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Drug- and herb-induced liver injury in 2016 with highly appreciated critical comments: related or not, that is the question!

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Out of 1,500 publications on drug-induced liver injury (DILI) as well as herb-induced liver injury (HILI) reported in 2016, O. Shahbaz, S. Mahajan, and J.H. Lewis [1] selected 101 papers of relevance and provided an expert-based critical view on actual issues in the field of liver injury including liver pathology. Most interesting and encouraging, it seemed that among the 101 referenced papers there were only few single drugs with a case of a liver injury newly published in 2016. Certainly, new reports of some older drugs with established hepatotoxicity have been published again in 2016 confirming previous reports from before 2016 [1-4]. For instance, among these were drugs such as statins and antituberculosis medications [2,3], which are known for their potential causing rare idiosyncratic DILI, and overdosed acetaminophen [4], known for its intrinsic hepatotoxicity.

An indepth analysis is provided on the issue of liver decompensation under the use of direct acting antivirals (DAAs) for hepatitis C in patients with liver cirrhosis [1]. Based on these conditions in 26 cases, which were classified as possible or probable-related, the US FDA issued a warning of serious liver decompensation and liver failure in patients with cirrhosis, seen specifically with Viekira Pak and Technivie [5]. Although such regulatory warning is absolutely correct, the FDA did not specify the adjudication process used in these 26 cases [1]. In particular, the FDA made not clear, whether liver decompensation or liver failure was due to DILI caused by DAAs, to specific actions of DAAs on hepatitis C viruses, or to the natural clinical course of the severe liver disease in its end stage [1,5]. A temporal association was described with a worsening of the liver injury starting with the medications and resolution following their discontinuation [1], suggesting but not proving DAAs as causally related products rather than flares of the underlying hepatitis C virus infection in some patients. In view of these uncertainties, liver injury experts from the FDA are encouraged to further analyze the cases and present final transparent results on the offending product(s). In particular, defined and scored elements should be used to assess causality as outlined below.

A large portion of this review covers issues related to correct diagnoses of liver injury cases and usage of causality assessment methods (CAMs) [1]. In 2016, more details were published on both, RUCAM (Roussel Uclaf Causality Assessment Method), which has now been updated and is the most commonly used CAM worldwide [6], and the method of the US DILIN (Drug-Induced Liver Injury Network) with its application restricted to the US [7]. Highly appreciated [1], RUCAM represents a standardized, structured, quantitative, transparent, and validated CAM for liver injury in real time when the patient is under medical care, whereby individual key elements with specific scores are the cornerstones of RUCAM and provide objective results [6]. Scored elements include alcohol use and age, validly established and based on cases with positive reexposure as gold standard [6]. Certainly and 25 years after RUCAM launch, other DILI cohort studies may now show small differences in case characteristics, which do not justify the consideration deleting arbitrarily elements of alcohol use or age from the RUCAM scale [1], that would require a new method validation using again cases with positive rechallenge. Indeed, many physicians, scientists, regulators, and pharmaceutical manufacturers use RUCAM without any overt problems regarding the scored RUCAM elements [6]. Interestingly, potential recommendations on element scorings do not target the DILIN method, which comes along without any systematic element scoring [7]. In detail, based on global introspection and thereby on own personal experience, and not routinely considering well predefined key elements with their quantitative scorings [7], assessors of the DILIN method finally may arrive at vague subjective conclusions derived from poorly documented and intransparent causality results that are hardly re-assessable [6]. As published [7] and outlined in the review [1], other shortcomings of the DILIN method include its less complete transparency, the expense in terms of requiring a large data coordinating center, the cumbersome nature of the adjudication process, since assessors often have to come together to discuss the cases in order to reach consensus, and the delayed assessments, which are retrospective [1,7] as opposed to RUCAM, for which a prospective use is recommended to allow collection of complete case data and to minimize inter-rater variability [6]. Despite these numerous shortcomings associated with the application of the DILIN method, over the last years DILIN has provided clinical information on nearly 200 drugs taken by more than 1200 patients [1], although confounding case duplication and triplication may have increased the numbers due to redundant publications of the DILIN registry. However, the quantity of overall reported DILI cases is less important than the quality of such reports.

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The review of Shahbaz *et al.* [1] references various prospective DILI registries, including those of Iceland, Spain, Latin America, Mexico, and Germany. Reviewing these referenced original papers, common to all registries is their use of RUCAM as the preferred tool for causality assessment, as also described earlier [6]. These RUCAM-based cases presented by well-established registries provided valid clinical features of liver injury caused by drugs and herbs. In 2016, RUCAM was also used for assessing DILI and HILI cases in China, which allowed a comparison of clinical characteristics of liver injury by Western drugs with those by herbal Traditional Chinese medicines (TCM) [8]. Unquestionable, a uniform causality approach such as RUCAM should be achieved by all worldwide registries in order to allow comparison of case features among countries and populations.

In 2016, cases of DILI and HILI and their causality assignments were more critically seen as compared to the years before [1], referring to some reports as examples [9-11]. In cases with discovered problems, RUCAM was used and facilitated detection of diagnostic flaws. In particular, problems of causality adjudication were analyzed for many DILI cases presented by the US FDA in its LiverTox website [9], and there is need to be more skeptical of case reports and case series that fail to provide a minimum threshold of clinical information to assess [1]. As the LiverTox website contains many assumed DILI cases that were not DILI [9], new efforts are mandatory to update this website by DILI and HILI cases, which received a thorough RUCAM-based causality assessment with high causality gradings of highly probable or probable. This website also needs an update of the causality assessment section, including now the updated RUCAM version. Another discussion focused on initially assumed causality in HILI cases by a herbal dietary supplement, called OxyELITE Pro (OEP) [1], for which causality could not be confirmed [10,11]. With respect to these OEP cases of unconfirmed causality [10,11], the authors of the review article came to the conclusion that CDC and the US FDA, which has issued warnings, that in retrospect it may have implicated the supplement erroneously [1], based on the more thorough analysis [10,11].

There is agreement that DILI and HILI cases require special attention regarding causality [1,6,12,13]. Potential risk factors and biomarkers of DILI were carefully listed [1] and should be based on cases with high RUCAM gradings. Diagnostic biomarkers as blood tests would be of great help for clinicians and regulators, and pharmaceutical manufacturers would be more comfortable if, in addition to RUCAM, causality of DILI can be objectively confirmed. Although some parameters are available to evaluate liver safety of drugs in patients, no valid diagnostic or prognostic biomarker exists currently for idiosyncratic DILI or HILI when a liver injury occurs. The main reasons are first, idiosyncratic DILI is typically a human disease and it is hardly reproducible in animals and second because the DILI cases used for testing the new biomarkers are not always correctly assessed for causality that would decrease substantially the power of the biomarker tested. Causality assessment of cases of suspected idiosyncratic DILI and HILI would be best achieved using RUCAM ensuring harmonized and verifiable approach of the identification of new markers.

In essence, the impression prevails that we are now much more critical regarding DILI and HILI cases, which require a robust, objective quantitative causality assessment such as RUCAM with clearly defined key elements and appropriate scorings to establish valid causality gradings of highly probable and probable. Such RUCAM-based cases of DILI and HILI will allow good case characterization and should be incorporated in the LiverTox website.

Conflict of interest statement

None declared.

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