Benefit of Tolvaptan on Time to End-Stage Renal Disease for Patients With Rapidly Progressing Autosomal Dominant Polycystic Kidney Disease: A Disease Progression Model

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BACKGROUND

- The efficacy and safety of tolvaptan in adults with autosomal dominant polycystic kidney disease (ADPKD) was initially established in a 3-year phase 3 clinical trial (TEMPO 3:4; NCT00428948[1]).
- An additional study (REPRISE; NCT02160145[2]) was conducted in patients with ADPKD at chronic kidney disease (CKD) stage 4, further demonstrating treatment efficacy.
- Since 2014, tolvaptan has been approved in Japan, the European Union, Canada, Republic of Korea, Switzerland, Hong Kong, Australia, New Zealand, Turkey, and Taiwan.
- Tolvaptan was approved in the United States in 2018 as a treatment for patients with ADPKD at high risk of progression.[3]
- Not all patients with ADPKD progress at the same rate.[4] Some patients progress more rapidly than others. A few guidances exist to identify patients with rapidly progressing ADPKD,[5] and the Mayo classification system has been demonstrated to accurately predict the rate of progression.[4]
  - European Renal Association–European Dialysis and Transplant Association (ERA-EDTA) Working Groups on Inherited Kidney Disorders and European Renal Best Practice recognized that rapid progression is likely in patients with Mayo subclasses 1C through 1E.[4,6]
  - In addition, the Canadian Working Group also recommended the use of the Mayo classification system to identify patients at high risk for rapid progression.[7]
- An ADPKD natural disease progression model predicted longer-term outcomes including estimated glomerular filtration rate (eGFR) decline and time to end-stage renal disease (ESRD) for a cohort of patients not receiving treatment with tolvaptan.[8]
- Unlike other models for ADPKD,[9-11] which assume the same disease progression for all patients with ADPKD, the model differentiated disease progression by Mayo subclass.
- The modeled population represented rapid progressors (Mayo subclasses 1C, 1D, and 1E) from the TEMPO 3:4 clinical trial beginning in CKD stages 1, 2, and 3.
  - The TEMPO 3:4 trial population was enriched for Mayo subclasses 1C-1E.[12]
  - Irazabal et al.[12] found that the effect of tolvaptan on eGFR was greater in subclasses 1C, 1D, and 1E (rapid progression) than in subclass 1B (slow progression).
- Model estimates for age at and time to ESRD for patients with ADPKD not receiving tolvaptan were validated[8] against published ADPKD models.[9-11]

OBJECTIVE

- To estimate the treatment benefit of tolvaptan, long-term outcomes were modeled using the previously presented model for patients treated with and without tolvaptan based on the TEMPO 3:4 cohort of rapid progressors.

METHODS

Population

- We conducted this analysis using the same baseline patient characteristics previously presented in Mader et al.[8] from the TEMPO 3:4 trial (Table 1).

Effectiveness

- For patients receiving tolvaptan, we applied a constant treatment effect to baseline natural history progression estimates[8] estimated via the Irazabal equation.[6]
- In the base-case analysis, the annual absolute reduction in eGFR decline for tolvaptan versus placebo of 1.20 mL/min/1.73m^2 from the TEMPO 3:4 trial[1] was applied to predicted eGFR decline in the absence of treatment.
- The model applies the treatment effect for tolvaptan at the subclass level regardless of CKD stage.
  - For example, a patient in subclass 1D receives the same treatment effect in both CKD 2 and CKD 3.
- We assumed a constant effectiveness for tolvaptan over time without decay.

Table 1. Baseline Population Characteristics

	Males			Females		
	Percentage of Patients	Mean Age (Years)	Mean eGFR (mL/min/ 1.73 m^2)	Percentage of Patients	Mean Age (Years)	Mean eGFR (mL/min/ 1.73 m^2)
CKD stage 1	**17.3%**	**33.6**	**105.9**	**17.6%**	**34.5**	**105.8**
Subclass 1C	7.0%	37.7	105.0	8.0%	38.6	102.9
Subclass 1D	6.5%	33.1	102.9	6.3%	33.8	107.3
Subclass 1E	3.9%	27.0	112.4	3.3%	26.0	109.8
CKD stage 2	**24.8%**	**39.3**	**74.5**	**21.9%**	**40.1**	**75.2**
Subclass 1C	9.8%	41.8	74.7	10.9%	42.5	75.6
Subclass 1D	9.6%	39.3	74.7	8.3%	39.1	74.4
Subclass 1E	5.4%	34.8	74.0	2.7%	33.0	76.2
CKD stage 3	**11.7%**	**41.3**	**50.8**	**6.6%**	**41.7**	**52.0**
Subclass 1C	2.9%	44.9	52.1	2.7%	44.6	52.5
Subclass 1D	5.2%	41.7	51.7	2.7%	41.7	51.2
Subclass 1E	3.7%	37.9	48.5	1.3%	35.8	52.4

Source: Rapid progressors from TEMPO 3:4.[13]

