Editorial Commentary

Update on herbal and dietary supplement-induced liver injury: current gaps and future directions

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Drug-induced liver injury (DILI) is a rare but potentially life-threatening condition, which accounts for the majority of acute liver failure cases in the US and EU. Unlike direct hepatoxicity, which is mainly caused by acetaminophen, idiosyncratic DILI is unpredictable and occurs unrelated to the dose or frequency of the medication. Interestingly, DILI cannot only be caused by a large variety of prescription drugs, but also by herbal and dietary supplements (HDS). While HDS-DILI has already played a role in Asian countries like China or Korea for a long time, there is also an increasing incidence of HDS-DILI in countries with formerly less HDS-DILI cases such as the US, presumably due to a rising usage of those remedies (1).

With those rising incidence rates, the recognition of HDS as potential hepatotoxic agents is also increasing. Consequently, an updated American Association for the Study of Liver Diseases (AASLD) practice guidance on drug, herbal, and dietary supplement–induced liver injury has recently been published by Fontana *et al.* (2). The guideline nicely points out a well-known problem for DILI experts: DILI is a diagnosis of exclusion and therefore remains a diagnostic challenge (3). Due to the lack of standardized diagnostic test or validated biomarkers, the current gold standard of DILI diagnosis is still expert consensus opinion (2,4). In addition, causality assessment tools can assist in establishing DILI diagnosis since they provide a systemic approach for the evaluation of the likelihood that a specific medication has caused liver injury. Moreover, such tools can help identifying the causative agent in polymedicated patients. There are several causality assessment methods available with the Roussel Uclaf Causality Assessment Method (RUCAM) being most frequently used. The RUCAM scores the likelihood of DILI according to different items comprised of latency from drug intake, evolution upon drug withdrawal, known risk factors, previous information on hepatoxicity and outcome upon rechallenge (5). However, when it comes to evaluating HDS-induced DILI, application of RUCAM has major limitations especially concerning the items previous hepatotoxicity and reaction to re-exposure.

With regards to the information on previous hepatoxicity the importance of researching for comparable DILI cases in medical databases, such as LiverTox was highlighted in the AASLD practice guidance (6). LiverTox gives a brief synopsis on typical patterns of liver injury reported for a large number of drugs. Moreover, a grading for the likelihood of hepatotoxicity caused by the specific drug according to the number of available reports on previous DILI cases is provided. However, with more than 100,000 different HDS sold alone in the USA (2), it is obvious that case reports most likely have not been reported for every HDS available. Moreover, an underreporting of previous

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cases in the medical literature has to be expected, since patients might not mention HDS intake and physicians might not ask about such intake since they do not perceive HDS as possibly harmful. Accordingly, Fontana *et al.* point out that while LiverTox provides information for more than 1,000 prescription drugs, only 60 HDS are listed in the database (2). Interestingly, we have previously shown that in addition to conventional medical databases, information on HDS-induced hepatotoxicity can also be gained from commercial websites: while only six cases of ashwagandha-induced liver injury could be found in medical databases (6), eleven consumers reported liver problems in the customers' reviews of one of major commercial websites selling Ashwagandha. Now, two of them even stating to have suffered from acute liver failure (7). Thus, in addition to focusing on professionally published case reports, previous information on hepatotoxicity should also be extracted from consumers' reviews.

Another challenge in diagnosis and identify HDS-DILI is the uncertainty of the actual HDS components. Due to changes in cultivation conditions, undeclared ingredients or contamination with bystander components, the composition of HDS can vary even within the same HDS preparation (1,2). In addition, intentional adulteration with pharmaceuticals with the aim to enhance the therapeutic effect the HDS is marketed with, has been described (1,2). Thus, evaluation of previous hepatoxicity and re-exposure can be complicated by incomplete knowledge of the specific ingredients. Even in the case of a (deliberate) re-exposure it cannot be assured that the patient is treated with the same type of compounds, on the other hand unintentional re-exposure might occur even when a supposedly different HDS is used. Therefore, RUCAM can be misleading in patients with suspected HDS-DILI and might favour prescription drugs over HDS as the underlying cause in patients with polymedication.

To overcome some of the limitations of the RUCAM, the so-called RECAM, an updated electronic version of the RUCAM is now available. This scale expands the scope of alternative diagnosis that should be excluded and excludes risk factors which according to newer data are in fact not related with increased DILI risk (8). However, RECAM was developed and validated within the US, validation in other geographical regions with different drug spectrums causing DILI and evaluation in HDS-induced DILI cases is still outstanding (8).

