3-1-2023

Clinical pattern of tolvaptan-associated liver injury in trial participants with autosomal dominant polycystic kidney disease (ADPKD): An analysis of pivotal clinical trials

David H Alpers

James H Lewis

Christine M Hunt

James W Freston

Vicente E Torres

See next page for additional authors

Authors

David H Alpers, James H Lewis, Christine M Hunt, James W Freston, Vicente E Torres, Hui Li, Wenchyi Wang, Molly E Hoke, Sharin E Roth, Lucas Westcott-Baker, and Alvin Estilo

Clinical Pattern of Tolvaptan-Associated Liver Injury in Trial Participants With Autosomal Dominant Polycystic Kidney Disease (ADPKD): An Analysis of Pivotal Clinical Trials

David H. Alpers, James H. Lewis, Christine M. Hunt, James W. Freston, Vicente E. Torres, Hui Li, Wenchyi Wang, Molly E. Hoke, Sharin E. Roth, Lucas Westcott-Baker, and Alvin Estilo

Rationale & Objective: Tolvaptan is associated with risk of drug-induced liver injury when used to treat autosomal dominant polycystic kidney disease (ADPKD). After this risk was described based on the clinical trials TEMPO 3:4 and TEMPO 4:4, additional data from the REPRISE trial and a long-term extension of TEMPO 4:4, REPRISE, and other tolvaptan trials in ADPKD have become available. To further characterize the hepatic safety profile of tolvaptan, an analysis of the expanded dataset was conducted.

Study Design: Analysis of safety data from prospective clinical trials of tolvaptan.

Setting & Participants: Multicenter clinical trials including more than 2,900 tolvaptan-treated participants, more than 2,300 with at least 18 months of drug exposure.

Intervention: Tolvaptan administered twice daily in split-dose regimens.

Outcomes: Frequency of liver enzyme level increases detected by regular laboratory monitoring.

Results: In the placebo-controlled REPRISE trial, more tolvaptan- than placebo-treated participants (38 of 681 [5.6%] vs 8 of 685 [1.2%]) experienced alanine aminotransferase level increases to >3× the upper limit of normal (ULN), similar to TEMPO 3:4 (40 of 957 [4.4%] vs 5 of 484 [1.0%]). No participant in REPRISE or the long-term extension experienced concurrent alanine aminotransferase level increases to >3× ULN and total bilirubin increases to >2× ULN ("Hy's Law" laboratory criteria). Based on the expanded dataset, liver enzyme increases most often occurred within 18 months after tolvaptan initiation and were less frequent thereafter. Increased levels returned to normal or near normal after treatment interruption or discontinuation. Thirty-eight patients were rechallenged with tolvaptan after the initial drug-induced liver injury episode, with return of liver enzyme level increases in 30; 1 additional participant showed a clinical "adaptation" after the initial episode, with resolution of the enzyme level increases despite continuation of tolvaptan.

Limitations: Retrospective analysis.

Conclusions: The absence of Hy's Law cases in REPRISE and the long-term extension trial support monthly liver enzyme monitoring during the first 18 months of tolvaptan exposure and every 3 months thereafter to detect and manage enzyme level increases, as is recommended on the drug label.

Funding: Otsuka Pharmaceutical Development & Commercialization, Inc.

Trial Registration: Trials included in the dataset were registered at ClinicalTrials.gov with study numbers NCT00428948 (TEMPO 3:4), NCT01214421 (TEMPO 4:4), NCT02160145 (REPRISE), and NCT02251275 (long-term extension).

Visual Abstract online

Complete author and article information provided before references.

Correspondence to D.H. Alpers (dalpers@wustl.edu)

Am J Kidney Dis. 81(3):281-293. Published online September 30, 2022.

doi: 10.1053/j.ajkd.2022.08.012

Autosomal dominant polycystic kidney disease (ADPKD) is the most common inherited kidney disorder and the fourth leading cause of kidney failure worldwide.[1] This condition is characterized by the development of slow-growing, fluid-filled cysts in the kidneys.

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Liver cysts appear in approximately 80% of affected patients by age 30 years, and, less commonly, cysts on other organs may develop.[1] Tolvaptan, a selective arginine vasopressin receptor type 2 antagonist, has been shown to reduce the rate of growth in kidney volume and to slow decline in kidney function in those with ADPKD who are at risk of rapid disease progression, based on 2 pivotal phase 3 trials (TEMPO 3:4 [ClinicalTrials.gov identifier NCT00428948] and REPRISE [NCT02160145]).[2,3] TEMPO 3:4 demonstrated significant slowing of kidney function decline with tolvaptan versus placebo over a period of 3 years in participants with predominantly early-stage chronic kidney disease (CKD) at baseline (83% in CKD glomerular filtration rate categories 1 and 2 [CKD G1-G2], corresponding to an estimated glomerular filtration rate ≥60 mL/min/1.73 m^2),[4] and REPRISE subsequently showed a similar result over 1 year of treatment in participants with later-stage CKD (95% in CKD G3-G4, corresponding to an estimated glomerular filtration rate of 15-59 mL/min/1.73 m^2).[3]

The potential for drug-induced liver injury (DILI) is a major concern in the pharmaceutical development process.

PLAIN-LANGUAGE SUMMARY

In early clinical trials of tolvaptan (TEMPO 3:4 and TEMPO 4:4), liver enzyme level increases in tolvaptan-treated participants indicated risk for drug-induced liver injury. We evaluated data from 2 subsequent large-scale clinical studies (REPRISE and a long-term extension of all 3 trials) that were conducted after monthly liver enzyme testing became required for patients enrolled in tolvaptan trials. No additional liver enzyme level increases meeting the criteria for greatest risk (ie, "Hy's Law" cases) were reported, and the less severe increases that did occur were seen mainly during the first 18 months of treatment. These results support the conclusion that monthly liver enzyme testing of tolvaptan-treated patients during the first 18 months of therapy enabled timely detection and intervention before severe drug-induced liver injury could occur.

Drugs may cause liver injury in a predictable, dose-dependent manner in preclinical models and in humans; such toxicity is termed "intrinsic DILI," with acetaminophen as the most common and well-known causative agent.[5] Complicating liver safety evaluation, rare, severe, and unpredictable DILI events known as "idiosyncratic DILI" may occur without a clear relationship to dose and be detected only after weeks to months of treatment. Several possible mechanisms are involved with idiosyncratic DILI, including induced stress placed on hepatocytes that results in neoantigen generation, triggering an attack on hepatocytes by the adaptive immune system; disruption of hepatocyte transporters; impairment of the bile salt excretory pump; and damage to mitochondria.[5] In some cases, genetic predisposition to liver injury can be found, the result of various metabolic polymorphisms.[5] Idiosyncratic DILI can take the clinical, biochemical, and histological forms of all acute and chronic forms of liver disease, making its diagnosis challenging in the absence of a specific DILI biomarker.[6] Even though the incidence of idiosyncratic DILI is considered quite rare (on the order of 3-20 cases per 100,000 persons),[6,7] the most common causes of idiosyncratic DILI are well-established hepatotoxins, including antimicrobial and anticonvulsant agents and various dietary and weight-loss supplements, as well as herbal compounds; more than 650 drugs have the potential to cause liver injury.[8]