RESULTS

Figure 1. Model-Predicted Benefit of Tolvaptan by CKD Stage and Mayo Subclass on Time to ESRD

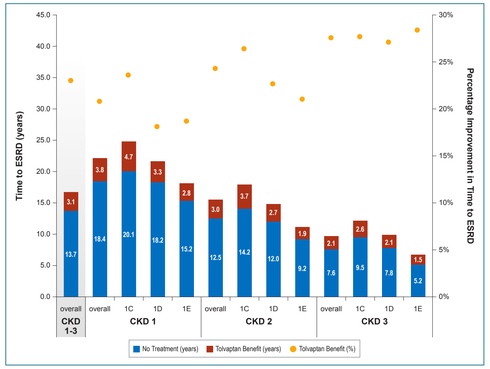
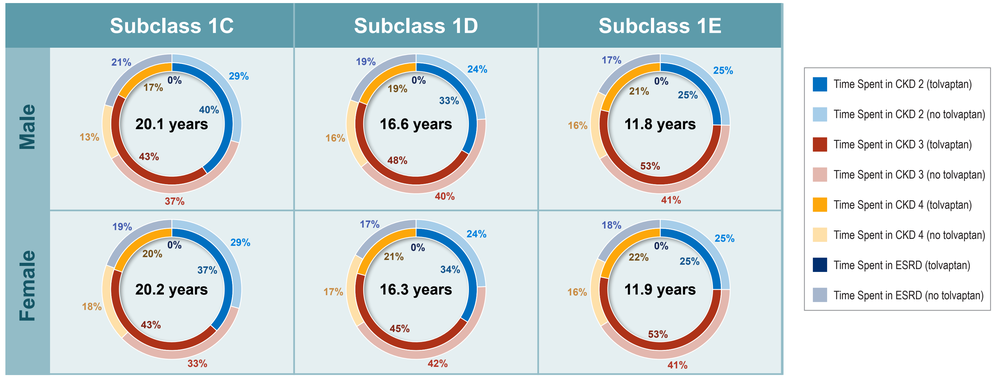
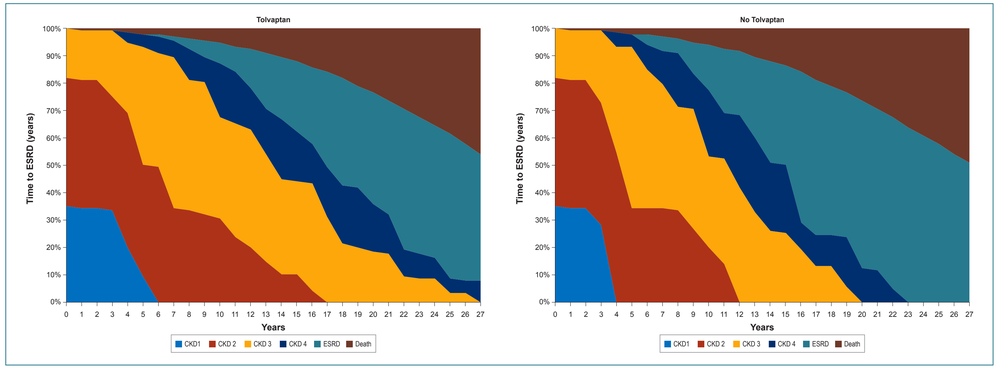


Figure 3. Model Estimates of Time to ESRD for Patients with Tolvaptan and Percentage of Time Spent in Each Health State Over That Time Period for Average TEMPO 3:4 Patient with Tolvaptan and No Tolvaptan by Mayo Subclass and Sex



Note: Baseline characteristics for the average TEMPO 3:4 patient are an eGFR of 81.6 mL/min/1.73 m^2 (CKD 2) and a baseline age of 38.7 years.

Figure 2. Model Distribution of Cohort Across Health States by Year For Patients Receiving Tolvaptan and No Tolvaptan



- The predicted time to ESRD was longer for all patients with subclasses 1C-1E in CKD stages 1-3 treated with tolvaptan, with greater estimated absolute benefit when treatment was initiated for patients in early CKD stages (Figure 1 and Figure 2).
- The overall base-case population, which is the baseline TEMPO 3:4 patient distribution of rapid progressors, is predicted to experience a 3.1-year delay to ESRD for patients treated with tolvaptan, roughly a 23% improvement compared with patients treated with no tolvaptan.
- When compared with patients treated without tolvaptan, patients beginning tolvaptan treatment in CKD stages 1, 2, and 3 are predicted to experience an estimated delay to ESRD of 3.8 years (21% improvement), 3.0 years (24% improvement), and 2.1 years (28% improvement), respectively.
- For patients receiving tolvaptan, the model estimates an increased delay to ESRD for females compared with males (Table 2).
- Given a patient's baseline characteristics (e.g., age, eGFR), disease progression and predicted time to ESRD depend on the patient's sex and Mayo subclass (Figure 3).
  - Despite variability in time to ESRD across Mayo subclasses, patients treated with tolvaptan experience a predicted delay to ESRD in all Mayo subclasses.

