A *Post Hoc* Analysis of Statin Use in Tolvaptan Autosomal Dominant Polycystic Kidney Disease Pivotal Trials

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Abstract

Background and objectives Tolvaptan is approved to slow kidney function decline in adults with autosomal dominant polycystic kidney disease (ADPKD) at risk of rapid progression. Because *in vitro* studies indicated that the tolvaptan oxobutyric acid metabolite inhibits organic anion–transporting polypeptide (OATP)1B1 and OATP1B3, United States prescribing information advises avoiding concurrent use with OATP1B1/1B3 substrates, including hepatic hydroxymethyl glutaryl–CoA reductase inhibitors (statins). This *post hoc* analysis of the pivotal phase 3 tolvaptan trials (Tolvaptan Efficacy and Safety in Management of Autosomal Dominant Polycystic Kidney Disease and Its Outcomes [TEMPO] 3:4 trial [NCT00428948] and Replicating Evidence of Preserved Renal Function: an Investigation of Tolvaptan Safety and Efficacy in ADPKD [REPRISE] trial [NCT02160145]) examined the safety of concurrent tolvaptan/statin use.

Design, setting, participants, & measurements The trials randomized a combined total of 2815 subjects with early- to late-stage ADPKD to tolvaptan (n=1644) or placebo (n=1171) for 3 years (TEMPO 3:4) and 1 year (REPRISE). Statin use was unrestricted, and 597 subjects (21.2% overall; 332 [20.2%] tolvaptan, 265 [22.6%] placebo) received statins. Statin use (duration, dose change, statin change, permanent discontinuation), incidences of statin-related adverse events, and hepatic transaminase elevations were determined for subjects who received tolvaptan+statin, placebo+statin, tolvaptan alone, and placebo alone.

Results No differences in statin use parameters between tolvaptan- and placebo-treated subjects were observed. No statistically significant increases in commonly reported statin-related adverse events (*e.g.*, musculoskeletal disorders, gastrointestinal symptoms) were seen between subjects receiving tolvaptan+statin and placebo+statin. For example, in TEMPO 3:4, frequencies were 5.4% and 7.8%, respectively, for myalgia (difference −2.4%; 95% confidence interval, −11.2% to 6.4%) and 9.3% and 7.8%, respectively, for abdominal pain (difference 1.5%; −7.9% to 10.9%). In an analysis that excluded participants concurrently using allopurinol, the frequency of alanine transaminase or aspartate transaminase >3× upper limit of normal in the pooled study populations was 3.6% for the tolvaptan+statin group and 2.3% for the placebo+statin group (difference 1.4%; −2.0% to 4.7%).

Conclusions Tolvaptan has been used safely in combination with statins in clinical trials.

CJASN 15: 643–650, 2020. doi: https://doi.org/10.2215/CJN.08170719

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Introduction

Tolvaptan is a vasopressin V_2-receptor antagonist with United States indications for the treatment of adults at risk of rapidly progressing autosomal dominant polycystic kidney disease (ADPKD) and certain adult populations with clinically significant hyponatremia (1,2). The efficacy and safety of tolvaptan in ADPKD were evaluated in two pivotal phase 3 trials: the 3-year Tolvaptan Efficacy and Safety in Management of ADPKD and Its Outcomes (TEMPO) 3:4 study and the 1-year Replicating Evidence of Preserved Renal Function: an Investigation of Tolvaptan Safety and Efficacy in ADPKD (REPRISE) study (3,4). TEMPO 3:4 demonstrated that tolvaptan therapy in subjects with preserved kidney function and high risk of ADPKD progression is associated with significant decreases in the rates of total kidney volume growth and kidney function decline. REPRISE showed that tolvaptan slows the rate of kidney function decline in subjects with more advanced ADPKD.

In patients with ADPKD, elevated LDL cholesterol and low HDL cholesterol levels are common, and statins are frequently used in these patients to improve cardiovascular outcomes (5). Statins are substrates of organic anion–transporting polypeptide (OATP)1B1 and OATP1B3 transporters (6,7). *In vitro* studies showed that the oxobutyric acid metabolite of tolvaptan (DM-4103) inhibits OATP1B1 and 1B3 transporters (data on file). DM-4103 has no known pharmacologic activity (data on file). On the basis of these observations, and on Food and Drug Administration (FDA) draft guidance that considers the potential for inhibition

on the basis of maximal doses and exposures of drug or metabolites, there is a potential that the oxobutyric acid metabolite may increase plasma concentrations of OATP1B1/1B3 substrates (8,9). Accordingly, the United States label for tolvaptan for the treatment of ADPKD advises against the coadministration of tolvaptan with statins (1).