Idiosyncratic DILI events may not be seen during clinical trials because of their rarity or because many trials have limited numbers of patients. As a result, laboratory monitoring of liver tests to identify signs of liver injury is nearly universally performed to assess the hepatic safety risk.[9] Aminotransferase level increases to more than 3 times the upper limit of normal (ULN) or increases in serum alkaline phosphatase levels are potential early indicators of DILI.[10] The clinical observations of Dr Hyman Zimmerman, starting in the 1960s, that drug-induced hepatocellular jaundice was associated with a poor prognosis—with a mortality rate (or need for liver transplant) due to acute liver failure in ≥10% of affected patients—led the US Food and Drug Administration (FDA) to introduce rules to reduce the risk of severe hepatotoxicity in clinical trials.[11] The FDA coined the term "Hy's Law," whereby a drug needs to be stopped immediately whenever alanine aminotransferase (ALT) or aspartate aminotransferase (AST) levels increase to >3× ULN with total bilirubin level >2× ULN. If these biochemical criteria are met, a causality assessment to exclude other possible causes of the liver injury must be conducted in order for Hy's Law to be invoked. Even a single verified Hy's Law case in a clinical trial can have severe regulatory consequences, including nonapproval or removal of a drug from the market, based on a risk-benefit assessment.[12]

In the tolvaptan clinical trial program for ADPKD, 3 participants met the criteria for Hy's Law: 2 from TEMPO 3:4 and 1 from its open-label extension known as TEMPO 4:4 (NCT01214421).[13] There was also a higher proportion of participants with ALT level >3× ULN in the tolvaptan arm (4.4%) than in the placebo arm (1.0%) in TEMPO 3:4.[14] Accordingly, on unblinding of TEMPO 3:4, the frequency of liver chemistry monitoring was increased. In TEMPO 3:4, monitoring was performed every 4 months; in TEMPO 4:4, it started at every 6 months but was changed to every 3 months and finally to monthly. An independent, blinded, expert hepatic adjudication committee (HAC) reexamined participant-level data from the TEMPO trials, as well as from participants without ADPKD who had received tolvaptan in clinical trials for other indications. A signature pattern of susceptibility was identified in which the onset of hepatocellular injury was generally between 3 and 18 months of starting tolvaptan treatment, with injury gradually resolving over 1-4 months following drug cessation.[14] It should be noted that, with rare exception, patients with ADPKD, including those with polycystic disease of the liver (seen in as many as 94% of patients), have normal liver biochemical test results, including for ALT, AST, alkaline phosphatase, and bilirubin.[15] As a result, ADPKD, even with polycystic disease of the liver, is not believed to be a likely cause of any liver abnormalities that develop.

Monthly liver chemistry testing was implemented in REPRISE, and no Hy's Law cases were reported.[3] Similarly, for those entering a long-term, open-label extension trial (NCT02251275) that included participants from TEMPO 4:4, REPRISE, or other tolvaptan trials in ADPKD, testing was monthly until 18 months of tolvaptan exposure, and then every 3 months.[16] The US label for JYNARQUE (tolvaptan) requires blood testing for ALT, AST, and bilirubin before drug initiation, at 2 and 4 weeks after initiation, monthly for 18 months, and once every 3 months thereafter.[17]

DILI is a diagnosis of exclusion, and positive rechallenge data are among the most confirmatory pieces of evidence.

When rechallenge data are available, it is an important variable in causality assessment and adjudication.[18] Gathering data on negative rechallenge is not as useful for causality assessment, but is helpful in determining if a drug can safely be readministered, especially when the benefit outweighs the risk, such as with the treatment of drug-resistant tuberculosis with isoniazid.[19] However, rechallenge can potentially be dangerous and lead to severe liver injury and death, so it should be performed only in the absence of prior hypersensitivity or severe liver injury and with patient consent, frequent liver enzyme testing, and the close follow-up of an experienced physician.

Since publication of the results from the HAC analysis,[14] additional safety data have become available from the REPRISE trial and the long-term, open-label extension trial. To further characterize the hepatic safety profile of tolvaptan in ADPKD, the HAC here presents an updated analysis based on the expanded dataset.

Methods

Analysis Population

The safety databases reviewed were generated in clinical trials that examined the efficacy and safety of tolvaptan in ADPKD. The trials included TEMPO 3:4, TEMPO 4:4, REPRISE, and the long-term, open-label extension. Study design, enrollment, and tolvaptan exposure are discussed in detail in Item S1.

Adjudication of Hepatic Safety Signals

The HAC comprised 4 expert hepatologists (DHA, JHL, CMH, and JWF) who examined data from TEMPO 3:4, TEMPO 4:4, REPRISE, and the long-term extension in participants with aminotransferase levels >3× ULN using the 5-point US DILI Network classification.[20] Per the adjudication charter, adjudication criteria included adverse events meeting any of the 5 hepatic standardized Medical Dictionary for Regulatory Activities queries or any of the following liver-related investigations: ALT level >3× ULN and total bilirubin level >2× ULN, AST level >3× ULN and total bilirubin level >2× ULN, and either ALT or AST level >5× ULN (lowered to >3× ULN as a more stringent and conservative approach to understand tolvaptan DILI). A total bilirubin level >2× ULN was originally included in the adjudication criteria but later dropped because the hepatology experts agreed that a patient with an isolated increase in serum total bilirubin level in the absence of the other selection criteria was not a DILI concern.[14]

For causality assessment, the HAC used "expert opinion"[21,22] rather than a structured scoring instrument (eg, Roussel Uclaf Causality Assessment Method).[23] The committee assessed causality of all adjudicated events based on comorbid conditions, concomitant medication use, onset, offset, and dose relationship. Events of interest were allocated into the following 5 causality groups as defined by the DILI Network[20,21] based on the likelihood that the injury was caused by the drug: "definite" (>95%), "highly likely" (75%-95%), "probable" (50%-74%), "possible" (25%-49%), and "unlikely" (<25%).[14]

Evaluation of Drug-Induced Serious Hepatotoxicity Assessments

Potential hepatocellular injury was visualized using the evaluation of Drug-Induced Serious Hepatotoxicity approach, which has been described previously.[14,24,25] In this graphical methodology, the logarithm of the peak serum ALT concentration is plotted for each participant along the x axis, and the logarithm of the peak serum total bilirubin concentration is plotted along the y axis. Each peak represents the maximal value of ALT or total bilirubin during an event, and each may occur on different days during the event. Four quadrants on the evaluation of Drug-Induced Serious Hepatotoxicity plot are defined by lines at ALT level 3× ULN and total bilirubin level 2× ULN. The upper-right quadrant is the Hy's Law quadrant of potentially severe liver injury, even though participants may also appear there as a result of cholestatic liver injury. To separate out these latter confounders, FDA guidance defines a participant in the upper-right quadrant as having severe DILI when the serum alkaline phosphatase level is <2× ULN and all other possible explanations of the injury (eg, viral hepatitis, alcohol hepatitis) have been ruled out.[11] An excess of participants in the lower-right quadrant (ie, the "Temple's Corollary Quadrant"[24]) for a trial drug relative to placebo also indicates a drug that may be capable of causing liver injury, even when examination of the Hy's Law quadrant is unrevealing.[11] This reflects the fact that ALT is a more sensitive indicator of hepatocellular injury than total bilirubin and that increases in ALT concentration may occur before or without accompanying increases in total bilirubin concentration.[26]

Rechallenge Assignments

Rechallenge criteria were included in the trial protocols for REPRISE and the long-term extension for participants who interrupted trial drug as a result of abnormal aminotransferase or bilirubin levels. The criteria specified that liver aminotransferase or bilirubin levels ≥2× ULN that had an uncertain or rapidly increasing trajectory should prompt at least temporary study drug interruption. The study drug should not be resumed until monitoring indicated that the abnormalities had resolved, were stable, or were not rapidly increasing, and then only with an increased frequency of monitoring. Participants would not typically be allowed to resume treatment with study drug if (1) aminotransferase levels increased to >8× ULN, (2) aminotransferase levels were >5× ULN for more than 2 weeks, or (3) there were concurrent increases of aminotransferase levels to >3× ULN and total bilirubin levels to >2× ULN. Participants with these levels of abnormality, however, could be rechallenged if the abnormalities were adjudicated as having a <50% likelihood of being related to study drug (per DILI Network probability criteria) by the independent HAC and the investigator and medical monitor agreed to an intensive monitoring plan to mitigate

risk. The participant must also have been willing to comply with these monitoring measures, be informed of the potential risks, and consent to study drug rechallenge.

