Herbs and Liver Injury: A Clinical Perspective

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Despite a perception that herbal and dietary supplements are safe, devastating liver injury has been reported to result from their use. The difficulty in characterizing liver injury attributable to herbal and dietary supplements stems from the permissive regulatory environment, the complexity of marketed products, and underreporting by the patients who use them. Despite these limitations, researchers, clinicians, and regulators have increasing awareness of the need for study in this area.

Keywords: Herbal and Induced Liver Injury; Dietary Supplements Induced Liver Injury; Causality Assessment in Drug-Induced Liver Injury.

Despite the perceived safety of herbal and dietary supplements (HDS), devastating liver injury has been reported. The goal of this review is to discuss the scope of use of HDS in the United States and their regulation and provide a clinical approach to diagnosis of HDS-induced liver injury (HILI).

The Scope of Use of Herbal and Dietary Supplements and Epidemiology of Herbal and Dietary Supplement–induced Injury

Dietary supplements are used for many reasons, including health maintenance, management of anxiety, obesity, diabetes, rheumatologic illness, cancer, cardiovascular disease, and pain, among others.[1] Liver disease is also a reason for use of HDS, which is demonstrated by the finding that 23% of patients enrolled in a long-term hepatitis C treatment trial reported use of HDS.[2]

The ease of access to HDS through many outlets leaves the consumer to assume that HDS are safe and their use is without consequences. Moreover, patients do not commonly divulge use of dietary supplements to health care providers because of the perceived bias against their use and the assumption that providers are uninformed about the supplements.[3]

Data from the National Health and Nutrition Examination Survey show that 52% of respondents reported using a dietary supplement.[4] Another survey has reported even higher rates of use, up to 73% in the noninstitutionalized U.S. adult population.[5] This extent of use translates into a large commercial enterprise, with the most recent reliable data indicating that more than $5 billion in commerce can be attributed to the dietary supplement industry.[6] In some Asian and African countries, up to 80% of the population use herbals as their primary means of medical care.[7]

Unfortunately, there are no U.S. data on the overall incidence of HILI or injury caused by any specific product. This results from lack of information on the overall use of HDS and not having a mandatory reporting mechanism to identify cases. Even in the few population-based studies on drug-related liver injury, injury attributable to HDS was only variably reported.[8–12]

The frequency of HILI can only be described in relative terms in Western studies; in prospective studies from Spain, medicinal herbal preparations accounted for only 1%–2% of cases of liver injury, with antibiotics being among the most common class implicated.[13,14] In keeping with their more common use, medicinal herbs were the most common cause for drug-related liver injury in Singapore where 71% of cases (22 of 31) were attributed to medicinal herbs, many adulterated with active drugs.[15] In Iceland, HILI has been observed with the use of Herbalife products.[16] In the United States, the Drug Induced Liver Injury Network (DILIN) promises to provide useful information on HILI. Preliminary data on HILI cases compiled by the DILIN provide a glimpse into the relative frequency of liver injury attributable to dietary supplements in the United States, compared with conventional drugs.[17] Among 109 patients in whom HDS were implicated in their liver injury, most (33%) used products intended for bodybuilding, followed by products used for weight loss (26%). Although it is not a population-based study per se, reports from the DILIN indicate that HDS are responsible for an increasing proportion of hepatotoxicity cases.[17]

Regulation for Herbal and Dietary Supplements

The current regulatory environment in the United States for dietary supplements was established by

Abbreviations used in this paper: **CIOMS, Council for International Organizations of Medical Sciences; DILI, drug-induced liver injury; DILIN, Drug Induced Liver Injury Network; FDA, Food and Drug Administration; GTE, green tea extract; HDS, herbal and dietary supplements; HILI, HDS-induced liver injury; RUCAM, Roussel Uclaf Causality Assessment Method.**

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Congress through the landmark Dietary Supplement Health and Education Act of 1994. Through this law, manufacturers were required to attest to a product's safety, but it gives no authority to the Food and Drug Administration (FDA) to approve HDS before marketing. It is only when a manufacturer introduces a new dietary ingredient that a premarket safety review is conducted.[18]

The "Final Rule for Dietary Supplement Current Good Manufacturing Practices," enacted in 2007, further aims to ensure the safety of marketed products by stipulating production standards.[19] However, not long after the final rule was published, instances of dietary supplements contaminated with various compounds became apparent, and the FDA issued a warning to manufacturers.[20] Routine analysis of products' contents by the FDA is performed on only a random basis.[18]