In the phase 3 trials, statin use was unrestricted. The tolvaptan summary of product characteristics for the treatment of ADPKD in Europe states that "statins commonly used in the tolvaptan phase 3 pivotal trial [TEMPO 3:4] (*e.g.*, rosuvastatin and pitavastatin) are OATP1B1 or OATP1B3 substrates, however no difference in [adverse event] profile was observed" (10). To further assess the adverse event profile of tolvaptan and statin coadministration, we conducted a *post hoc* analysis of data from the phase 3 TEMPO 3:4 and REPRISE trials. We examined whether administering tolvaptan plus a statin altered patterns of statin use (duration of statin treatment, statin dose adjustments, changes from one statin to another, and permanent discontinuation of statin therapy), the incidence of common statin-related adverse events, or the incidence of elevations in alanine transaminase (ALT) >2× or >3× upper limit of normal.

Materials and Methods

Study Design

TEMPO 3:4 and REPRISE were both phase 3, multicenter, randomized, double-blind, placebo-controlled trials. TEMPO 3:4 enrolled subjects from January of 2007 through January of 2009; for REPRISE, enrollment dates were May of 2014 through March of 2016. Detailed descriptions of the study designs and methods have been published (3,4). Briefly, in TEMPO 3:4, subjects were randomly assigned on a 2:1 basis to receive tolvaptan 60 mg (45 mg in the morning; 15 mg 8 hours later), which was titrated weekly on the basis of tolerability to 60/30 mg and ultimately 90/30 mg. After the 3-week titration period, subjects received tolvaptan 90/30 mg or the highest tolerated dose for 36 months.

In REPRISE, subjects entered an 8-week prerandomization phase, which consisted of a 1- to 2-week screening phase; a single-blind, 1-week placebo run-in phase; and a single-blind, 5-week tolvaptan titration and run-in phase during which they were titrated to 60/30 mg or 90/30 mg to establish tolerability. Subjects who could not tolerate at least the 60/30 mg dose during the 2-week titration and 3-week run-in phase were discontinued from the trial. Following tolvaptan run-in, subjects were randomized on a 1:1 basis to double-blind tolvaptan or placebo for 1 year, with down-titration permitted according to tolerability. Statin use was unrestricted in both trials. The following statins were used as concomitant medications during the phase 3 trials: atorvastatin, fluvastatin, lovastatin, pitavastatin, pravastatin, rosuvastatin, simvastatin, and simvastatin/ezetimibe.

In TEMPO 3:4, serum chemistry evaluation (which included assessment of hepatic transaminases) was performed at baseline and randomization, weekly during titration, every 4 months during double-blind treatment (monthly in Japan), and twice between 1 and 6 weeks after the completion of treatment at month 36. In REPRISE, hepatic transaminase assessments were performed before randomization (*i.e.*, during screening, at the end of the placebo run-in, during tolvaptan titration, and again during tolvaptan run-in) and monthly throughout double-blind treatment. Subjects in REPRISE underwent three follow-up laboratory assessments between 7 and 40 days after the final dose of their assigned regimen.

Participants

In TEMPO 3:4, eligible subjects were aged 18−50 years (mean, 39 years) with a total kidney volume ≥750 ml and a creatinine clearance of ≥60 ml per minute estimated using the Cockcroft–Gault equation (11). With regard to CKD stage associated with ADPKD, TEMPO 3:4 participants had early (CKD stages 1 and 2) or moderate (CKD stage 3) disease. Although subjects with stage 3 CKD were included, >80% of the study population had stage 1 or 2 CKD.

The REPRISE population was older (mean age, 47 years) and included subjects with more advanced ADPKD. Eligible subjects were either aged 18–55 years with a GFR, estimated by the CKD Epidemiology Collaboration equation (12), of 25–65 ml/min per 1.73 m^2, or aged 56–65 years with an eGFR of 24–44 ml/min per 1.73 m^2. Subjects in the older group also had to have historical evidence of a decline in eGFR >2.0 ml/min per 1.73 m^2 per year. Seventy-five percent of subjects in REPRISE had moderate disease (CKD stage 3), 20% had severe disease (CKD stage 4), and 5% had mild disease (late CKD stage 2, *i.e.*, eGFR 60–65 ml/min per 1.73 m^2).

