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Review

Acute Liver Failure Due to Assumed Drug Induced Liver Injury but Lack of Any Validated Causality Algorithm: Evidence by 36 Cohort Reports with 21,709 Cases

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Abstract

Liver transplantation (LT) can be the only option for patients with acute liver failure (ALF) where medical approaches are ineffective. Causes of ALF are multiple and commonly easily detectable, but uncertainty remained on the role of drug-induced liver injury (DILI) within the published ALF cohorts. Therefore, an analysis was undertaken to clarify which drugs may have caused the DILI and how the diagnosis of the liver injury was established. Using the PubMed database and Google Science, the search term of acute liver failure combined with drugs provided 36 publications of ALF cohorts, which included 21,709 DILI cases. Whereas non-drug causes were detectable by specific diagnostic biomarkers, the diagnosis of DILI among the ALF cohorts was neglected, as evidenced by the lacking use of a validated diagnostic algorithm like the Roussel Uclaf Causality Assessment Method (RUCAM), best qualified to verify causality for individual drugs or combined drugs. This lack of firm diagnosis leads to a long list of drugs with highly questionable causality of suspected DILI, prevents calculation of incidence or prevalence data of DILI among ALF cohorts, and cannot help find an appropriate therapy for

selected cases of drug-induced autoimmune hepatitis (DIAIH) or overdosed N-acetyl-para-aminophenol (APAP) also known as paracetamol, aiming to prevent LT. Under discussion is also the high rate of indeterminate cases of up to 78% among the published cohorts, which confounds any quantitative approach in this setting. In conclusion, there is much room for improvement in future ALF cohorts, requiring the application of validated tools.

Keywords
Liver transplantation; acute liver failure; drug-induced liver injury; RUCAM; Roussel Uclaf Causality Assessment Method; indeterminate causes

1. Introduction

Liver transplantation (LT) is often the ultimate chance for patients with acute liver failure (ALF) where drug cessation and medical therapy have failed. Yet in 2024, reports on ALF were continuously published in Europe [1] and worldwide in countries including China [2], Germany [3], Greece [4], India [5, 6], Iran [7], Mexico [8], Pakistan [9], Spain [10], and the US [11, 12]. Information on LT and ALF focused on the clinical practice guidelines of the European Association for the Study of the Liver (EASL) [1] and mechanisms leading to ALF, the role of pyroptosis as a form of lytic programmed cell death, and the involvement of damage-associated molecular patterns (DAMPs) [2]. Other details were provided for the epidemiology and etiology [3], the artificial intelligence (AI) used for better outcomes [4], and prognostic models with a focus on management [5]. Promoted were consensus recommendations of the Indian Society of Pediatric Gastroenterology, Hepatology, and Nutrition (ISPGHAN) regarding the diagnosis and management of pediatric acute liver failure [6], the role of circulating lncRNAs HOTTIP and HOTAIR as potential biomarkers in ALF of Crigler-Najjar syndrome [7], and the management update and prognosis [8]. Discussions were expanded on the causes and clinical parameters in acute-on-chronic liver failure [9], a practical update on ALF [10], highlights from the American College of Gastroenterology (ACG) guidelines for acute liver failure [11], and the future of LT [12]. Limited interest was attributed to idiosyncratic drug-induced liver injury (iDILI), its incidence or prevalence, and how the diagnosis was established. For several decades, shortcomings were known for ALF as an outcome of patients with iDILI requiring a liver transplant, with major diagnostic issues of indeterminate causes and lacking validated causality assessment.

This review aims to analyze published reports on ALF cohorts due to DILI regarding causative drugs and the use of a robust, validated causality assessment that may help provide a firm characterization of clinical features and proposals for medical treatment to prevent LT.

2. Search Method and Terms

Using the PubMed database and Google Science, the search term of acute liver failure combined with drugs provided 36 publications of ALF cohorts, which included 21,709 DILI cases. They were analyzed through the use of a validated causality assessment.