There are no universally agreed-upon threshold values to define a positive drug rechallenge, with suggested ALT level thresholds ranging from 2× to 5× ULN with drug rechallenge.[23,27-29] In the clinical trials of tolvaptan in participants with ADPKD, in some cases, the original ALT increase did not reach >3× ULN and was still determined to represent DILI. Therefore, in this analysis, a DILI case was deemed a "positive rechallenge" when there was a doubling from baseline in ALT level following tolvaptan rechallenge at any dose. A positive rechallenge was followed by a recovery to normal or near-normal ALT levels while continuing to receive or discontinuing tolvaptan. A negative rechallenge is commonly defined by ALT level increases observed temporally related to the suspect drug, followed by rechallenge and ALT levels that are unchanged or <3× ULN.[29] However, similar to what was found in DILI positive rechallenge with tolvaptan, a DILI was deemed a "negative rechallenge" if the ALT level was less than double the baseline level following rechallenge. If discontinuation of tolvaptan never occurred, regardless of whether the dose remained the same or was reduced, and the ALT levels stabilized or returned to normal or near-normal levels, the DILI was deemed "adaptation." If the participant was dechallenged and not rechallenged, or if there were not sufficient data to definitively determine positive or negative rechallenge, the participant was excluded from the rechallenge analysis.

Statistical Analyses

For this assessment of safety data, summary statistics are presented. All comparisons were based on empirical results without hypothesis testing.

Compliance With Ethical Standards

All ADPKD clinical trials were supported by Otsuka Pharmaceutical Development & Commercialization, Inc, and were conducted in compliance with the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use Good Clinical Practice guideline, the ethical principles originating in the Declaration of Helsinki, and all other applicable regional regulatory requirements. Each trial site was approved by its local institutional review board or ethics committee according to regional requirements. Written informed consent was obtained from all participants before initiation of any procedure being performed.

Results

Participants

Tolvaptan exposure in the 4 ADPKD trials was extensive (>2,300 participants had ≥18 months of exposure; Fig 1). Nearly 800 participants, namely those entering the long-term extension from TEMPO 4:4, had at least 5 years of exposure, and 86 participants had more than 10 years of exposure.

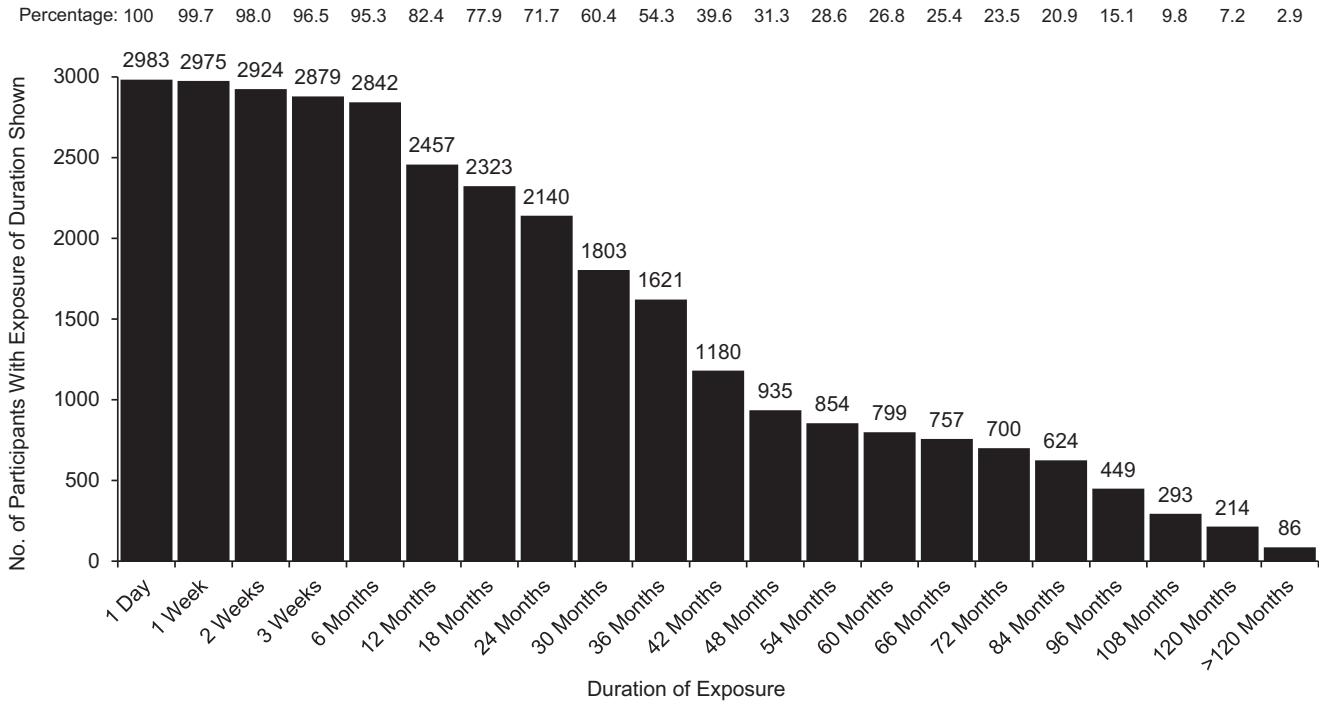

Figure 1. Duration of exposure to tolvaptan in the 4 phase 3 autosomal dominant polycystic kidney disease trials (TEMPO 3:4, TEMPO 4:4, REPRISE, long-term extension).