Outcomes and Analysis

For this *post hoc* analysis, the on-treatment incidence of investigator-reported adverse events, classified by Medical Dictionary for Regulatory Activities preferred term, was determined for subjects receiving tolvaptan+statin, placebo+statin, tolvaptan alone, and placebo alone. The adverse events and laboratory parameters assessed in this analysis were on the basis of those reported for pooled analyses across clinical trials as listed in statin prescribing information (13–15) and included liver function abnormalities and musculoskeletal adverse events, for which there are warnings. Also assessed were elevated blood glucose, gastrointestinal symptoms, and nervous system disorders, which were among the most frequent adverse events occurring during statin clinical trials. The incidences of statin-related adverse events were compared between the tolvaptan+statin and placebo+statin groups, and between the tolvaptan alone and placebo alone groups. The Fisher exact test was used to compare the adverse event frequencies, and normal approximation was used to construct the 95% confidence interval for difference in adverse event proportions. Significance was defined as $P<0.05$.

Summary statistics on statin use (duration of statin use, discontinuations, dose adjustments, and changes from one statin to another statin) in the different treatment groups were collected. Tolvaptan has been associated with elevations in liver enzyme levels (16). Summary data were therefore also obtained on the incidence of ALT increases >2× and >3× the upper limit of normal, as measured by laboratory testing. The ALT elevation data were analyzed by couse of statins with or without allopurinol because of the potential

confounding effects of allopurinol, a common antigout medication associated with liver enzyme elevations (17).

Results

Study Population and Statin Use

In TEMPO 3:4, 1445 subjects were randomized to receive tolvaptan (n=961) or placebo (n=484) (Table 1). A single subject assigned to the placebo group discontinued before receiving the first dose and was excluded from the analysis. Of the 1444 treated subjects, 129 (13.4%) received tolvaptan+statin and 64 (13.2%) received placebo+statin (Table 2).

In REPRISE, 1496 subjects entered the 8-week prerandomization period, and, of these, 1370 subjects were subsequently randomized to receive tolvaptan (n=683) or placebo (n=687; Table 2). Of the 1366 subjects included in the safety analysis, 203 (29.7%) received tolvaptan+statin and 201 (29.3%) received placebo+statin.

In both TEMPO 3:4 and REPRISE, there were no significant differences between tolvaptan- and placebo-treated subjects with respect to duration of statin use, statin permanent discontinuation, statin dose decreases, statin dose increases, or changes from one statin to another. Additionally, tolvaptan discontinuations were no more frequent in the tolvaptan+statin group (21 of 129; 16.3%) than in the tolvaptan alone (200 of 832; 24.0%) group in TEMPO 3:4 or in the tolvaptan+statin group (8 of 203; 3.9%) than in the tolvaptan alone group (21 of 480; 4.4%) in the double-blind phase of REPRISE.

TEMPO 3:4—Adverse Events by Statin Use

In this population of patients with ADPKD at CKD stages 1–3, statin-related adverse events (*i.e.*, gastrointestinal symptoms, blood glucose elevations, musculoskeletal adverse events, and nervous system disorders) occurred at similar rates in subjects who received tolvaptan+statin compared with those who received placebo+statin, with no significant between-group differences (Table 3). Several gastrointestinal symptoms were numerically higher in frequency with tolvaptan+statin versus placebo+statin (constipation, 8.5% versus 3.1% [P=0.23]; diarrhea, 13.2% versus 7.8% [P=0.34]; dyspepsia, 12.4% versus 4.7% [all P=0.12]). A similar pattern was seen with tolvaptan alone versus placebo alone (constipation, 8.4% versus 2.4% [P<0.001]; diarrhea, 13.3% versus 11.5% [P=0.37]; dyspepsia, 7.2% versus 3.1% [P=0.003]). ALT and aspartate transaminase (AST) elevations in the tolvaptan+statin group (7.8% and 9.3%, respectively) were numerically but nonsignificantly higher than they were in the placebo+statin group (6.3% and 4.7%, respectively; P>0.99 for the between-group comparison of ALT and P=0.39 for the between-group comparison of AST). The liver enzyme elevations shown here were by investigator report; no objective criteria were used.

REPRISE—Adverse Events by Statin Use

In patients with ADPKD at late CKD stage 2 to CKD stage 4, statin-related adverse events in the tolvaptan+statin group occurred at similar rates compared with the placebo+statin group, with no significant differences (Table 4). Gastrointestinal adverse events exhibited no consistent pattern in the tolvaptan+statin group relative to the placebo+statin group. Nonsignificant increases in the rates of ALT and AST elevations were observed in the tolvaptan+statin group (4.4% and 3.0%, respectively) compared with the placebo+statin group (2.0% and 2.0%, respectively; P=0.26 for the between-group comparison of ALT and P=0.75 for the between-group comparison of AST). Slight increases in ALT and AST elevations also occurred with tolvaptan alone (3.3% and 1.9%, respectively) compared with placebo alone (1.0% and 1.4%, respectively; P=0.02 for ALT and P=0.62 for AST). As with the TEMPO 3:4 data, the incidences of liver enzyme elevations shown here were on the basis of subjective investigator reporting.