Diagnosis of Herbal and Dietary Supplement–induced Liver Injury

The key diagnostic elements for drug-induced liver injury (DILI), as discussed at an important Clinical Research Workshop, apply to HDS as well.[21] Fundamentally, the diagnosis of HILI depends first on having a suspicion that a supplement may be accountable for injury. The time to onset of injury can be variable with HILI because products consumed during long periods of time must be considered, because injury could be cumulative, or products and their contents may change over time.[22]

The clinical features should be recognized as hepatocellular, cholestatic, or mixed. The R ratio can be calculated at various times during the course of injury, although conventionally, it is determined at onset.[23] Observing the course of liver injury after cessation of an agent is an important component to diagnosis, because a deceleration of the enzyme abnormalities or clinical symptoms is expected (dechallenge). Improvement is not necessarily *sine qua non* for the diagnosis, because some HDS have been shown to lead to chronic, self-perpetuating injury, even after cessation.[22] Finally, recrudescence of liver injury on incidental re-exposure to a suspect supplement provides compelling evidence of a causal association.

The most decisive approach to the diagnosis of HILI, after documentation of the ingestion of an agent that precedes injury, is exclusion of other liver diseases that may present similarly (Figure 1).

Causality Assessment in Herbal and Dietary Supplement–induced Liver Injury

Causality assessment refers to the process of assembling evidence that may link a drug or dietary supplement to liver injury. Instruments for causality assessment are based predominantly on clinical criteria, such as patient age, alcohol use, exclusion of underlying liver diseases, and temporal exposure to a drug. The use of a universal assessment method when assessing potential DILI provides for increased evaluator agreement. However, even with the use of these causality assessment methods, variability among evaluators remains a concern.[24] A few causality assessment methods deserve mention in the context of HILI. An early causality assessment process is the Naranjo scoring system, or Adverse Drug Reaction Probability Scale.[25] The Naranjo system has been applied in the causality assessment process with natural products,[26] but this has drawn criticism because of its lack of specificity for liver-related drug reactions.[27,28]

The Roussel Uclaf Causality Assessment Method (RUCAM) was created in 1989 as the first liver-specific instrument and addresses many features unique to drug liver injury. It has been applied widely to HILI cases.[23] The RUCAM assigns points to specific categories and has been validated and found to be a sensitive and relatively specific way to support a diagnosis of DILI.[29]

A modification of the RUCAM, the Maria and Victorino scale, is commonly used in determining the likelihood of DILI.[30] Unlike the RUCAM, there is no requirement for a product label warning to assign the highest possible score for previous information on an agent.

Arguably, the most comprehensive approach to causality assessment, and the one that may be most adaptable to the nuances of HILI, is the expert opinion process, as used by the DILIN.[31] The DILIN has made significant inroads into the causality assessment process,

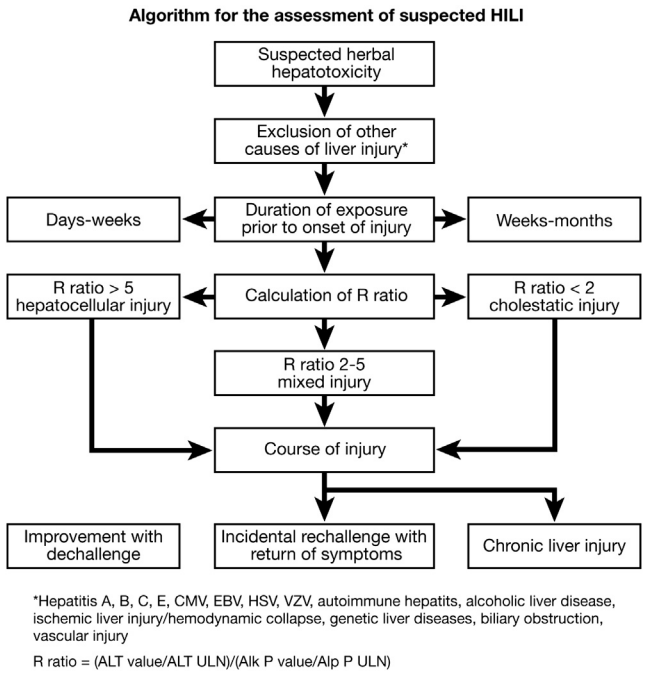

Figure 1. Algorithm for assessment of suspected HILI. Alk P, alkaline phosphatase; ALT, alanine aminotransferase; CMV, cytomegalovirus; EBV, Epstein–Barr virus; HSV, herpes simplex virus; ULN, upper limit of normal; VZV, vesicular stomatitis virus.