Much Ado About Something: The Clinical Pattern of Tolvaptan-Associated Liver Injury in Participants With ADPKD

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Autosomal dominant polycystic kidney disease (ADPKD) is the most common genetic kidney disorder with a risk of significant morbidity, including kidney failure. The prognosis of the disease may differ between individuals, although loss of kidney function over time is inevitable. The quest for a treatment to slow down the loss of kidney function and progression to kidney failure has spanned decades. Three large phase 3 clinical trials—TEMPO 3:4 (Tolvaptan Efficacy and Safety in Management of Autosomal Dominant Polycystic Kidney Disease and Its Outcomes 3:4 Trial), TEMPO 4:4,2 and REPRISE (Replicating Evidence of Preserved Renal Function: an Investigation of Tolvaptan Safety and Efficacy in ADPKD)—showed that tolvaptan decreased rate of kidney growth and kidney function loss. Its use for ADPKD was approved by the European Renal Association (ERA) in 2016 and US Food and Drug Administration (FDA) in 2018. However, the risk of tolvaptan-induced hepatic injury remains a major concern.

In this issue of AJKD, Alpers et al conducted a retrospective study of tolvaptan safety data from clinical trials to address this concern. They analyzed data from more than 2,900 tolvaptan-treated study participants, including more than 2,300 with ≥18 months of drug exposure. The intervention in all clinical trials was twice-daily dosing of tolvaptan. The main outcome was an elevation above the upper limit of normal (ULN) of ≥3 × (in alanine aminotransferase [ALT] or aspartate aminotransferase [AST] level) or of ≥2 × (in total bilirubin level). In TEMPO 3:4, there were 2 patients who experienced concurrent elevations in levels of ALT/AST and bilirubin. No one had persistent liver dysfunction. During the TEMPO 3:4 study period, 1.2% of the participants needed to discontinue the trial owing to liver injury. Later, Endo et al published a case report of a patient with tolvaptan-induced acute liver failure requiring liver transplantation, which proved that clinicians’ concerns were relevant. In the REPRISE trial, ALT elevations >3 × ULN were more frequently seen in the tolvaptan arm compared to the placebo arm, but no participant in REPRISE had a concomitant increase in total bilirubin. The analysis by Alpers et al showed that liver enzyme abnormalities were more common in the first 18 months of tolvaptan use, and liver enzyme levels improved or returned to normal after stopping tolvaptan.

To date, our understanding of tolvaptan-associated drug-induced liver injury (DILI) is that this can occur in 4%-5% of patients and has an idiosyncratic time to onset. For the vast majority, these episodes of DILI will resolve without complication within 1-3 months; however, recurrence is common, and in general rechallenge should be done with caution. Tolvaptan presents a clear benefit to patients with ADPKD, and close monitoring will allow for a more informed decision of the patient-specific risks and benefits. Alpers et al provide data to inform several components of clinical decision-making: (1) the prevalence of DILI requiring discontinuation was 1.2%; (2) the majority of DILI cases occur before 18 months, although this may be limited by the duration of follow-up in this study; (3) few patients were rechallenged and among those who were, most had a “positive” rechallenge (meaning the increase in ALT was repeated), even when restarted at a lower dose of tolvaptan; (4) continuation despite elevated ALT was rare—too rare to make any meaningful observations—occurring in 1 person who demonstrated adaptation. Overall, the data presented by Alpers et al highlight that close monitoring (ie, monthly) of transaminases and bilirubin is paramount. Their data do support that monthly measurement of transaminase and bilirubin levels for 18 months and every 3 months thereafter is sufficient. This conclusion supports the FDA’s Risk Evaluation and Mitigation Strategy (REMS) requirements as well. In our practice, our highly informed patient population appreciates a conservative approach to temporary discontinuation of tolvaptan in the setting of abnormalities in liver function tests and possible DILI. We seek other explanations for such abnormalities and then rechallenge all willing patients at a lower dose of tolvaptan, in some cases at subtherapeutic levels (eg, 15 mg twice a day). If rechallenge is negative, we cautiously advance the dose back to standard dosing (45 mg upon waking plus 15 mg after 8 hours).

The authors went beyond these data to create a hepatic adjudication committee to analyze rechallenge assignments made in REPRISE and the long-term extension study—an attempt to define the clinical probability of the DILI reported being associated with tolvaptan. The 4 hepatologists on the committee assessed causality using “expert opinion” interpretation of comorbid conditions, concomitant medication use, onset, offset, and dose relationship. The causality groups were defined as “definite,” “highly likely” (75%-95%), “probable” (50%-74%), “possible” (25%-49%), and “unlikely” (<25%) according to the possibility of drug-induced injury as an underlying etiology. A total of 125 hepatic events met the criteria for adjudication in REPRISE and the long-term extension, but...
none of them were categorized into “highly likely” or “definite” groups per the retrospective analysis by Alpers et al. This appears reassuring on its surface; however, even with participant-level data, given the polypharmacy many patients with ADPKD experience and the idiosyncratic timing of tolvaptan-associated DILI, interpretation of this adjudication is difficult. For example, with statins being prescribed in at least 20% of ADPKD participants in clinical trials, as well as possible use of acetaminophen for pain and limited ability to quantify alcohol use, any post hoc interpretation of causality has limitations. Nevertheless, data exist to suggest safe use of tolvaptan with statins and in clinical practice, real-time assessment of competing explanations for liver function test abnormalities not meeting criteria for tolvaptan-associated DILI can be made.

In summary, tolvaptan is the only disease mechanism–specific FDA-approved drug for ADPKD patients at risk of rapid disease progression, slowing cyst growth and kidney function decline in patients with early and advanced chronic kidney disease. DILI has been consistently observed in tolvaptan-treated patients in clinical settings and clinical trials for drug safety. In this study by Alpers et al, the liver safety data from major tolvaptan trials in ADPKD patients were summarized. Monthly liver function test monitoring during the first 18 months of treatment and every 3 months thereafter is currently mandated by REMS and is appropriate and necessary to protect the safety of the rare patients who experience DILI from tolvaptan. Future studies examining different approaches to rechallenge patients after initial tolvaptan-induced liver injury will help to determine optimal management of those patients, while identification of risk factors for DILI susceptibility and the development of prediction models could improve the clinical approach.

More genotype data from tolvaptan-exposed patients with pathogenic variants in PKD1 or PKD2, no variant detected, and variants of unknown significance could also help to gauge the risk–benefit ratio with respect to potential for clinical benefit and liver safety profile. Nevertheless, given the recent disappointments faced by the ADPKD community with tesevatinib, venglustat, and lixivaptan, we must not allow fear of tolvaptan-induced liver injury to prevent use of this important medication.

Article Information

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