Table 1. Baseline characteristics of participants with autosomal dominant polycystic kidney disease enrolled in the TEMPO 3:4 and REPRISE trials

Characteristic	TEMPO 3:4		REPRISE	
	Tolvaptan (n=961)	Placebo (n=484)	Tolvaptan (n=683)	Placebo (n=687)
Age, yr	39±7	39±7	47±8	47±8
Male sex, no. (%)	495 (52)	251 (52)	347 (51)	333 (48)
Height, cm	174±10	174±8	174±10	173±10
Weight, kg	79±18	79±18	85±20	82±19
Race, no. (%)				
White	810 (84)	408 (84)	626 (92)	632 (92)
Asian	121 (13)	62 (13)	22 (3)	19 (3)
Other	30 (3)	14 (3)	35 (5)	36 (5)
eGFR, ml/min per 1.73 m^2	81±21	82±23	41±11	41±11
eGFR category, ml/min per 1.73 m^2, no. (%)				
≥90	330 (34)	172 (36)	0	0
60–89	465 (48)	224 (46)	32 (5)[a]	39 (6)[a]
45–59	135 (14)	70 (14)	209 (31)	202 (29)
30–44	28 (3)	15 (3)	303 (44)	315 (46)
15–29	0	0	139 (20)	128 (19)

Values are mean±SD or n (%). TEMPO 3:4, Tolvaptan Efficacy and Safety in Management of Autosomal Dominant Polycystic Kidney Disease and Its Outcomes 3:4 trial; REPRISE, Replicating Evidence of Preserved Renal Function: an Investigation of Tolvaptan Safety and Efficacy in ADPKD trial. [a]Per eligibility criteria for REPRISE, subjects in this eGFR category were in the range 60–65 ml/min per 1.73 m^2.

Table 2. Statin use in TEMPO 3:4 and REPRISE

Variable	TEMPO 3:4		REPRISE	
	Tolvaptan	Placebo	Tolvaptan	Placebo
Use of statins, *n*	129	64	203	201
Percentage of randomized subjects	13	13	30	29
Duration of statin use, d				
Mean	746	779	313	328
Median	1065	1049	359	358
SD	427	392	102	79
10th percentile, 90th percentile	27, 1102	24, 1097	101, 365	188, 364
Minimum, maximum	1, 1120	1, 1110	1, 387	14, 383
Statin permanent discontinuations, *n* (%)	48 (37)	27 (42)	14 (7)	14 (7)
Decreased statin dose, *n* (%)	9 (7)	4 (6)	4 (2)	4 (2)
Increased statin dose, *n* (%)	12 (9)	2 (3)	5 (2)	2 (1)
Changed statin, *n* (%)	16 (12)	10 (16)	10 (5)	6 (3)

TEMPO 3:4, Tolvaptan Efficacy and Safety in Management of Autosomal Dominant Polycystic Kidney Disease and Its Outcomes 3:4 trial; REPRISE, Replicating Evidence of Preserved Renal Function: an Investigation of Tolvaptan Safety and Efficacy in ADPKD trial.

Liver Enzyme Results by Laboratory Testing

In TEMPO 3:4 and REPRISE, ALT elevations were analyzed by statin use with and without allopurinol use, a drug known to be associated with liver enzyme elevations. In TEMPO 3:4, 69 of 961 (7.2%) subjects in the tolvaptan group and 25 of 484 (5.2%) subjects in the placebo group were taking allopurinol; 18 allopurinol-treated subjects in the tolvaptan group and seven allopurinol-treated subjects in the placebo group were also taking statins. In REPRISE, 101 of 683 (14.8%) subjects in the tolvaptan group and 99 of 687 (14.4%) subjects in the placebo group were taking allopurinol; 44 allopurinol-treated subjects in the tolvaptan group and 42 allopurinol-treated subjects in the placebo group were also taking statins. In subjects not taking concomitant allopurinol, rates of ALT elevation >2× and >3× upper limit of normal with tolvaptan+statin and placebo+statin were similar in both TEMPO 3:4 and REPRISE (Table 5).

In a separate analysis, the frequency of elevations in either ALT or AST >3× upper limit of normal was only slightly higher than for ALT alone. In the pooled TEMPO 3:4/REPRISE population excluding allopurinol users, the number of subjects with ALT or AST >3× upper limit of normal was: tolvaptan+statin, ten of 276 (3.6%); placebo+statin, five of 221 (2.3%) (difference 1.4%; 95% confidence interval, −2.0 to 4.7); tolvaptan alone, 63 of 1196 (5.3%); placebo alone, eight of 823 (1.0%) (difference 4.3%; 95% confidence interval, 2.8 to 5.8).