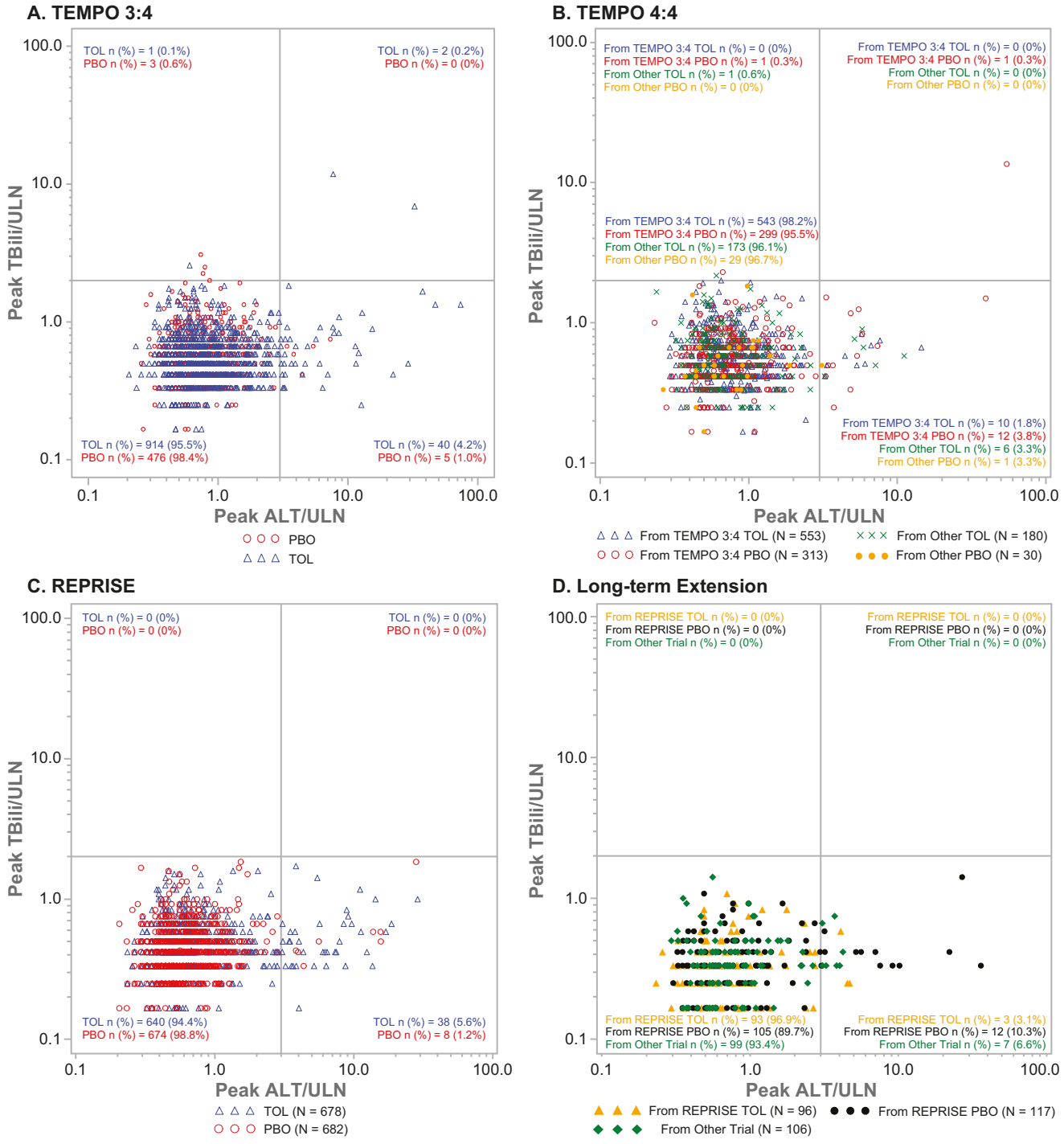

Figure 2. Evaluation of drug-induced serious hepatotoxicity plots for the 4 pivotal autosomal dominant polycystic kidney disease trials: peak alanine aminotransferase (ALT) level (x axis) versus peak total bilirubin (TBili) level (y axis). Vertical lines correspond to ALT levels >3× the upper limit of normal (ULN). Horizontal lines correspond to TBili levels >2× ULN. Participants in the lower-left quadrant have relatively normal levels, and participants meeting Hy's Law laboratory criteria for potentially severe liver injury (ALT level >3× ULN and TBili level >2× ULN with serum alkaline phosphatase level <2× ULN) are shown in the upper-right quadrant. (B and D) Participants in the TEMPO 4:4 extension and the long-term extension are categorized by trial before entry: TEMPO 4:4 participants entered from TEMPO 3:4, TEMPO 2:4, NOCTURNE, trial 156-06-260, trial NCT01336972, and trial NCT01210560; and long-term extension participants entered from TEMPO 3:4, NOCTURNE, TEMPO 4:4, and REPRISE (Table S1). Abbreviations: PBO, placebo; TOL, tolvaptan. A is reproduced with permission from Watkins et al[14]; original graphic ©2015 Watkins et al.

Hepatic Events

As previously reported, more tolvaptan- than placebo-treated participants with at least one postbaseline assessment of hepatic injury exhibited ALT levels >3× ULN in TEMPO 3:4 (40 of 957 [4.4%] vs 5 of 484 [1.0%], respectively).[14] Similar to TEMPO 3:4, in REPRISE, more participants treated with tolvaptan experienced ALT increases to >3× ULN compared with those who received placebo (38 of 681 [5.6%] vs 8 of 685 [1.2%]).[3] In all cases, the increased liver enzyme levels returned to normal or near-normal after the interruption or discontinuation of treatment.[3,14] Participants with ALT level >3× ULN and total bilirubin level >2× ULN are depicted in evaluation of Drug-Induced Serious Hepatotoxicity plots in Fig 2. No participant in REPRISE or the long-term extension experienced a concurrent increase of ALT level to >3× ULN and total bilirubin level to >2× ULN (Hy's Law laboratory criteria).

A total of 125 events in as many tolvaptan- or placebo-treated participants were identified that met the trigger criteria for adjudication in REPRISE (72 events) and the long-term extension (53 events; Table 1). Using data in which treatment information had been masked, 15 events were adjudicated as probable and 39 as possible in REPRISE, and another 2 were rated as probable and 24 as possible in the long-term extension. No events in REPRISE or the long-term extension were adjudicated as definite or highly likely. Figures S1-S42 illustrate liver enzyme levels over time in participants with events adjudicated as having at least a probable relationship to tolvaptan.

In REPRISE, ALT or AST concentration increases started to occur approximately 2-3 months after the initiation of tolvaptan and continued to be reported during the 12-month trial period.[3] The temporal pattern in REPRISE and the long-term extension (Fig 3) was consistent with the window of susceptibility observed in TEMPO 3:4, ie, increases in liver enzyme levels occurred within 18 months after the initiation of tolvaptan and were less frequent thereafter. No event observed after 18 months of tolvaptan treatment was adjudicated as having more than a possible relationship with tolvaptan, suggesting that monthly liver chemistry tests for the first 18 months of treatment and then every 3 months were sufficient. In Fig 3B, participants entering the long-term extension from the REPRISE placebo arm were newly exposed to long-term tolvaptan after 1 year of receiving placebo, accounting for the higher rate of increases. This rate was comparable with the REPRISE tolvaptan arm in Fig 3A but not quite as high, and both curves reached plateaus at approximately the same time (≥350 days of exposure).

In each of the trials, baseline characteristics were generally similar between tolvaptan-treated participants who experienced hepatic events that were adjudicated as probable, highly likely, or definite and participants who

Table 1. Adjudication Results of Hepatic Events in Tolvaptan- and Placebo-Treated Participants

	TEMPO 3:4	TEMPO 4:4	REPRISE	Long-term Extension	Total
Tolvaptan and placebo combined					
No. of participants adjudicated	46	39	72	53	210
Definite (>95%)	0	0	0	0	0
Highly likely (75%-95%)	1	3	0	0	4
Probable (50%-74%)	17	6	15[a]	2	40
Possible (25%-49%)	11	11	39	24	85
Unlikely (<25%)	17	19	18	23	77
Insufficient data	0	0	0	4	4
Tolvaptan					
No. of participants adjudicated	35	39	62	53	189
Definite (>95%)	0	0	0	0	0
Highly likely (75%-95%)	1	3	0	0	4
Probable (50%-74%)	16	6	15	2	39
Possible (25%-49%)	9	11	33	24	77
Unlikely (<25%)	9	19	14	23	65
Insufficient data	0	0	0	4	4
Placebo					
No. of participants adjudicated	11	0	10	0	21
Definite (>95%)	0	0	0	0	0
Highly likely (75%-95%)	0	0	0	0	0
Probable (50%-74%)	1	0	0	0	1
Possible (25%-49%)	2	0	6	0	8
Unlikely (<25%)	8	0	4	0	12
Insufficient data	0	0	0	0	0

[a]Includes 11 events previously reported[3] and 4 additional events.

