAID drugs, 114 cases)

Mean VAS for causality of a drug (in groups), *n* (%)	Final WHO causality score			
	Possible, *n* (%)	Unlikely–possible, *n* (%)	Unrelated, *n* (%)	Unrelated–unlikely, *n* (%)
NA	27 (26.5)	1 (25.0)	31 (34.8)	1 (5.6)
0–10	0 (0.0)	0 (0.0)	52 (58.4)	8 (44.4)
10–20	0 (0.0)	0 (0.0)	5 (5.6)	8 (44.4)
30–40	1 (1.0)	0 (0.0)	1 (1.1)	1 (5.6)
40–50	5 (4.9)	2 (50.0)	0 (0.0)	0 (0.0)
50–60	23 (22.5)	1 (25.0)	0 (0.0)	0 (0.0)
60–70	41 (40.2)	0 (0.0)	0 (0.0)	0 (0.0)
≥70	5 (4.9)	0 (0.0)	0 (0.0)	0 (0.0)

NA not available, *WHO* World Health Organization, *VAS* visual analogue scale, *NSAID* non-steroidal anti-inflammatory drug

5 Conclusion

This study confirms that in cases of acute liver failure resulting in registration for liver transplantation, causality assessment does not really contribute to the differential evaluation of drug risks. The main differentiating characteristic for drugs used within the 30 days preceding the reaction onset was the previous knowledge of possible hepatotoxicity. Purely epidemiological approaches, such as the case-population approach used in the SALT, seem to give more relevant results than a case-based approach using individual causality assessment of cases, which in addition is extremely labor-intensive.

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Contributorship statement Nicholas Moore and Dominique Larrey had the original idea for the study several years ago and proposed it to the sponsor and to the Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA). Nicholas Moore was the overall study supervisor, intervening when necessary for the smooth operation of the study. Dominique Larrey was chairman of the scientific committee and of the case adjudication committee (CAC) and was the everyday hepatology counsel for the study. George-Philippe Pageaux was the vice-chairman of the CAC and contributed enormously to case understanding and adjudication.

Sinem Ezgi Gulmez and Séverine Lignot were the scientific and operational study coordinators, devising the initial document generation under the control of the scientific committee, organizing negotiations with transplant centers, study data retrieval, writing the study reports and draft article, and verifying all contents. The study coordination team also included Sophie Micon and Fatima Hamoud, who coordinated the scientific and CAC activities. Régis Lassalle and Jérémy Jove provided data management and statistical analyses. Patrick Blin was the study epidemiological overseer, contributing to study design, operations, analysis, and understanding. Jacques Bernuau, Franco Bissoli, Yves Horsmans, Jean-Louis Montastruc, Bruno Stricker, and Douglas Thorburn were members of the CAC and performed causality assessments.

All authors contributed comments on the final version of this paper.

Exclusive licence statement Corresponding authors have completed and signed the copyright assessment.

Corresponding authors had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis, which was conducted independently from the financer.

Competing interest statement All authors have completed the unified competing interest form, and declared their competing interest if any. Dr Bruno Stricker has received travel reimbursements. Drs Yves Horsmans and Franco Bissoli have declared being consultants for Helsinn Pharmaceutical Company.

No specific conflict of interest is declared with regard to this study, by any of the authors, inasmuch as for a number of the authors who are employees of the University of Bordeaux, the University of Bordeaux received compensation as described below. Authors participating in the committees received compensation from the University of Bordeaux for the time spent on the committees.

A contributorship statement is included in the manuscript.

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The report of this study has been sent to the regulatory authorities and was presented to the CHMP on 17 May 2011.

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