Discussion

The oxobutyric acid metabolite of tolvaptan has a $t_{1/2}$ of about 180 hours in healthy subjects (data on file) and accumulates to reach steady state concentrations at about 8 weeks. Using data from two large clinical trial populations of subjects with ADPKD, this *post hoc* analysis of the TEMPO 3:4 and REPRISE trials examined whether long-term use of tolvaptan—and the associated accumulation of metabolite concentrations—with OATP1B1/B3 substrate statins might alter the frequency of common statin-related adverse events. The use of statins by 13% of subjects in TEMPO 3:4 and 29% of subjects in REPRISE suggests frequent statin use in the ADPKD population, with increasing use in later stages of the disease, and highlights the importance of determining whether tolvaptan and a statin can be safely coadministered.

Concurrent administration of tolvaptan with a statin was not associated with alterations in statin usage when compared with use with placebo. Within each trial, the percentage of subjects who discontinued use of a statin, switched to another statin, or decreased the dose was similar between tolvaptan and placebo subjects.

Among subjects taking tolvaptan+statin, incidences of statin-related adverse events were not statistically different than those observed with placebo+statin. Statin use is associated with increased risk for musculoskeletal toxicity and liver enzyme elevations, and gastrointestinal symptoms are commonly reported (18–20). No significant increases in statin-related musculoskeletal events or gastrointestinal symptoms were seen in the tolvaptan+statin groups versus the placebo+statin groups across the TEMPO 3:4 and REPRISE studies, suggesting no increased risk of these adverse events in patients receiving tolvaptan and a statin.

The United States labels for tolvaptan and statins include language stating that hepatic transaminases should be measured before initiation of treatment and during treatment (1,13–15). ALT elevations by investigator report were nonsignificantly more frequent in subjects taking tolvaptan+statin compared with placebo+statin in TEMPO 3:4 (7.8% versus 6.3%) and REPRISE (4.4% versus 2.0%). Investigator-reported AST elevation was also nonsignificantly more frequent in the tolvaptan+statin group versus the placebo+statin group in TEMPO 3:4 (9.3% versus 4.7%) and REPRISE (3.0% versus 2.0%). Taken together, the data suggest that the combination of tolvaptan and statins may result in a small increase in risk for liver enzyme elevations, especially in those with earlier disease. It is important to note that the Risk Evaluation and Mitigation Strategy for tolvaptan in the United States requires that these patients are frequently monitored for hepatotoxicity and that the drug is discontinued if appropriate. The slight increases in the incidence of ALT and AST elevations observed in the tolvaptan+statin group versus the placebo+statin

Table 3. TEMPO 3:4: treatment-emergent, statin-related adverse events by system organ class and Medical Dictionary for Regulatory Activities preferred term