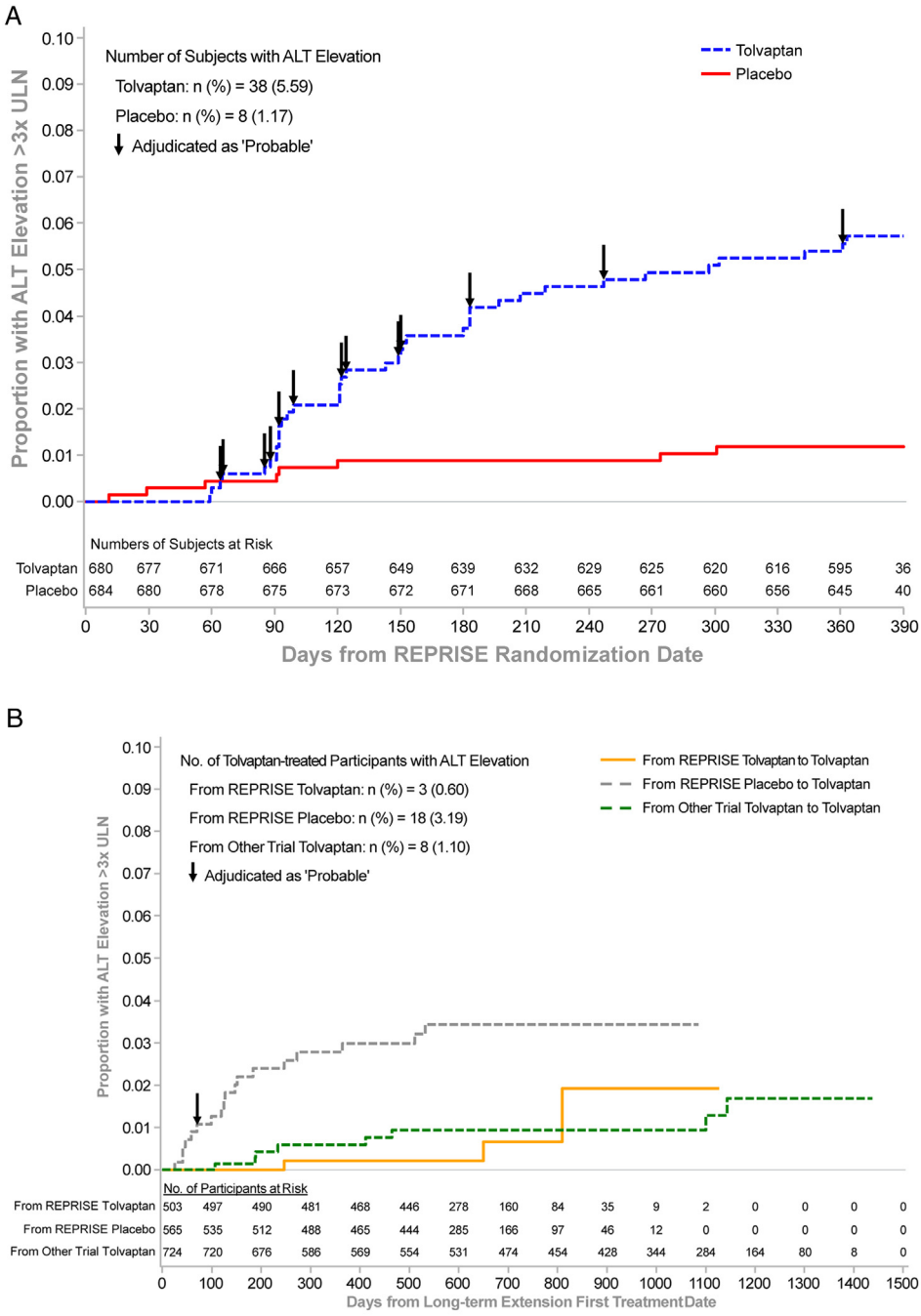

Figure 3. Kaplan-Meier curves of time to first increase in alanine aminotransferase (ALT) level to >3× the upper limit of normal (ULN) in REPRISE (A) and the long-term extension (B). Arrows indicate time to first increase to >3× ULN adjudicated as having a "probable" relationship to tolvaptan for each participant. (A) Shown are 11 events previously reported[3] and 2 additional events. The hepatic adjudication committee deemed 2 additional hepatic events (one participant at day 382; the other at day 387) with ALT level increases to <3× ULN (data not shown) to be probably related to tolvaptan. (B) Participants in the long-term extension categorized by their trial prior to entry; participants in the "Other Trial" group had received tolvaptan previously in TEMPO 3:4, NOCTURNE, TEMPO 4:4, and/or REPRISE (Table S1). The hepatic adjudication committee deemed one additional hepatic event in a participant who had received tolvaptan for 158 days and exhibited ALT level increases to <3× ULN (data not shown) to be probably related to tolvaptan in the long-term extension.

did not (Table 2). Participants with events adjudicated as at least probable had lower estimated glomerular filtration rates.

In participants who provided DNA samples, no correlations between PKD1 or PKD2 genotype and HAC adjudication result were evident (Table 3). However, all participants

Table 2. Baseline Characteristics of Tolvaptan-Treated Participants With and Without Hepatic Event Causality Adjudicated as "Probable" or Higher

	TEMPO 3:4		TEMPO 4:4		REPRISE		Long-term Extension	
Parameter	Probable+[a]	Other	Probable+[a]	Other	Probable+[a]	Other	Probable+[a]	Other
No. of participants	17[b]	944	9	1,074	15	668	2	1,801
Age, y	41.1 ± 6.1	38.5 ± 7.1	42.3 ± 3.3	41.7 ± 7.8	46.3 ± 8.8	47.3 ± 8.2	54.5 ± 12.0	47.4 ± 8.1
Female sex	12 (71%)	454 (48.1%)	6 (67%)	510 (47.5%)	8 (53%)	328 (49.1%)	1 (50%)	873 (48.5%)
Height, cm	168.5 ± 13.0	173.6 ± 10.3	176.6 ± 7.0	174.6 ± 10.6	174.5 ± 9.8	173.7 ± 10.4	170.5 ± 3.5	173.8 ± 10.6
Weight, kg	73.6 ± 19.7	79.6 ± 18.2	81.7 ± 14.1	82.1 ± 18.3	81.7 ± 15.5	84.7 ± 19.9	71.1 ± 7.0	84.0 ± 19.4
Race and ethnicity								
White	12 (71%)	798 (84.5%)	9 (100%)	1,024 (95.3%)	13 (87%)	613 (91.8%)	2 (100%)	1,687 (93.7%)
Black	0	16 (1.7%)	0	16 (1.5%)	2 (13%)	23 (3.4%)	0	48 (2.7%)
Hispanic[c]	0	13 (1.4%)	0	1 (0.1%)	1 (7%)	43 (6.4%)	1 (50%)	101 (5.6%)
Asian	5 (29%)	116 (12.3%)	0	10 (0.9%)	0	22 (3.3%)	0	42 (2.3%)
Other	0	1 (0.1%)	0	23 (2.1%)	0	10 (1.5%)	0	24 (1.3%)
eGFR, mL/min/1.73 m^2	77.2 ± 21.5	81.4 ± 21.0	52.4 ± 24.6	70.0 ± 25.2	39.3 ± 11.6	40.7 ± 10.9	36.7 ± 7.9	47.1 ± 20.7

Abbreviation: eGFR, estimated glomerular filtration rate (calculated using the 2009 Chronic Kidney Disease Epidemiology Collaboration creatinine equation).
[a]"Probable+" indicates hepatic event causality adjudicated as "probable," "highly likely," or "definite."
[b]One participant in TEMPO 3:4 who was adjudicated as probable or higher was in the placebo group, so 18 participants are shown as probable or higher in Table 1 and 17 are shown here.
[c]Because Hispanic ethnicity did not exclude race categories, percentages for race and ethnicity may add up to >100%.

with DILI episodes adjudicated as at least probable also had a PKD1 variant, which is associated with more rapidly progressive disease.