3. DILI Types

By convention, two types of DILI are described: the idiosyncratic and the intrinsic one. Both forms traditionally lack overt immune features [13-15]. In addition to the non-immune idiosyncratic DILI (iDILI) form, four subtypes of iDILI were identified with auto-immune or immune characteristics found in four cohorts. Accordingly, the first two types refer to the idiosyncratic drug-induced autoimmune hepatitis (DIAIH) [16-21] to be differentiated from the classic drug-unrelated idiosyncratic autoimmune hepatitis (AIH) [22] and the human leucocyte antigen (HLA) based idiosyncratic drug-induced autoimmune hepatitis [23-26]. The third and fourth types consider the anti-cytochrome P450 (CYP) based idiosyncratic drug-induced autoimmune hepatitis [16, 18, 27-29] and the immune-based idiosyncratic drug-induced liver injury associated with Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) [1, 30-32]. Listed iDILI reports were all assessed for causality using the Roussel Uclaf Causality Assessment Method (RUCAM).

4. RUCAM

RUCAM was published in 1993 as a novel diagnostic algorithm method to assess causality in iDILI, resulting from international consensus meetings with participants known for their expertise in iDILI issues [33]. Among these experts were J. P. Benhamou (France), J. Bircher (Germany), G. Danan (France), W. C. Maddrey (USA), J. Neuberger (UK), F. Orlandi (Italy), N. Tygstrup (Denmark), and H. J. Zimmerman (USA) [33, 34]. Using iDILI cases with positive reexposure test results serving as a gold standard, RUCAM was well validated in the course of the internal validation process [34]. In 2016, the updated RUCAM was published, and it is now the preferred algorithm to assess iDILI [13]. International support of RUCAM came from external validation [35-39], including interrater reliability [35-37]. RUCAM represents a structured diagnostic algorithm for objective, standardized, and quantitative causality assessment in iDILI cases [13, 33] and is a means of assigning points for clinical, biochemical, reexposure, and serologic features and searching for non-drug causes. Summing up the individual scores derived from each key element provides final RUCAM causality gradings: score ≤0, excluded causality; 1–2, unlikely; 3–5, possible; 6–8, probable; and ≥9, highly probable, which reflects the likelihood that the hepatic injury is due to a specific medication [13, 33]. RUCAM is applied up to now throughout the world in almost 100,000 iDILI cases [40] and outperforms any other method [13, 16] concerning both method quality and case numbers [16]. Its high appreciation may be traced back to being user-friendly and cost-effective, with results available in time and without the need for expert rounds that commonly provide subjective and arbitrary opinions [13, 16]. RUCAM helps clarify epidemiology aspects related to iDILI [41, 42] and is, with its inventors and users, well, esteemed as outlined by a scientometric investigation [43].

5. Published Reports of Acute Liver Failure by Suspected DILI

There is little valid information on the percentage contribution of DILI cases among study cohorts that included instances of transplantation performed for ALF due to various causatives. Using the PubMed database and Google Science for the search terms of acute liver failure combined with drugs, abundant reports were provided. In addition to verified causatives of the ALF, in many case series, offending agents often remained unknown, making it difficult to give a firm percentage contribution of iDILI. Even worse, inhomogeneity among the study cohorts prevailed due to lumping

together iDILI with intrinsic DILI and conventional drugs with non-drugs such as herbal medicines, including traditional Chinese medicine (TCM). Drugs causing assumed DILI with ALF are listed (Table 1) [44-78].

Table 1 Compounds inducing suspected DILI among ALF cohorts.