SOC / Adverse Event	Tolvaptan+Statin (n=129) n (%)	Placebo+Statin (n=64) n (%)	Difference in Proportions % (95% CI)	P Value Tolvaptan+ Statin versus Placebo+Statin	Tolvaptan Alone (n=832) n (%)	Placebo Alone (n=419) n (%)	Difference in Proportions % (95% CI)	P Value Tolvaptan Alone versus Placebo Alone	P Value for the Interaction[a]
Gastrointestinal disorders									
Abdominal distension	5 (3.9)	1 (1.6)	2.3 (−3.4 to 8.0)	0.67	42 (5.0)	15 (3.6)	1.5 (−1.0 to 4.0)	0.25	0.61
Abdominal pain	12 (9.3)	5 (7.8)	1.5 (−7.9 to 10.9)	1.00	50 (6.0)	27 (6.4)	−0.4 (−3.5 to 2.6)	0.80	0.66
Constipation	11 (8.5)	2 (3.1)	5.4 (−2.2 to 13.0)	0.23	70 (8.4)	10 (2.4)	6.0 (3.5 to 8.6)	<0.001	0.76
Diarrhea	17 (13.2)	5 (7.8)	5.4 (−4.6 to 15.3)	0.34	111 (13.3)	48 (11.5)	1.9 (−2.1 to 5.9)	0.37	0.47
Dyspepsia	16 (12.4)	3 (4.7)	7.7 (−1.1 to 16.6)	0.12	60 (7.2)	13 (3.1)	4.1 (1.5 to 6.7)	0.003	0.81
Flatulence	1 (0.8)	0 (0.0)	0.8 (−1.9 to 3.5)	1.00	7 (0.8)	1 (0.2)	0.6 (−0.4 to 1.6)	0.28	0.71
Nausea	9 (7.0)	7 (10.9)	−4.0 (−13.9 to 6.0)	0.41	89 (10.7)	50 (11.9)	−1.2 (−5.2 to 2.7)	0.51	0.51
General disorders and administration site conditions									
Asthenia	7 (5.4)	2 (3.1)	2.3 (−4.7 to 9.3)	0.72	50 (6.0)	25 (6.0)	0.0 (−2.9 to 3.0)	1.00	0.50
Investigations									
ALT increased	10 (7.8)	4 (6.3)	1.5 (−7.2 to 10.2)	1.00	29 (3.5)	13 (3.1)	0.4 (−1.9 to 2.6)	0.87	0.87
AST increased	12 (9.3)	3 (4.7)	4.6 (−3.8 to 13.0)	0.39	24 (2.9)	13 (3.1)	−0.2 (−2.4 to 2.0)	0.86	0.27
Blood ALP increased	0 (0.0)	0 (0.0)	—	—	3 (0.4)	1 (0.2)	0.1 (−0.7 to 0.9)	1.00	—
Blood bilirubin increased	1 (0.8)	0 (0.0)	0.8 (−1.9 to 3.5)	1.00	1 (0.1)	2 (0.5)	−0.4 (−1.2 to 0.5)	0.26	0.25
Blood CPK increased	2 (1.6)	0 (0.0)	1.6 (−1.8 to 4.9)	1.00	4 (0.5)	1 (0.2)	0.2 (−0.6 to 1.1)	0.67	0.50
Blood glucose increased	3 (2.3)	0 (0.0)	2.3 (−1.4 to 6.1)	0.55	4 (0.5)	1 (0.2)	0.2 (−0.6 to 1.1)	0.67	0.41
Musculoskeletal and connective tissue disorders									
Arthralgia	9 (7.0)	4 (6.3)	0.7 (−7.8 to 9.3)	1.00	60 (7.2)	24 (5.7)	1.5 (−1.5 to 4.5)	0.34	0.85
Back pain	17 (13.2)	12 (18.8)	−5.6 (−17.9 to 6.8)	0.39	116 (13.9)	76 (18.1)	−4.2 (−8.8 to 0.4)	0.06	0.81
Myalgia	7 (5.4)	5 (7.8)	−2.4 (−11.2 to 6.4)	0.54	43 (5.2)	11 (2.6)	2.5 (0.2 to 4.9)	0.04	0.11
Pain in extremity	8 (6.2)	6 (9.4)	−3.2 (−12.6 to 6.3)	0.56	34 (4.1)	21 (5.0)	−0.9 (−3.6 to 1.7)	0.47	0.71
Nervous system disorders									
Headache	32 (24.8)	20 (31.3)	−6.4 (−21.2 to 8.3)	0.39	209 (25.1)	101 (24.1)	1 (−4.2 to 6.2)	0.73	0.30

Myopathy and rhabdomyolysis were not reported by any subject. TEMPO 3:4, Tolvaptan Efficacy and Safety in Management of Autosomal Dominant Polycystic Kidney Disease and Its Outcomes 3:4 trial; SOC, system organ class; 95% CI, 95% confidence interval; ALT, alanine transaminase; AST, aspartate transaminase; ALP, alkaline phosphatase; —, numbers not sufficient for analysis; CPK, creatine phosphokinase.

[a]Derived by the Breslow–Day test to evaluate the interaction of statin use with the odds ratio of an adverse event.

Table 4. REPRISE: treatment-emergent, statin-related adverse events by system organ class and Medical Dictionary for Regulatory Activities preferred term