Thirty-nine patients were rechallenged with tolvaptan (n = 38) or adapted while continuing to receive tolvaptan (n = 1) after the initial DILI episode (Table 4). Following ALT recovery from the initial DILI, most of the 38 rechallenged patients (n = 27 [71%]) were rechallenged with a reduced tolvaptan dose. Among all rechallenged patients, most (n = 30 [79%]) experienced a positive rechallenge, with 23 (61%) exhibiting ALT recovery off tolvaptan and 7 (18%) experiencing ALT recovery despite continued tolvaptan administration after positive rechallenge. Eight of 38 rechallenged patients (21%) experienced a negative rechallenge, and an additional patient was not rechallenged but exhibited adaptation while continuing to receive tolvaptan. No events of liver failure were observed. Plots of liver enzyme concentrations versus time shown in Fig S43A-C are representative examples of positive rechallenge when the original or rechallenge ALT peak was ≤3× ULN but at least double the baseline measurement.

The 8 patients who were deemed to have a negative rechallenge all had a peak ALT ≤20× ULN, and half were rechallenged at a reduced dose (Table 4). Figure S43D depicts liver enzyme levels over time in a patient with negative rechallenge, showing a rapid increase in ALT level and a return to baseline after dechallenge. Upon rechallenge, ALT levels remained normal to near-normal for the remainder of the trial.

In another clinical pattern of tolvaptan DILI, adaptation (Table 4), the initial DILI episode typically results in dose reduction of 45 or 60 mg total daily dose but can also be observed with a maintained original 120-mg total daily dose. One patient had 3 ALT peaks: after the first, the dose was reduced to 90 mg total daily dose; after the second, tolvaptan was discontinued; and, after the third, the patient continued tolvaptan treatment at a total daily dose of 60 mg and was deemed to have shown adaptation based on the third ALT peak (Fig S43E).

Discussion

Similar to TEMPO 3:4, more participants treated with tolvaptan in REPRISE experienced ALT level increases to >3× ULN compared with those who received placebo (5.6% vs 1.2%). Although comparisons with placebo are limited to the randomized trials TEMPO 3:4 and REPRISE, it is notable that no additional Hy's Law cases beyond those that occurred in the TEMPO program were reported in REPRISE or the long-term extension, even though the REPRISE population had more advanced ADPKD than the TEMPO 3:4 population. These findings suggest that increasing liver chemistry monitoring to monthly helped to identify hepatic enzyme concentration increases early and prevented severe liver injury with more rapid interruption or discontinuation of treatment. In most liver injury, ALT is more liver-specific and exhibits higher activity than AST.[30]

Table 3. PKD1 and PKD2 Genotype for Adjudicated Tolvaptan-Treated Participants With DNA Samples

	Adjudication Categorization							All Tolvaptan Participants With Variant
	Definite	Highly Likely	Probable	Possible	Unlikely	Insufficient Data	Total	
TEMPO 3:4 and TEMPO 4:4								
No. of participants	0	3	7	7	11	0	28	982[a]
PKD1 truncating	–	2 (67%)	6 (86%)	4 (57%)	8 (73%)	–	20 (71%)	586 (60%)
PKD1 nontruncating	–	1 (33%)	1 (14%)	2 (29%)	2 (18%)	–	6 (21%)	263 (27%)
PKD2 truncating	–	–	–	–	–	–	–	87 (9%)
PKD2 nontruncating	–	–	–	1 (14%)	1 (9%)	–	2 (7%)	19 (2%)
No variant detected	–	–	–	–	–	–	–	27 (3%)
REPRISE and long-term extension								
No. of participants	0	0	16	47	25	2	90	1,127
PKD1 truncating	–	–	10 (63%)	21 (45%)	15 (60%)	1 (50%)	47 (52%)	634 (56%)
PKD1 nontruncating	–	–	6 (38%)	20 (43%)	7 (28%)	–	33 (37%)	302 (27%)
PKD2 truncating	–	–	–	5 (11%)	3 (12%)	1 (50%)	9 (10%)	125 (11%)
PKD2 nontruncating	–	–	–	–	–	–	–	12 (1%)
HNF1B truncating	–	–	–	–	–	–	–	1 (0.1%)
No variant detected	–	–	–	1 (2%)	–	–	1 (1%)	53 (5%)

Participants with >1 event are included in the table once under the highest adjudicated causality (ie, "probable" > "possible" > "unlikely" > "insufficient data"). Because all participants in REPRISE underwent a tolvaptan run-in period, the table includes participants who were randomized to placebo and had an event during the tolvaptan run-in or who were not randomized as a result of an event during tolvaptan run-in.
[a]Total excludes 4 participants who withdrew consent and 2 for whom genotype could not be determined.

In REPRISE and the long-term extension, tolvaptan was found to be generally safe and well tolerated when administered twice daily in a split dose (ie, 45/15, 60/30, 90/30 mg). Tolvaptan exposure in this population was extensive, with 1,571 (87.3%) participants having more than 18 months of tolvaptan treatment. Events of liver

Table 4. Comparison of Baseline Characteristics and First Increased ALT Events Between Participants With Negative Rechallenge, Positive Rechallenge, or Adaptation

Characteristic	Positive Rechallenge[a]		Negative Rechallenge[b] (n = 8 [21%])	Adaptation[c] (n = 1 [3%])
	Recovery off Drug (n = 23 [59%])	Recovery on Drug (n = 7 [18%])		
Age, y				
Mean ± SD	48 ± 8	47 ± 6	49 ± 11	37
Median	48 (33-63)	46 (39-57)	53 (33-63)	37 (37-37)
Female sex	14 (61%)	3 (43%)	3 (38%)	0
Race				
Asian	1 (4%)	0	0	0
White	22 (96%)	7 (100%)	8 (100%)	1 (100%)
Peak category of first increased ALT events				
ALT ≤3× ULN	7 (30%)	4 (57%)	2 (25%)	0
ALT >3-5× ULN	8 (35%)	2 (29%)	3 (38%)	0
ALT >5-8× ULN	4 (17%)	1 (14%)	1 (13%)	1 (100%)
ALT >8-20× ULN	3 (13%)	0	2 (25%)	0
ALT >20× ULN	1 (4%)	0	0	0
Time to onset of first increased ALT events, d	214.0 (63-1,391)	239.0 (118-307)	611.0 (185-1,901)	8.0 (8-8)
Time from onset to recovery of first increased ALT events, d	91.0 (17-482)	36.0 (30-112)	60.5 (15-110)	117.0 (117-117)
Rechallenged with reduced dose				
Yes	17 (74%)	6 (86%)	4 (50%)	NA
No	6 (26%)	1 (14%)	4 (50%)	NA
Time to recurrence of increased ALT after rechallenge, d	55.0 [14-114]	89.0 [27-147]	NA	NA

Values presented as median (range) or median [5th-95th percentile]. Abbreviations: ALT, alanine aminotransferase; NA, not applicable; ULN, upper limit of normal.
[a]Doubling in ALT level following tolvaptan rechallenge.
[b]ALT level less than doubled following tolvaptan rechallenge.
[c]If discontinuation of tolvaptan never occurred, regardless of whether the dose remained the same or was reduced, and ALT level returned to normal or near-normal levels.

injury were reversible in REPRISE and the long-term extension, consistent with earlier experience in the TEMPO trials.

