Review

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Causality assessment methods in drug induced liver injury: Strengths and weaknesses

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Summary

Diagnosis of drug-induced liver injury (DILI) remains a challenge and eagerly awaits the development of reliable hepatotoxicity biomarkers. Several methods have been developed in order to facilitate hepatotoxicity causality assessments. These methods can be divided into three categories: (1) expert judgement, (2) probabilistic approaches, and (3) algorithms or scales. The last category is further divided into general and liver-specific scales.

The Council for International Organizations of Medical Sciences (CIOMS) scale, also referred to as the Roussel Uclaf Causality Assessment Method (RUCAM), although cumbersome and difficult to apply by physicians not acquainted with DILI, is used by many expert hepatologists, researchers, and regulatory authorities to assess the probability of suspected causal agents. However, several limitations of this scale have been brought to light, indicating that a number of adjustments are needed. This review is a detailed timely criticism to alert the readers of the limitations and give insight into what would be needed to improve the scale. Instructions on how to approach DILI diagnosis in practice are provided, using CIOMS as an aid to emphasize the topics to be addressed when assessing DILI cases.

Amendments of the CIOMS scale in the form of applying authoritative evidence-based criteria, a simplified scoring system and appropriate weighting given to individual parameters based on statistical evaluations with large databases will provide wider applicability in the clinical setting.

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Abbreviations: ADR, adverse drug reaction; ALT, alanine aminotransferase; ALP, alkaline phosphatase; DILI, drug induced idiosyncratic liver injury; CIOMS, council for international organizations of medical science; RUCAM, Roussel Uclaf Causality Assessment Method.

Introduction

Drug induced liver injury (DILI) is today a leading global health problem. Idiosyncratic DILI, together with acetaminophen overdose, rank as the first cause of acute liver failure in the US and Sweden and are the main reasons for postmarketing regulatory decisions, such as withdrawal of drugs from the market [1–3]. Almost any pharmaceutical or xenobiotic compound may induce liver injury, rendering the diagnosis of DILI a challenging task for health care professionals. In addition, robust DILI biomarkers specific and sensitive enough to distinguish DILI from other causes of liver injury are absent. The development of such biomarkers would not only facilitate DILI diagnosis, but would also enhance DILI research and human risk assessments.

Efforts to enhance the identification of adverse hepatic reactions and to obtain reliable information about the epidemiology and pathogenesis are being made worldwide. The Spanish DILI Registry, set up in 1994, is a multicenter collaborative network with a large database of prospectively recorded DILI cases [4]. The Drug Induced Liver Injury Network (DILIN) was established in the US in 2003 to conduct research into the causes of DILI, while DILIGEN is operating in England [5,6]. Collections of hepatotoxicity cases identified through pharmacovigilance systems have also been set up, such as the Swedish adverse drug reactions advisory committee (SADRAC) [7] and the EUDAGRENE project [8]. These collaborative networks provide opportunities to agree upon common definitions, diagnostic criteria, terminologies, and improvements in causality assessment.

This review presents a summary of the most commonly used causality assessment methods for adverse drug reactions (ADRs) focusing on their strengths and drawbacks in determining causality in potential DILI cases and give insight into what would be needed to improve the CIOMS scale. This review is also intended

to give the reader detailed instructions on how to approach the diagnosis of DILI in practice, using the CIOMS as a reminder of the topics that need to be addressed when approaching DILI cases.

Diagnosis of DILI

Prompt recognition of a culprit drug as the cause of liver injury is the most important aspect in hepatotoxicity management, since it appears to decrease the risk of progression to acute liver failure or chronic liver injury [9]. Several aspects of DILI complicate its diagnosis. Primarily, DILI may resemble any acute or chronic liver disease and the "signature" (consistent clinical, pathological, and latency presentations) for a given drug can vary. Secondly, there is currently no "gold standard" for DILI verification. The diagnosis, therefore, depends heavily on exclusion of other causes of liver injury with no end to possible exclusions that could be sought.