SOC/ Adverse Event	Tolvaptan+Statin (n=203) n (%)	Placebo+Statin (n=201) n (%)	Difference in Proportions % (95% CI)	P Value Tolvaptan+ Statin versus Placebo+Statin	Tolvaptan Alone (n=478) n (%)	Placebo Alone (n=484) n (%)	Difference in Proportions % (95% CI)	P Value Tolvaptan Alone versus Placebo Alone	P Value for the Interaction[a]
Gastrointestinal disorders									
Abdominal distension	0 (0.0)	3 (1.5)	−1.5 (−3.7 to 0.7)	0.12	6 (1.3)	11 (2.3)	−1.0 (−2.9 to 0.9)	0.33	0.21
Abdominal pain	3 (1.5)	1 (0.5)	1.0 (−1.4 to 3.4)	0.62	22 (4.6)	14 (2.9)	1.7 (−0.9 to 4.3)	0.18	0.61
Constipation	7 (3.4)	9 (4.5)	−1.0 (−5.3 to 3.3)	0.62	15 (3.1)	9 (1.9)	1.3 (−0.9 to 3.5)	0.22	0.22
Diarrhea	12 (5.9)	6 (3.0)	2.9 (−1.6 to 7.4)	0.23	35 (7.3)	17 (3.5)	3.8 (0.7 to 6.9)	0.01	0.92
Dyspepsia	3 (1.5)	5 (2.5)	−1.0 (−4.2 to 2.2)	0.50	13 (2.7)	7 (1.4)	1.3 (−0.7 to 3.3)	0.18	0.17
Flatulence	1 (0.5)	0 (0.0)	0.5 (−1.0 to 2.0)	1.00	1 (0.2)	2 (0.4)	−0.2 (−1.1 to 0.7)	1.00	0.25
Nausea	8 (3.9)	10 (5.0)	−1.0 (−5.6 to 3.5)	0.64	24 (5.0)	20 (4.1)	0.9 (−2.0 to 3.7)	0.54	0.44
General disorders and administration site conditions									
Asthenia	0 (0.0)	3 (1.5)	−1.5 (−3.7 to 0.7)	0.12	10 (2.1)	7 (1.4)	0.6 (−1.2 to 2.5)	0.47	0.06
Investigations									
ALT increased	9 (4.4)	4 (2.0)	2.4 (−1.5 to 6.4)	0.26	16 (3.3)	5 (1.0)	2.3 (0.3 to 4.4)	0.02	0.64
AST increased	6 (3.0)	4 (2.0)	1.0 (−2.6 to 4.5)	0.75	9 (1.9)	7 (1.4)	0.4 (−1.4 to 2.3)	0.62	0.87
Blood ALP increased	1 (0.5)	0 (0.0)	0.5 (−1.0 to 2.0)	1.00	2 (0.4)	2 (0.4)	0.0 (−1.0 to 1.0)	1.00	0.37
Blood bilirubin increased	0 (0.0)	0 (0.0)	—	—	0 (0.0)	2 (0.4)	−0.4 (−1.2 to 0.4)	0.50	—
Blood glucose increased	0 (0.0)	1 (0.5)	−0.5 (−2.0 to 1.0)	0.50	0 (0.0)	0 (0.0)	—	—	—
Musculoskeletal and connective tissue disorders									
Arthralgia	7 (3.4)	8 (4.0)	−0.5 (−4.7 to 3.7)	0.80	16 (3.3)	17 (3.5)	−0.2 (−2.7 to 2.3)	1.00	0.88
Back pain	9 (4.4)	11 (5.5)	−1.0 (−5.8 to 3.7)	0.65	25 (5.2)	30 (6.2)	−1.0 (−4.1 to 2.2)	0.58	0.94
Myalgia	6 (3.0)	1 (0.5)	2.5 (−0.6 to 5.5)	0.12	10 (2.1)	7 (1.4)	0.6 (−1.2 to 2.5)	0.47	0.21
Pain in extremity	7 (3.4)	3 (1.5)	2.0 (−1.6 to 5.5)	0.34	14 (2.9)	9 (1.9)	1.1 (−1.1 to 3.2)	0.30	0.63
Nervous system disorders									
Headache	13 (6.4)	18 (9.0)	−2.6 (−8.2 to 3.1)	0.36	42 (8.8)	41 (8.5)	0.3 (−3.4 to 4.1)	0.91	0.36

Myopathy and rhabdomyolysis were not reported by any subject. REPRISE, Replicating Evidence of Preserved Renal Function: an Investigation of Tolvaptan Safety and Efficacy in ADPKD trial; SOC, system organ class; 95% CI, 95% confidence interval; ALT, alanine transaminase; AST, aspartate transaminase; ALP, alkaline phosphatase; —, numbers not suffient for analysis.
[a]Derived by the Breslow–Day test to evaluate the interaction of statin use with the odds ratio of an adverse event.

Table 5. Subjects with alanine transaminase elevations >2× and >3× upper limit of normal by statin and allopurinol use