The temporal pattern of ALT level increases to >3× ULN was consistent across TEMPO 3:4 and REPRISE; in both trials, the increases occurred between 60 and 240 days after the initiation of tolvaptan and became less frequent thereafter.[3] Additionally, as the signature of the drug has become clearer over time, a pattern has emerged whereby aminotransferase levels may continue to increase for as long as several weeks after stopping the drug (as seen in many of the cases in Figs S1-S42) before returning to normal or near-normal, a pattern usually indicative of an adaptive immune response.[5]

The mechanisms of DILI have been illustrated more fully in recent years,[9,31] and it is possible to propose tolvaptan-specific DILI mechanisms. Metabolized extensively by cytochrome P450 3A,[32] tolvaptan and its metabolites are largely eliminated through liver metabolism and fecal excretion.[33,34] Systemic tolvaptan exposure increases in patients with reduced creatinine clearance (<30 mL/min) compared with those with more preserved kidney function,[35] an increase that may be associated with tolvaptan-related liver injury in susceptible patients.[36] The main metabolites of tolvaptan include an oxybutyric acid metabolite (DM-4103), whose half-life in apparently healthy individuals is more than 180 hours, and a hydroxybutyric acid metabolite (DM-4107).[33,34] After one 60-mg dose of ^{14}C-tolvaptan, plasma concentrations of DM-4103 were detectable for more than 450 hours.[34,36] The long half-life of DM-4103 may explain the observation that liver enzyme concentrations can continue to increase and stay increased for days or weeks after stopping tolvaptan before returning to normal or near-normal. This underscores the need to stop tolvaptan when liver injury is detected, as most DILI improves with prompt drug cessation.[9]

Tolvaptan's DM-4103 metabolite inhibits multiple human hepatic proteins involved in bile acid transport, which may negatively impact bile acid homeostasis. Compared with tolvaptan and its DM-4107 metabolite, the DM-4103 metabolite is a more potent inhibitor of the bile salt export pump (BSEP), with approximately 7.5 and 29 times more inhibitory potency as measured by 50% inhibitory concentration (IC_{50}) than tolvaptan and DM-4107, respectively. Inhibition of BSEP by DM-4103 is best described as competitive inhibition, whereas tolvaptan appears to be a noncompetitive inhibitor. Regarding the potential of causing an interaction with other BSEP inhibitors based on the maximal concentration observed at steady state (C_{max}) versus the inhibitory potential (ie, IC_{50}), DM-4103 was determined to be a potential inhibitor, whereas tolvaptan and DM-4107 were not of concern.[36]

Quantitative hepatic exposures of tolvaptan and its 2 metabolites in vitro were used by Woodhead et al in DILIsym pharmacokinetic modeling to simulate tolvaptan liver injury in vivo.[37] These analyses revealed that exposure to tolvaptan and the DM-4103 metabolite, combined with the inhibition of BSEP and mitochondrial respiration, could account for tolvaptan-initiated DILI.[37] DM-4107 did not affect bile acid transporters or mitochondrial function. Because mitochondria provide the hepatocellular energy required by bile acid transporters for bile acid efflux, drugs impairing bile acid transport and mitochondrial function are associated with more severe DILI than those that exert only one mechanism of injury.[38] Bile acid accumulation and immune-mediated mechanisms of injury in vivo were not evaluated.

FDA research reports that oral medications of high lipophilicity (logP >3), with daily doses >100 mg, or that form reactive metabolites are associated with an increased risk of DILI.[39,40] Tolvaptan has high lipophilicity (logP of 4.31),[41] a total maximum daily dose of 120 mg, and no known reactive metabolites. Highly lipophilic drugs are more likely to inhibit BSEP and mitochondrial function,[42] as noted for tolvaptan in DILIsym analyses.[37] Animal, in vitro, and DILIsym modeling have implicated multidrug resistance protein 2 (MRP2) dysfunction in polycystic kidney disease[43] and reduced biliary efflux of DM-4103 in the susceptibility to tolvaptan-associated hepatocellular injury.[44] There is no known association between tolvaptan exposure and liver enzyme levels.[14]

With no alternative therapy licensed for the treatment of ADPKD and prior events of serious liver injury, tolvaptan rechallenge following DILI was performed infrequently and occasionally resulted in adaptation to liver injury; however, no known factors predict adaptation. When rechallenge was pursued, the tolvaptan dose was lowered in most cases (27 of 38 [71%]), sometimes by half the initial dose (eg, 60 mg from an initial 120 mg or a lesser amount if the original dose was ≤90 mg; Table 4; Fig S43). The willingness to continue with tolvaptan treatment following a DILI event depends on many factors, including the severity of the DILI episodes, the presence or absence of confounding factors (eg, concomitant medications), and shared decision-making of the patient and/or physician to continue with therapy. For a critical medicine, suspect drug rechallenge after a DILI event may be considered when the patient is likely to derive objective benefit that exceeds the safety risk. Rechallenge should be considered only if (1) no safer alternative therapies are available, (2) the (potentially lower) tolvaptan dose will likely provide objective benefit, (3) the patient understands the benefits and risks, has not exhibited severe, symptomatic liver injury or hypersensitivity (fever, rash, eosinophilia), will report hepatitis symptoms (nausea, anorexia, fatigue, abdominal pain), and will adhere to follow-up.[29] As seen in the presented cases, tolvaptan rechallenge was associated with reasonable safety when accompanied by more frequent enzyme testing and clinical follow-up after an informed decision in the absence of prior hypersensitivity or severe injury. Per FDA guidance, rechallenge should, in general, be performed only in patients who experienced mild aminotransferase level increases and be avoided in those who experienced increases

to >5× ULN.[11] The US label for tolvaptan specifies that the drug may be reinitiated with increased frequency of monitoring as long as ALT and AST levels remain <3× ULN. However, per the US label, tolvaptan should not be restarted in patients with signs or symptoms consistent with hepatic injury or who have had an ALT or AST level >3× ULN during treatment with tolvaptan unless there is another explanation for liver injury and the injury has resolved.[17]

The pattern of positive drug rechallenge was the most commonly observed, ie, the initial DILI episode resulted in tolvaptan cessation, and a rechallenge with a lower tolvaptan dose was followed by a rapid increase in ALT level and a later decrease to normal or near-normal levels with dechallenge. Whereas recovery from the initial DILI episode could take 2-3 months or longer, the tolvaptan rechallenge usually resolved within 1 month.

Importantly, a negative dechallenge does not exonerate the drug, as adaptation may have been responsible. Although this pattern is usually referred to as a negative rechallenge, it may also represent adaptation or may be due to an alternative cause of the original liver injury.

Hepatic adaptation following an episode of DILI is a well-described phenomenon seen in ∼20% of patients, even though the mechanisms of adaptation are unknown.[45] Normalization of ALT values may be related to a dose effect, adaptation to drug injury, or an alternative cause of the initial injury (eg, biliary event) that is no longer present. Even though no dose-response relationship was evident in an earlier evaluation of tolvaptan-induced DILI cases,[14] decreasing the tolvaptan dose led to enzyme level normalization in 10 of 27 DILI cases (Table 4). Therefore, a dose relationship at the population level is still uncertain.