Key Points

- Until specific biomarkers for DILI become available the diagnosis relies on a systematic approach where chronology of drug administration and dechallenge with regard to the hepatic disease and careful exclusion of potential competing causes are crucial.
- It is unlikely that a single instrument would accommodate all forms of DILI presentation unless there is a dynamic weighting of the component variables.
- Among the available scoring methods for assessing DILI in clinical practice the CIOMS scale, although cumbersome and with flaws in intra- and interrater reliability, is currently the preferred method when approaching a suspicion of DILI. However, it does not substitute clinical judgment.
- Complex instructions, selection, and weighting of the criteria discrimination among concomitant drugs need to be addressed more adequately in the CIOMS scale. Likewise, liver biopsy findings and immunoallergic features should be incorporated in the scoring system.
- A future "tailored" computerised assessment scale that could incorporate information on known signatures, specific risk factors and authoritative evidence-based criteria for a given drug could be feasible through the analyses of current large databases of DILI patients.

Diagnosis of idiosyncratic DILI requires high levels of suspicion and is usually made after a retrospective review of the available data has been done. Evaluation of cases is not a homogeneous process due to work-up variabilities resulting from differences in clinical approaches and patient data availability. Polypharmacy and the presence of concomitant diseases can further impede DILI diagnosis. Gathering the necessary information at the time the illness is just unfolding improves the chances of accurate diagnosis and consequently patient outcome. A careful step-by-step approach to diagnosis is recommended (Fig. 1).

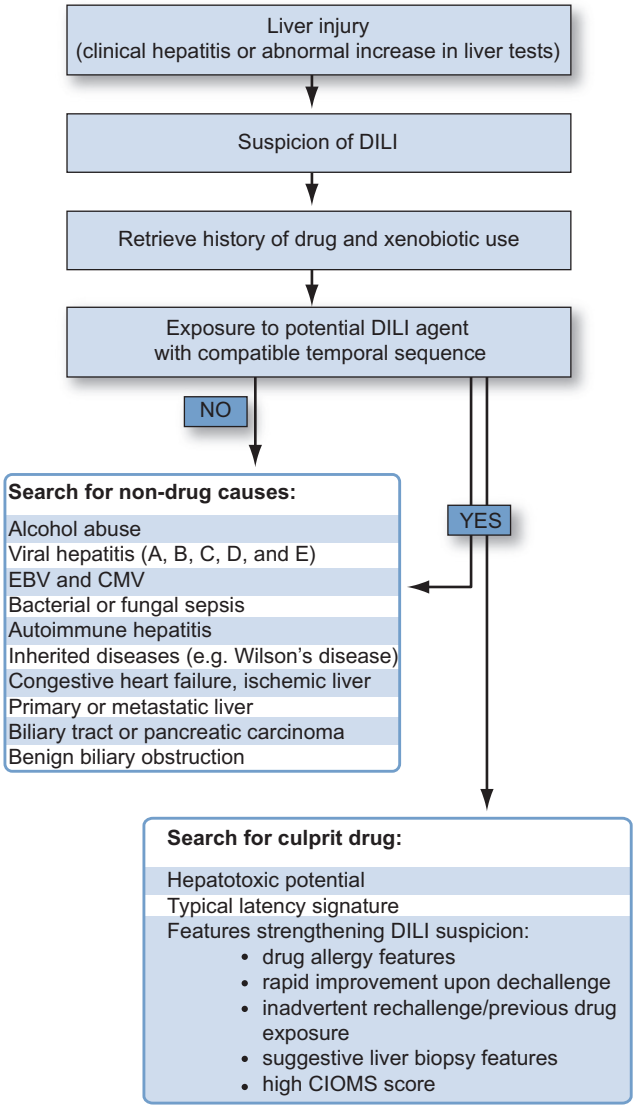

Fig. 1. Approaching a suspected drug-induced hepatotoxicity case.

Initiatives to homologize DILI assessments have been taken, with a recently held international clinical research workshop focused on standardizing current nomenclature and terminology implicated in DILI research [10]. Likewise, the International Severe Adverse Events Consortium (iSAEC) Phenotyping Standardization Project (PSP) is currently working towards achieving consistency, homogeneity, and objectivity in the definition, characterization, and classification of clinical DILI syndromes [11].

Causality assessment methods

DILI causality assessment has been a subject of interest and debate for years. Several standardized systems have been proposed to assess the relationship between drugs and the appearance of adverse events. Those systems belong to three categories: expert judgement, probabilistic methods, and algorithms or scales.

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