Selected drugs implicated in suspected ALF due to DILI	DILI cases of ALF (n)	Validated causality assessment of DILI	References
APAP in overdose	310	NO	O'Grady, 1989 [44]
Halothane hepatitis	34		
Idiosyncratic drug reactions	11		
APAP	1	NO	Daas, 1995 [45]
Chlorzoxazone	1		
Halothane	1		
Naprosyn	1		
Phenytoin	1		
Unidentified drug	1		
APAP toxicity	34	NO	Shakil, 2000 [46]
Idiosyncratic DILI	21		
Anti-tuberculosis drugs	4	NO	Kato, 2001 [47]
5-Fluorouracil	2		
Halothane	2		
Amoxicillin	1		
APAP	1		
Mercazole	1		
APAP overdose	120	NO	Ostapowicz, 2002 [48]
Idiosyncratic drug reactions	40		
APAP	12	NO	Tessier, 2002 [49]
Isoniazid	2		
Salazopyrine	1		
Erythromycin	1		
Azithromycin	1		
Cyproterone	1		
Naproxen	1		
APAP poisoning	29	NO	Gow, 2004 [50]
APAP	47	NO	Wigg, 2005 [51]
DILI	19		
APAP	6	NO	Escorsell, 2007 [52]
Anti-tuberculosis drugs	13		
Anti-tuberculosis drugs	2	NO	Mudawi, 2007 [53]
APAP	117	NO	Wei, 2007 [54]
DILI	42		
Anti-tuberculosis drugs	2	NO	Dukauskiene, 2008 [55]
APAP	1		

Halothane	1		
Lamisil	1		
Trifluoperazine	1		
Drugs and toxins	44	NO	Bhatia, 2008 [56]
APAP	18	NO	Hadem, 2008 [57]
Phenprocoumon	7		
Other drugs	5		
Halothane	3		
APAP	532	NO	Lee, 2008 [58]
Anti-tuberculosis drugs	19		
Sulfonamides	10		
Phenytoin	7		
Disulfiram	4		
Troglitazone	4		
Propylthiouracil	4		
Bromfenac	4		
APAP	579	NO	Marudanayagam, 2009 [59]
Isoniazid	18		
Ecstasy	8		
Augmentin	2		
Carbamazepine	2		
Halothane	2		
Sulfasalazine	2		
Voltarol	2		
Amiodarone	1		
Azathioprine	1		
Antabus	1		
Clarithromycin	1		
Chlordiazepoxide	1		
Chloroquine	1		
Dothiepin	1		
Flucloxacillin	1		
Fluoxetine	1		
Glivec	1		
Norethisterone	1		
Omeprazole	1		
Orlistat	1		
Phenytoin	1		
Rifampicin	1		
Sulfasalazine	1		
Trimethoprim	1		
DILI	46	NO	Oketani, 2011 [60]
Aspirin	1	NO	Bariş, 2012 [61]
Diphenyl-hydantoin	1		

Indomethacin + Leflunomide	1		
Meronem + Isoniazid + Rifampin + Pyrazinamide	1		
APAP	536	NO	Germani, 2012 [62]
Other DILI	496		
APAP	787	NO	Lee, 2012 [63]
Other DILI	202		
DILI	12	NO	Mendizabal, 2014 [64]
APAP	0		
APAP	916	NO	Bernal, 2015 [65]
Other DILI	220		
Lamotrigine	5	NO	Kathemann, 2015 [66]
Amoxicillin			
APAP	858	NO	Donnelly, 2017 [67]
Other DILI	34		
APAP	0	NO	Moini, 2017 [68]
DILI	6		
APAP	3	NO	Somasekar, 2017 [69]
DILI	3		
APAP	45	NO	Ganger, 2018 [70]
Other DILI	24		
APAP	1115	NO	Tujios, 2018 [71]
Idiosyncratic DILI	261		
APAP	113	NO	Hey, 2019 [72]
Antibiotics	4		
Infliximab	2		
Chlorambucil	1		
Fenofibrate	1		
Moxonidine	1		
NSAIDs	1		
Anti-tuberculosis drugs	12	NO	Nabi 2019 [73]
APAP	8091	NO	Thanapirom, 2019 [74]
Anti-tuberculosis drugs	1873		
Anti-viral drugs	1235		
DILI	36	NO	Amoroso 2020 [75]
APAP	1	NO	Chiou, 2022 [76]
Co-trimoxazole	1		
DILI	82	NO	Patel, 2023 [77]
APAP	1261	NO	Stravitz, 2023 [78]
DILI	284		
APAP	652	NO	Amaris, 2024 [79]
DILI	325		

Abbreviations: APAP, N-acetyl-para-aminophenol, also known as paracetamol; DILI, Drug induced liver injury; NSAIDs, Non-steroidal anti-inflammatory drugs.