Predictive functional or genetic markers of tolvaptan-induced liver injury are needed. Research is ongoing to elucidate the mechanism of tolvaptan-induced liver injury and to identify safety biomarker(s) that can be used in the management of tolvaptan treatment. The availability of archived, broadly consented biospecimens has been instrumental in these research efforts, highlighting the importance of biobanking in clinical trials.[46]

A strength of this analysis is its inclusion of more than 2,000 participants with ADPKD who received tolvaptan for 18 months or longer and were followed with more frequent liver chemistry monitoring over time to detect potential liver injury. An additional strength is the inclusion of ancillary studies describing the dual inhibition of bile acid efflux and mitochondria as a mechanism of liver injury related to tolvaptan and its long-lived DM-4103 metabolite. This analysis is limited by its retrospective methodology and the lack of mechanistic models that represent immune-mediated injury. Insufficient information to adjudicate causality precluded the evaluation of some liver injury events. In other cases, the available information was sufficient to adjudicate, but the level of proof required for a determination of a probable or stronger relationship to drug (typically a positive rechallenge or data ruling out other causes of liver disease) was unavailable, so an adjudication of possible causality was made, as is standard for the expert opinion process. Additionally, DNA samples were available for only a subset of the trial participants, restricting the dataset for genetic analysis.

Liver safety results from REPRISE and the long-term extension are consistent with those of TEMPO 3:4. Reversible increases in ALT/AST levels developed with a latency period that was usually between 3 and 18 months. The results support the conclusion that monthly hepatic monitoring during the first 18 months of tolvaptan exposure and every 3 months thereafter, as required by the prescribing information in countries where tolvaptan has been approved to treat ADPKD, enables the effective early detection of aminotransferase level increases that could result in prompt action to cease tolvaptan therapy.

Supplementary Material

Supplementary File (PDF)

Figures S1-S42: Liver enzyme levels over time in participants with events adjudicated as having a "probable" or greater relationship to tolvaptan.

Figure S43: Liver chemistries over time plots of patients with ADPKD who were rechallenged after an initial ALT increase due to tolvaptan-induced liver injury.

Item S1: Description of clinical trials included in the analysis.

Table S1: Clinical trial enrollment of participants before entry into TEMPO 4:4 and the long-term extension.

Article Information

Authors' Full Names and Academic Degrees: David H. Alpers, MD, James H. Lewis, MD, Christine M. Hunt, MD, MPH, James W. Freston, MD, PhD, Vicente E. Torres, MD, PhD, Hui Li, MS, Wenchyi Wang, PhD, Molly E. Hoke, PhD, Sharin E. Roth, MS, Lucas Westcott-Baker, MS, and Alvin Estilo, MD.

Authors' Affiliations: Division of Gastroenterology, John T. Milliken Department of Medicine, Washington University School of Medicine, St Louis, Missouri (DHA); Georgetown University School of Medicine, Washington, DC (JHL); Duke University Medical Center and Durham Veterans Affairs Health Care System, Durham, North Carolina (CMH); University of Connecticut Health Center, Farmington, Connecticut (JWF); Mayo Clinic, Rochester, Minnesota (VET); and Otsuka Pharmaceutical Development & Commercialization, Inc, Rockville, Maryland (HL, WW, MEH, SER, LW-B, AE). Current affiliation for MEH: Passage Bio, Philadelphia, PA.

Address for Correspondence: David H. Alpers, MD, Division of Gastroenterology, John T. Milliken Department of Medicine, Washington University School of Medicine in St Louis; Geriatrics, 660 S Euclid Ave, 8031-14-003, St Louis, MO 63110. Email: dalpers@wustl.edu

Authors' Contributions: Data acquisition: MEH, SER, AE; data analysis/interpretation: DHA, JHL, CMH, JWF, VET, HL, WW, MEH, SER, LW-B, AE; statistical analysis: HL, WW. Each author contributed important intellectual content during manuscript drafting or revision and agrees to be personally accountable for the individual's own contributions and to ensure that questions

pertaining to the accuracy or integrity of any portion of the work, even one in which the author was not directly involved, are appropriately investigated and resolved, including with documentation in the literature if appropriate.

Support: The trials analyzed here and retrospective safety analysis were supported by Otsuka Pharmaceutical Development & Commercialization (Rockville, MD). The sponsor participated in the design of the study; collection, analysis, and interpretation of data; writing the report; and the decision to submit the report for publication. Alice Walton, PhD, and Andrew Horgan, PhD, of BioScience Communications, Inc (New York, NY) assisted in drafting the manuscript, activity that was also funded by Otsuka. Each author participated in decisions on which data and outcomes were to be reported and in the interpretation of the data and the conclusions to be drawn.

Financial Disclosure: Drs Alpers, Lewis, and Hunt are paid consultants to Otsuka. Drs Alpers, Lewis, Hunt, and Freston are members of the HAC for tolvaptan, which is sponsored by Otsuka. Dr Alpers is the chair and Drs Lewis, Hunt, and Freston are members of the HAC for the phase 3 ALERT trial for lixivaptan, which is sponsored by Palladio Biosciences. Dr Hunt also reports consulting for Galmed and Akebia Therapeutics Inc. Dr Torres reports grants from Otsuka Pharmaceutical, Palladio Biosciences, Sanofi Genzyme, Blueprint Medicines, and Mironid outside the submitted work. Dr Wang, Ms Li, Ms Roth, Mr Westcott-Baker, and Dr Estilo are employees of Otsuka. Dr Hoke is a former employee of Otsuka.

Acknowledgments: The authors thank Peter C. Harris, PhD, of Mayo Clinic (Rochester, MN) for generating the PKD1/PKD2 genotyping data.

Data Sharing: To submit inquiries related to Otsuka clinical research, or to request access to individual participant data (IPD) associated with any Otsuka clinical trial, please visit https://clinicaltrials.otsuka.com/. For all approved IPD access requests, Otsuka will share anonymized IPD on a remotely accessible data sharing platform.

Peer Review: Received March 2, 2022. Evaluated by 2 external peer reviewers and a methods reviewer, with direct editorial input from an Associate Editor and the Editor-in-Chief. Accepted in revised form August 6, 2022.

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Tolvaptan-Associated Liver Injury in Participants With ADPKD

Setting & Participants

Retrospective analysis of
- **2 randomized trials:** *TEMPO 3:4* and *REPRISE*
- **2 extension trials:** *TEMPO 4:4* and a long-term extension study

>2,900 patients treated with tolvaptan
- ADPKD diagnosis
- Broad range of kidney function

Exposure

Tolvaptan administered twice daily in split-dose regimens

- **> 2,300 patients with ≥18 months tolvaptan exposure**
- **~ 800 patients with ≥5 years tolvaptan exposure**
- **~ 80 patients with ≥10 years tolvaptan exposure**

Liver Safety Findings

Trial	ALT >3x upper limit of normal	
	Tolvaptan	Placebo
TEMPO 3:4	4.4%	1.0%
REPRISE	5.6%	1.2%

No Hy's Law cases in REPRISE or long-term safety extension studies after monthly liver function testing required

TEMPO 3:4
TEMPO 4:4
3 cases

Monthly Testing

REPRISE Long-Term Extension
0 cases

CONCLUSION: Monthly liver enzyme monitoring during the first 18 months of tolvaptan exposure and every 3 months thereafter enabled timely detection and intervention before severe DILI* could occur.

*DILI: Drug-induced liver injury

David H. Alpers, James H. Lewis, Christine M. Hunt, et al
@AJKDonline | DOI: 10.1053/j.ajkd.2022.08.012