Validation

- Bennett and colleagues[11] reported results from an analysis using the ADPKD Outcomes Model (ADPKD-OM), which estimates time to ESRD and ESRD delay for patients receiving tolvaptan and not receiving tolvaptan.
- Bennett and colleagues[11] used the ADPKD-OM to conduct an analysis of the effect of tolvaptan on longer-term disease progression using the TEMPO 3:4 overall population (rapid progressors and non-rapid progressors).
- Table 3 shows key outcomes generated by Bennett and colleagues[11] and using the current model.
- In addition, Bennett et al.[11] reported that 96% of patients reached ESRD before death in the no therapy group. In the current model, 91% of patients in the no tolvaptan cohort reached ESRD before death.
- The ADPKD-OM differs from the current model in several key ways:
  - Bennett et al.[11] and this model use different predictors to estimate future eGFR.
  - The ADPKD-OM used all-cause mortality rates from the World Health Organization, whereas this model uses life tables from the Centers for Disease Control and Prevention adjusted by an odds ratio by CKD stage from the United States Renal Data System.[14]
  - The base-case analysis in Bennett et al.[11] assumes no discontinuation for patients receiving tolvaptan. Our model results assume discontinuation, upon which treatment effect also discontinues.
    - Discontinuation was applied in the ADPKD-OM via a scenario analysis, which reduced the delay of ESRD onset for patients in CKD stages 1-3 from 5.1 years to 3.8 years,[11] which is similar to this model.
  - In the base-case analysis, Bennett et al.[11] used a percentage reduction in eGFR decline as a treatment effect, whereas, in this model, we use an absolute reduction in eGFR decline.
  - In a scenario analysis, Bennett and colleagues[11] calculated the tolvaptan treatment effect of 1.11 for rapidly progressing patients (Mayo subclasses 1C, 1D, and 1E) using the difference in annual eGFR slope between patients receiving tolvaptan (–2.82 mL/min/1.73 m^2) and patients receiving placebo (–3.93 mL/min/1.73 m^2) in TEMPO 3:4.

Table 2. Model Estimated Average Time to Onset of ESRD for TEMPO 3:4 Cohort, By Sex

	Tolvaptan	No Tolvaptan	Absolute Difference	Relative Difference
Male	16.1 years	13.1 years	3.0 years	22.5%
Female	17.6 years	14.3 years	3.3 years	23.4%

Note: Relative difference calculated based on values without rounding.

Table 3. Model Estimates of Time to ESRD: Validation Results

	Bennett et al.[11]	Current Model[a]
Time to ESRD (natural history)		
CKD stages 1-3	~13 years	13.7 years
CKD stage 1	~19 years	18.4 years
CKD stage 2	~12 years	12.5 years
CKD stage 3	~7 years	7.6 years
Delay of ESRD onset (tolvaptan)		
CKD stages 1-3	5.1 years	2.9 years
CKD stage 1	6.6 years	3.5 years
CKD stage 2	4.7 years	2.8 years
CKD stage 3	2.7 years	1.8 years

[a]Estimated using an annual constant treatment effect of 1.11 mL/min/1.73 m^2 across all Mayo subclasses[11] in contrast to our estimate of an annual treatment effect of 1.20 mL/min/1.73 m^2 for all patients in TEMPO 3:4.

DISCUSSION

- Time to ESRD is a primary outcome of interest when treating patients with ADPKD, and a potential clinical benefit of treatment with tolvaptan is the delay of ESRD onset.
- When compared with patients without tolvaptan treatment, patients treated with tolvaptan are estimated to live longer and progress more slowly to ESRD according to the presented model.
- When compared with patients without tolvaptan treatment, patients treated with tolvaptan are estimated to spend more time in earlier CKD stages 1-4, where they have an improved quality of life[15-17] and require fewer hospitalizations and medical care visits,[18] resulting in cost savings.[19]
- Model estimates of age at ESRD, time to ESRD, and delay of ESRD have been validated against published studies.[9-11]
- Although the ADPKD-OM[11] and this model use different baseline population characteristics and the approach to underlying disease progression is not the same between the two models, both capture the estimated clinical value associated with tolvaptan intervention in patients with rapid ADPKD progression.

CONCLUSIONS

- The model projects that patients treated with tolvaptan versus no treatment spend more time in earlier CKD stages and experience later onset of ESRD.
- Results were consistent across CKD stages and Mayo subclasses.
- Findings highlight the potential long-term value of early intervention with tolvaptan in patients at risk of rapid ADPKD progression.

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DISCLOSURES

This study was sponsored by Otsuka Pharmaceutical Development & Commercialization, Inc.

MS and DO are employees of Otsuka. GM, MP, and DM are employees of RTI Health Solutions, which received funding for this research from Otsuka.

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Supported by funding from Otsuka Pharmaceutical Development and Commercialization, Inc.

Presented at: Kidney Week 2020 Reimagined; October 22-25, 2020