Statin/Allopurinol Couse	ALT Elevations	TEMPO 3:4				REPRISE			
		Tolvaptan *n* (%)	Placebo *n* (%)	Difference in Proportions % (95% CI)	Total *n* (%)	Tolvaptan *n* (%)	Placebo *n* (%)	Difference in Proportions % (95% CI)	Total *n* (%)
With statins		134	68		202	204	202		406
	>2×ULN	11 (8.2)	3 (4.4)	3.8 (−2.9 to 10.5)	14 (6.9)	14 (6.9)	6 (3.0)	3.9 (−0.3 to 8.1)	20 (4.9)
	>3×ULN	6 (4.5)	2 (2.9)	1.5 (−3.8 to 6.9)	8 (4.0)	10 (4.9)	3 (1.5)	3.4 (0.0 to 6.8)	13 (3.2)
With statins but not allopurinol		116	61		177	160	160		320
	>2×ULN	8 (6.9)	3 (4.9)	2.0 (−5.1 to 9.1)	11 (6.2)	9 (5.6)	5 (3.1)	2.5 (−2.0 to 7.0)	14 (4.4)
	>3×ULN	4 (3.4)	2 (3.3)	0.2 (−5.4 to 5.7)	6 (3.4)	5 (3.1)	2 (1.3)	1.9 (−1.3 to 5.1)	7 (2.2)
With allopurinol but not statins		51	18		69	57	57		114
	>2×ULN	8 (15.7)	2 (11.1)	4.6 (−13.0 to 22.2)	10 (14.5)	4 (7.0)	1 (1.8)	5.3 (−2.2 to 12.7)	5 (4.4)
	>3×ULN	3 (5.9)	2 (11.1)	−5.2 (−21.1 to 10.7)	5 (7.2)	2 (3.5)	0	3.5 (−1.3 to 8.3)	2 (1.8)
With neither allopurinol nor statins		776	397		1173	420	426		846
	>2×ULN	60 (7.7)	9 (2.3)	5.5 (3.1 to 7.8)	69 (5.9)	36 (8.6)	8 (1.9)	6.7 (3.7 to 9.7)	44 (5.2)
	>3×ULN	30 (3.9)	1 (0.3)	3.6 (2.2 to 5.1)	31 (2.6)	26 (6.2)	5 (1.2)	5.0 (2.5 to 7.5)	31 (3.7)

Data are on the basis of laboratory values and not adverse event reporting as in Tables 3 and 4. ALT, alanine transaminase; TEMPO 3:4, Tolvaptan Efficacy and Safety in Management of Autosomal Dominant Polycystic Kidney Disease and Its Outcomes 3:4 trial; REPRISE, Replicating Evidence of Preserved Renal Function: an Investigation of Tolvaptan Safety and Efficacy in ADPKD trial; 95% CI, 95% confidence interval; ULN, upper limit of normal.

group suggest that the effects of tolvaptan and statins were additive, with no interaction effect. Furthermore, in an analysis of liver enzyme elevations by laboratory testing, the incidences of ALT elevations >2× and >3× upper limit of normal were similar with tolvaptan+statin and with tolvaptan alone.

The United States label for tolvaptan cites a single-dose study in which concurrent administration of tolvaptan and lovastatin did not produce clinically relevant increases in the exposures of lovastatin or its active lovastatin β-hydroxy acid metabolite (1). After administration of a single tolvaptan dose in that study, concentrations of the oxobutyric acid metabolite were very low, so OATP1B1 inhibition would not be expected. Analyses conducted in subjects receiving tolvaptan with statins in the 3-year TEMPO 3:4 trial and 1-year REPRISE trial assessed safety when exposures to both tolvaptan and the oxobutyric acid metabolite were maximal.

A limitation of this analysis is that it was retrospective in nature. FDA guidance on evaluating drug-drug interaction potential states that retrospective studies can be useful in identifying drug-drug interactions, but that they lack the precision of studies designed specifically to assess interaction potential (6). A second limitation is that adverse events were used as a surrogate for drug interaction potential. No measurement of statin concentrations was performed. It is therefore not possible to definitively attribute the similarity between groups with respect to safety and tolerability to a similarity of drug exposures during concurrent tolvaptan/statin use. Finally, it should be noted that in REPRISE, subjects who could not tolerate a tolvaptan daily split dose of at least 60/30 mg before randomization were excluded from the study, which may have led to the exclusion of subjects with a different response to tolvaptan+statin from this dataset. Despite these limitations, this *post hoc* analysis shows that tolvaptan has been safely administered with concurrent statin therapy in clinical trials for patients with ADPKD.

Data Sharing Statement

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://clinical-trials.otsuka.com/. For all approved IPD access requests, Otsuka will share anonymized IPD on a remotely accessible data sharing platform.

Disclosures

The authors are employees of Otsuka Pharmaceutical Development & Commercialization, Inc. (Rockville, MD; Princeton, NJ).

Funding

This research was supported by Otsuka Pharmaceutical Development & Commercialization, Inc. Editorial support for this article, also funded by Otsuka Pharmaceutical Development & Commercialization, Inc., was provided by Andrew J. Horgan, of Bioscience Communications Inc. (New York, NY).

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Received: July 15, 2019 **Accepted:** February 26, 2020

Published online ahead of print. Publication date available at www.cjasn.org.