Correspondence

Need for Causality Assessment Tool for Drug-induced Acute Kidney Injury

Dear Dr. Shader:

Kidneys are important organs of the excretory system with crucial roles in not only maintaining homeostasis by eliminating waste products, protecting acid-base and water balance, and secreting hormones but also eliminating many drugs and their metabolites. If there is deterioration in these roles due to unexpected functional changes or structural deformation, acute kidney injury (AKI) is observed. Recently, the term AKI has replaced the term acute renal failure.[1,2]

AKI is briefly defined as an abrupt decrease in glomerular filtration rate resulting in an increased serum creatinine level or decreased urine output. This definition includes both structural damages leading to acute obstruction and functional loss. It is a broad clinical syndrome encompassing various etiologies, including specific kidney diseases (ie, acute interstitial nephritis, acute glomerular renal diseases, renal vasculitis) and nonspecific conditions (ie, ischemia, toxic injury), as well as extrarenal pathologies (ie, perfusion-related injury, acute obstruction).

There has been intensive research to define the most appropriate criteria to standardize the diagnosis of AKI and to be able to predict prognosis. These guidelines have progressed, from RIFLE (risk of renal failure, injury to the kidney, failure of kidney function, loss of kidney function, and end-stage renal failure)[2] to AKIN (Acute Kidney Injury Network criteria),[3] to improve the sensitivity and the ability of predictivity. The latest and current criteria for AKI diagnosis were published by KDIGO (Kidney Disease: Improving Global Outcomes) in 2012 to fulfill the need for a single definition for clinical practice, research, and public health.[4] Despite the evolution for a better standardized definition of AKI, neither of these guidelines (RIFLE, AKIN, and KDIGO) focus on drug-induced acute kidney injury (DIAKI), and a guideline has not been developed. In the current Letter, a call is made for developing a specific causality tool for DIAKI assessment.

Far too many drugs or drug classes are involved in DIAKI with one or more pathophysiological mechanisms and with different renal manifestations. Nephrotoxic medication intake accounts for 18% to 27% of all AKI cases in US hospitals,[5] and they contribute to 14% to 21% of the AKI cases in critically ill patients.[4] DIAKI may be costly and increase morbidity, especially in critically ill patients.[6–8] Some common risk factors encountered in the occurrence of DIAKI are older age, drug dose, presence of underlying renal disease, and the concomitant use of >1 nephrotoxic drug. Nephrotoxic drugs can cause kidney damage through 2 main mechanisms: dose-dependent reactions and idiosyncratic reactions. Mechanisms of nephrotoxicity include direct tubular toxicity, glomerular vasoconstriction, allergic interstitial nephritis, and urinary crystallization, all of which can lead to AKI. Nephrotoxic acute tubular necrosis is an example of a dose-dependent event that frequently occurs in patients with a high risk of renal injury.[9]

The term "drug-induced" is mostly reserved only for instances of kidney injury verified by a rechallenge or where every other specified cause of kidney injury has been excluded, and complete follow-up of the patient is available for determining a positive dechallenge response. A decrease in renal function (which is commonly recognized by an increase in serum creatinine level) after drug exposure could signal the possibility of DIAKI.

The time interval of a possible drug-induced renal dysfunction is another important parameter and is usually between 7 to 14 days after drug exposure. Earlier development of DIAKI is also possible if the patient has a greater sensitivity. A challenging issue is that the clinical manifestations of DIAKI could be unrecognized, particularly for short drug exposures. Most episodes of DIAKI are reversible if the renal impairment is recognized early and the drug is discontinued.

Mehta et al[10] propose 4 phenotypes of drug-induced kidney disease based on clinical presentation (AKI, glomerular, tubular, and nephrolithiasis), along with primary and secondary clinical criteria to support the

phenotype definition. These phenotypes would definitely be supportive for causality assessment of DIAKI, as such phenotypes should be listed in the "DIAKI-specific causality scale" for which we are making the call. Identifying phenotypes is only one of the steps to perform causality assessments, and it is not enough.

Causality assessment plays an important role within the different aspects of pharmacovigilance, and it is intended for all exposed drugs. Because it is the first step in case assessment, it determines whether there is a reasonable possibility that the medication is causally related to the adverse event (AE). Causality assessment is not required for spontaneous reports that are serious and unexpected because they are presumed to be possibly related.