With regards to the exclusion of alternative diagnoses, Fontana *et al.* mention the importance of testing and excluding viral hepatitis. In line with this, it was stated that of all suspected DILI cases in the US DILI network (DILIN) 1.3% and 3% were later tested positive for hepatis C or E, respectively (2). However, while testing for and therefore excluding viral hepatis can be routinely performed in suspected DILI case, exclusion of autoimmune hepatitis (AIH) can pose greater challenges. Regarding this topic, the AASLD guidance recommends to test for autoantibodies, e.g., antinuclear and anti-smooth muscle antibodies (ANA and ASMA) as well as serum Ig levels during the hepatological work-up. Moreover, it is mentioned that DILI with an AIH-like phenotype can occur, however, without further specification on definition, diagnosis or management (2). The acceptance of drug-induced autoimmune-like hepatitis (DI-ALH) as an independent entity which should be differentiated from idiopathic AIH and DILI has been recently underscored by an expert meeting report published on the nomenclature, diagnosis and management of DI-ALH (9). Nevertheless, distinguishing DILI from AIH and also from DI-ALH can be challenging and even impossible in some cases, since clinical, laboratory and histopathological features might be indistinguishable (9-11). While Fontana *et al.* focus on testing for antibodies presumably specific for AIH, it has been previously shown that DILI as well as DI-ALH can also present with positive autoantibodies especially ANA (12). Thus, the presence of autoantibodies in acute liver injury does not exclude DILI as a diagnosis. Nevertheless, differentiating DILI and DI-ALH from AIH is of high importance for the individual patient, since patients with DILI or DI-ALH rarely need lifelong immunosuppression in contrast to idiopathic AIH (9). Moreover, while in some DI-ALH cases, liver injury might resolve upon discontinuation of the drug without immunosuppression, a relevant proportion of patients with DI-AIH require extended immunosuppression when compared to conventional DILI (11). In the absence of diagnostic tests for DILI or validated DILI biomarkers the only reliable diagnostic criterion in those unclear cases is the evolution under immunosuppression and tapering of such. In this regard, it has been previously shown that rapid reduction of alanine aminotransferase (ALT) indicates towards DILI rather than AIH being the cause of liver injury (13). Thus, positive testing for autoantibodies in suspected DILI or HDS-DILI should not per se exclude the possibility DILI or DI-ALH and tapering of immunosuppression with close monitoring of liver parameters, especially ALT, should be considered early on, in particular in the cases with rapid ALT decline.

The practice guidance also discusses the natural history and management of idiosyncratic DILI in general and of HDS-DILI in specific, highlighting the poor outcome of patients with drug-induced liver failure as well as emphasizing the importance of referral of those cases to transplant centres (2,4). Most likely due to delay in identification of HDS as the causative agent in DILI, patients with HDS-induced liver failure have an even higher risk of needing liver transplantation or death when compared to patients with DILI caused by prescription drugs (2,14). However, while liver injury can be life-threatening in a relevant number of cases, treatment options are limited. In drug-induced liver failure, treatment with N-acetylcysteine in accordance with recommendations for acetaminophen-induced liver injury is suggested (2). In addition, positive effects for corticosteroids or ursodeoxycholic acid have been described (2,13), however, randomized controlled trials are still missing. In the current AASLD guidance statements, the use of methylprednisolone as the corticosteroid of choice is mentioned, possibly in accordance with international recommendations on treatment of immune checkpoint inhibitor-induced liver injury. Nevertheless, while being a rare condition, methylprednisolone-induced liver injury has been observed as highlighted by case series recently published by us (15). Therefore, we recommend using prednisolone rather than methylprednisolone in case corticosteroid treatment is initiated in a potential DILI patient.

In conclusion, the AASLD guidance shows us that despite the numerous limitations and obstacles in the diagnosis of HDS-related DILI, early recognition of HDS-DILI cases is of high importance, in particular due to the poor outcome of HDS-induced liver failure.

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References

1. Navarro VJ, Khan I, Björnsson E, et al. Liver injury from herbal and dietary supplements. Hepatology 2017;65:363-73.
2. Fontana RJ, Liou I, Reuben A, et al. AASLD practice guidance on drug, herbal, and dietary supplement-induced liver injury. Hepatology 2023;77:1036-65.
3. Weber S, Gerbes AL. Challenges and Future of Drug-Induced Liver Injury Research-Laboratory Tests. Int J Mol Sci 2022;23:6049.
4. Kullak-Ublick GA, Andrade RJ, Merz M, et al. Drug-induced liver injury: recent advances in diagnosis and risk assessment. Gut 2017;66:1154-64.
5. 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;46:1323-30.
6. LiverTox: clinical and research infor-mation on drug-induced liver injury. Bethesdam, MD: National Institute of Diabetes and Digestive and Kidney Diseases; 2012.
7. Weber S, Gerbes AL. Ashwagandha-Induced Liver Injury:

Self-Reports on Commercial Websites as Useful Adjunct Tools for Causality Assessment. Am J Gastroenterol 2021;116:2151-2.
8. Hayashi PH, Lucena MI, Fontana RJ, et al. A revised electronic version of RUCAM for the diagnosis of DILI. Hepatology 2022;76:18-31.
9. Andrade RJ, Aithal GP, de Boer YS, et al. Nomenclature, diagnosis and management of drug-induced autoimmune-like hepatitis (DI-ALH): An expert opinion meeting report. J Hepatol 2023;79:853-66.
10. Suzuki A, Brunt EM, Kleiner DE, et al. The use of liver biopsy evaluation in discrimination of idiopathic autoimmune hepatitis versus drug-induced liver injury. Hepatology 2011;54:931-9.
11. Weber S, Gerbes AL. Relapse and Need for Extended Immunosuppression: Novel Features of Drug-Induced Autoimmune Hepatitis. Digestion 2023;104:243-8.
12. Weber S, Benesic A, Buchholtz ML, et al. Antimitochondrial Rather than Antinuclear Antibodies Correlate with Severe Drug-Induced Liver Injury. Dig Dis 2021;39:275-82.
13. Weber S, Benesic A, Rotter I, et al. Early ALT response to corticosteroid treatment distinguishes idiosyncratic drug-induced liver injury from autoimmune hepatitis. Liver Int 2019;39:1906-17.
14. Kesar V, Channen L, Masood U, et al. Liver Transplantation for Acute Liver Injury in Asians Is More Likely Due to Herbal and Dietary Supplements. Liver Transpl 2022;28:188-99.
15. Allgeier J, Weber S, Todorova R, et al. Acute liver injury following methylprednisolone pulse therapy: 13 cases from a prospectively collected cohort. Eur J Gastroenterol Hepatol 2022;34:457-61.

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