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CORRESPONDENCE

Suspected Liver Injury and the Dilemma of Causality

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Abstract For causality assessment in cases of suspected liver injury, RUCAM provides objective and transparent results and should be the preferred tool rather than the DILIN method, which is based on subjective opinion.

Keywords RUCAM · Liver injury · Causality assessment · Liver injury · OxyELITE Pro

Dear Sir,

Dr. Heidemann and her colleagues [1] are to be congratulated for illustrating shortcomings of the DILIN method and advantages of RUCAM, assessing causality in cases of suspected liver injury by OxyELITE Pro (OEP). Using RUCAM in their seven-case series, they found that causality was unlikely in one patient, possible in four, and probable in two [1]. This matched low or lacking RUCAM causality levels in similar OEP cases [2–4]. Based on opinion, the DILIN method upgraded causality levels to definite, highly likely, and probable in 6/7 cases, despite confounding variables in all cases: comedications by numerous drugs and dietary supplements (cases 1, 2, 5–7); incomplete diagnostic exclusion of numerous alternative causes (cases 1, 2, 4–7), also of chronic hepatitis B virus infection causing acute liver failure with the need of liver transplantation and lack of antiviral therapy of hepatitis B flares (case 7); intermittent OEP use (case 5); and lacking HEV exclusion by HEV-DNA analyses (cases 1–7) [1]. Overall, causality attribution with either method is questionable since the type of OEP used was not identified and chemical analysis was not done [1].

Causality of OEP as a suspected liver toxin was heavily disputed, as discussed in detail and outlined previously [2–4]. Problems in previous cases included incomplete case data [2–4], incorrect use and intentional upgrading of RUCAM scores [2–4], incorrect transfer of clinical data from available documents to the RUCAM scale [3, 4], and using the disputed MedWatch database as source of cases provided mostly by non-professionals not familiar with case details and liver injury-specific issues, an unacceptable approach [4].

When compared to RUCAM, this report confirms [1] that the DILIN method is a retrospective tool and has many disadvantages (Table 1) [5] since decisions are based on subjective experts' opinion, and causality percentage ranges are arbitrarily provided without a structured approach, clearly defined criteria of hepatotoxicity, or individually scored items [1, 5, 6]. Consequently, DILIN gradings are vague, unscored, not quantitative, and not transparent [1], impeding reassessment by peers outside of DILIN, a close-knit US-based group [5]. Recently, a DILIN member [6] critically analyzed the weaknesses of the DILIN method, describing it as an expert opinion process of imperfect standard without translation into daily clinical practice and by definition without validation by any gold standard. Reported are also lengthy conversations about overlooked case data, weakness in reasoning, and unconsidered new publications that emerge during the DILIN consensus process, which is also described as cumbersome, time-consuming, and costly; approaches to improve it are continually sought [6]. Confined to the US and the inventing group [5], this method cannot replace RUCAM [5].

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Table 1 Causality assessment methods: core elements of RUCAM as compared to the DILIN method

Clearly defined core elements individually scored items	RUCAM	DILIN
• Time frame of latency period	+	?
Scored item	+	0
• Time frame of dechallenge	+	?
Scored item	+	0
• Recurrent ALT or ALP increase	+	?
Scored item	+	0
• Risk factors	+	?
Scored items	+	0
• All comedications	+	?
Scored items	+	0
• Individual comedication	+	?
Scored item	+	0
• Exclusion of alternative causes	+	?
Scored items	+	0
• Markers of HAV, HBV, HCV, HEV	+	?
Scored items	+	0
• Markers of CMV, EBV, HSV, VZV	+	?
Scored items	+	0
• Cardiac hepatopathy	+	?
Scored item	+	0
• Liver and biliary tract imaging	+	?
Scored item	+	0
• Doppler sonography of liver vessels	+	?
Scored item	+	0
• Prior known hepatotoxicity of drug	+	?
Scored item	+	0
• Unintentional reexposure	+	?
Scored item	+	0
• Laboratory hepatotoxicity criteria	+	+
• Laboratory hepatotoxicity pattern	+	?
• Hepatotoxicity-specific method	+	+
• Structured, liver-related method	+	0
• Quantitative, liver-related method	+	0
• Validated method (gold standard)	+	0

Listing compilation of core elements of RUCAM and the DILIN method, adapted from a previous report which contains additional details [5]. The symbol + shows that this specific item is published, and the symbol 0 indicates lacking publication

ALT alanine aminotransferase, *ALP* alkaline phosphatase, *CMV* cytomegalovirus, *EBV* Epstein–Barr virus, *HAV* hepatitis A virus, *HBV* hepatitis B virus, *HCV* hepatitis C virus, *HEV* hepatitis E virus, *HSV* herpes simplex virus, *VZV* varicella zoster virus

In contrast, RUCAM is the most popular causality assessment method [5]. Applied worldwide in cases of suspected liver injury, it is an objective, structured, standardized, and hepatotoxicity-specific diagnostic tool that attributes scores to individual key items and provides final quantitative gradings of causality [5]. In many countries and for more than two decades, physicians, regulators, case-report authors, and pharmaceutical companies have successfully applied the well-validated RUCAM [5]. Of note, our critical analyses on suspected OEP hepatotoxicity [2, 3] received encouraging support by US scientists including a DILIN member [7]. All agree that dietary supplements must be effective and safe [1, 8]. The best method for assessing whether they are hepatotoxic is RUCAM, not the DILIN method.