A number of algorithms and tools have been developed for the causality assessment to have a structured approach. However, there are currently no internationally agreed upon standards or criteria for assessing causality in individual cases, especially for events that often occur spontaneously (eg, stroke, pulmonary embolism). The causality assessment should ideally include the following parameters: evaluation of temporal relationships, dechallenge/rechallenge information, association with (or lack of association with) underlying disease, presence (or absence) of a more likely cause, and biological plausibility. A good example is the French Imputability Method, which includes: (1) chronologic criteria (challenge—dechallenge—rechallenge); and (2) semiologic criteria (semiology per se, favoring factor, alternate nondrug explanation, and specific laboratory tests).[11] An ideal causality assessment tool should also produce validity and reproducibility,[12,13] in which validity is the capability of catching cases regardless of whether they are related to drugs, and reproducibility is the ability of the tool to provide a decision independent of time and person factors.

Causality assessment tools could be either nonspecific or organ specific. Nonspecific tools include the French imputation systems,[11] the Naranjo Adverse Drug Reaction Probability Scale, the World Health Organization causality categories, 9-points of consideration, the European ABO Systems, and probability calculation (Bayes' Theorem). Bayes' Theorem, a decision support algorithm, can be used to generate data on signal detection, indicating a potential safety issue in the future, thereby supporting robust assessment of causality.[12–17] It is possible to use nonspecific causality tools for DIAKI; however, to the best of our knowledge, such nonspecific tools have not been evaluated for the causality scoring of DIAKI. Organ-specific tools, such as the Roussel Uclaf Causality Assessment Method, have criteria that are specifically adapted to hepatotoxicity, and they remain the reference method for less severe hepatotoxicity except in clinical trials.[12,13] All these causality tools are based on different methods of assessment with different scales (numeric or lexical).

It is clear that assessment of drug causality is challenging. Once DIAKI is considered, adjudication may not be performed appropriately or may not be performed at all. Current nonspecific causality assessment tools lack the assessment of DIAKI risk factors. Such challenges in assessing the incidence, severity, and long-term consequences of DIAKI set the need for the development of a structured kidney-specific causality assessment tool. We therefore make a call for developing a specific causality-assessment tool for DIAKI. Developing a DIAKI-specific causality assessment tool is a complex and expertise-needed work. We are, by our Letter, making this call and inviting experts from different fields to start the process and create the DIAKI-specific causality assessment tool. To start the process, we offer some main parameters that a kidney-specific causality assessment tool should include:

(1) Clinical criteria:
   (a) Patient- and disease-specific risk factors (eg, age, presence of underlying renal disease);
   (b) Drug-specific risk factors (eg, dose, concomitant use of >1 nephrotoxic drug);
   (c) Exclusion of other possible causes (eg, viral diseases, autoimmune diseases);
(2) Drug exposure—specific criteria:
   (a) Onset of drug exposure (must be at least 24 hours before the event);
   (b) Current temporal relationship;
   (c) "Prechallenge" (previous exposure to suspect drug) assessing both positive prechallenge (adverse drug reaction [ADR] occurred in past when patient was exposed to drug) and negative prechallenge (ADR did not occur in past when patient was exposed to drug);
   (d) Challenge (appearance of ADR); (e) Positive dechallenge (disappearance of ADR); (f) Positive rechallenge (reappearance of ADR);

(g) Presence of a similar problem with the same drug; presence of a similar problem with the related drug or drug class; explorations for dose dependency, adaptation, and tolerance to certain AEs (eg, nausea, somnolence);
(h) Drug–demographic, drug–disease, and drug–drug interactions, and severity analysis of the AE.

Assessing causality is legally required for regulatory measures by most health authorities, including the US Food and Drug Administration and the European Medicines Agency, for all serious AEs. It is also used to determine whether the AE should be considered in the signaling review and benefit/risk determination and whether it should be listed in the labeling (eg, package insert, summary of product characteristics) as per patient care and communication routines. Another obvious purpose for causality assessment is for scientific publications. Causality assessment tools serve to describe and to picture different cases, ensure the consensus among the assessors, and help the decision-making process by inexperienced assessors.

There are certainly challenges in assessing causality, especially when there are multidrug exposures and concurrent AKI risks. Until recently, causality assessment depended on expert judgment, in which an individual expert or panel of experts would make a decision based on their medical expertise. Although expert judgment has been considered the gold standard, variability of clinical judgment remains that highlights the increasing need to maintain uniformity by decreasing the disagreement between the assessors. Our call is not for the diagnosis, management, or defining of phenotypes of DIAKI but ultimately and clearly for the development of a DIAKI-specific causality assessment tool. Such a tool would not only be a very structured and systematic option for assessing the involvement of drugs/drug classes in AKI but also to overcome the challenges for assessing causality mentioned in this and many other articles, as well as to support the expert consensus adjudication process when performed.

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CONFLICTS OF INTEREST

The authors have indicated that they have no conflicts of interest regarding the content of this article.

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