The current analysis of the 36 published ALF reports and DILI caused by 21,709 drugs and drug combinations as potential causes provides shortcomings (Table 1) [44-79]: (1) with respect to DILI used as term, the inhomogeneity of ALF study cohorts due to lumping iDILI together with intrinsic DILI cases, and if N-acetyl-para-aminophenol (APAP) syn paracetamol as an agent of intrinsic DILI is mentioned, it is often unclear whether DILI is caused by overdose (often) or as iDILI due to recommended dose; (2) it is questionable when a report entitled "Acute liver failure induced by idiosyncratic reaction to drugs" attributes ALF etiology to APAP that causes intrinsic DILI in 46% of the study cohort versus iDILI with a contribution of only 11% [72]; (3) included are also unspecified toxins [49, 56] that have nothing to do with DILI; (4) not listed in the Table 1 but in various reports were herbal products including herbal traditional Chinese Medicines (TCM) or herbal dietary supplements [7, 49, 58, 59], all of which can cause herb induced liver injury (HILI) rather than DILI; (5) the percentage contribution of ALF cases due to DILI among the ALF cohort remains clouded because high rates of unknown causes were found in all reports with values of up to 70% [74] or 78% [60]; even worse (6) the diagnosis of iDILI cases was not verified by using the RUCAM for individual or combined drugs implicated in DILI, ignoring the fact that many cases of suspected DILI were not due to drugs but must be attributed to alternative non-drug causes [80, 81]; (7) as the 36 reports considered ALF cases with respect on all potential causes, there are no specific data on how many patients with ALF due to DILI finally received a liver transplant or and/or died; (8) there was no stratification regarding non-immune iDILI, which corresponds only partially to steroid treatment, and DIAIH, which as autoimmune triggered disorder fully respond to steroid treatments preventing LT in most cases; and finally (9) due to the above mentioned shortcomings of case analysis there are no appropriate data available to define exact epidemiology figures of DILI among the ALF cohort focusing on incidence, which reflects the number of new cases of a given medical condition in a population within a specified period of time, while *prevalence* considers the proportion of a particular population found to be affected by a medical condition at a specific time.

6. Future Perspectives

Future cohort studies on patients with ALF requiring LT should include detailed information on iDILI to be different from intrinsic DILI due to overdosing APAP as opposed to iDILI due to APAP intake at regular doses. Essential is the mandatory use of RUCAM, now the updated RUCAM of 2016, to rule out any alternative causes of the liver injury that may confound the diagnosis of iDILI; Appreciated are reports that include data on natural course with complete remission, need of a LT, or death.

7. Conclusion

ALF cohorts commonly provide good data on causatives like hepatitis viruses through specific serum antibody and RNA measurements or genetic liver diseases such as Wilson disease or hemochromatosis through particular tests. Still, such careful analyses are largely missing when the question comes up whether the injury is caused by a drug. In these cases, the use of RUCAM helps establish the diagnosis of DILI and excludes alternative, non-drug causes commonly viewed as confounders in DILI cohorts. Established therapeutic approaches are available for patients with DIAIH where steroids are effectively applied for the immunology disruption and for patients with APAP overdose where N-acetylcysteine (NAC) is effectively applied. As a result, only an exact

diagnosis of DILI can provide appropriate medical therapy in selected cases with the chance of preventing the need for a LT or death.

Author Contributions

RT and AE developed the outline of this invited article; AE provided the literature and the draft of Table 1; RT wrote the first draft, which was edited by AE. All authors agreed to the final version to be submitted.

Competing Interests

None of the authors have a conflict of interest regarding this article.

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