Reply

In response to the comments of Teschke et al., we offer the following:

Aim of the Study: Severe hepatotoxicity associated with OxyELITE Pro use in 2013 prompted an investigation by the FDA and CDC that included a detailed review of 114 reported cases [9]. They concluded that "a causal link likely existed between OxyELITE Pro ingestion and liver injury." Interestingly, all six of the confirmed OxyELITE Pro cases enrolled in the Drug-Induced Liver Injury Network (DILIN) prospective study were reported in mid to late 2013 (the case that was reported in 2011 was considered only possibly related). In Table 1, the extensive phenotyping of each of these prospectively identified and followed patients is provided, including concomitant medications and the exclusion of alternative causes. Contrary to the assertions of Teschke et al., liver imaging was obtained in all of the patients; no patient had evidence of occult HEV and HCV infection using appropriate serological and PCR-based testing. Liver biopsies from three of the cases were consistent with severe hepatic necrosis and injury. Therefore, a detailed clinical description of seven cases of severe acute hepatocellular injury attributed to OxyELITE Pro is provided for consideration by the broader medical and scientific communities.

Causality Assessment: The DILIN prospective protocol assesses causality after six months of follow-up using a structured expert opinion-based, semi-quantitative five-point scale as well as RUCAM scoring [10]. The experts adjudicating the case review a comprehensive battery of diagnostic testing for competing causes of liver injury, lifetime exposure to the suspect drug, and clinical and laboratory information detailing the course of the illness. Prior studies have demonstrated that expert opinion has superior reliability compared to RUCAM scoring due to ambiguous instructions on how to score several of the RUCAM domains [11]. The expert opinion scores of the OxyELITE Pro cases were possible [9], probable [11], highly likely [9], and definite [9], whereas the RUCAM scores were unlikely [9], possible [12], and probable [10]. Prior studies demonstrate that RUCAM scores are usually lower than expert opinion scores due to the former's lack of flexibility, limited number of data elements, and inclusion of non-evidence-based "risk factors" such as subject age, pregnancy, and alcohol consumption. Furthermore, RUCAM scoring of patients with acute liver failure, pre-existing liver disease, and suspected herbal and dietary supplement (HDS) hepatotoxicity is particularly challenging. A lack of dechallenge laboratory data (i.e., change after drug discontinuation) in patients who die or undergo transplantation is inevitably associated with lower RUCAM scores despite more serious consequences [12]. Furthermore, RUCAM scores of suspected HDS cases are inevitably lower due to the lack of previously published or "labelled" information on the products hepatotoxicity. Lastly, many HDS products contain a multitude of ingredients and botanicals complicating the identification of the specific hepatoxicant. In the case of OxyELITE Pro, chemical analyses conducted by the FDA demonstrated a combination of several new ingredients including aegeline, higenamine, caffeine, and yohimbine, none of which were listed on the product label [9].

The RUCAM's potential for underscoring is particularly apparent in severe HDS cases. For example, a non-drinking, 54-year-old male who sustains a liver injury from a single course of an HDS product, not previously reported to be hepatotoxic, could score a maximum of just 7 (probable) by RUCAM. And if there are no dechallenge data due to fatality, the maximum score obtainable falls to only 4 (possible). Therefore, the RUCAM carries an intrinsic structural bias against higher causality scores for severe HDS injuries because there are few if any published data regarding the safety and efficacy of most HDS products in humans including adverse events.

In conclusion, using a systematic, structured, and unbiased approach, we report seven well-phenotyped cases of severe acute hepatocellular injury attributed to OxyELITE Pro. Since publication, no further evidence of alternative causes of liver injury has been identified in any of these cases. Furthermore, additional cases have not been enrolled after the OxyELITE Pro formulation was removed from the marketplace in late 2013. Efforts are underway to identify and improve causality assessment methods that will include sensitive and specific laboratory-based biomarkers. Furthermore, modifications to the RUCAM that remove unnecessary data elements such as unproven risk factors, improve inter-observer reliability, and involve evidence-based weighting of data elements that may be drug- or HDS-specific are being explored. Lastly, with the increasing attention to HDS hepatotoxicity, several groups are undertaking studies to better define the hepatotoxic constituents of implicated HDS products.

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Compliance with ethical standards

Conflict of interest Rolf Teschke received an honorarium by Merz Pharmaceuticals and Max Zeller Pharmaceuticals for lectures at scientific meetings, and by Covington & Burling LLP Washington DC and Weber & Weber Inc. for consultation. Axel Eickhoff received no honoraria or has a conflict of interest.

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