Tolvaptan: a Possible Treatment for Autosomal Dominant Polycystic Kidney Disease

Ray Lin

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Tolvaptan: a Possible Treatment for Autosomal Dominant Polycystic Kidney Disease

Abstract

Background: Autosomal-dominant polycystic kidney disease (ADPKD) is an inherited renal cystic disease that leads to end-stage renal disease. Patients who present with symptoms at an early age are more likely to live to develop end stage renal disease. Patients with ADPKD and renal failure are most commonly treated with hemodialysis. Tolvaptan is expected to be effective in the treatment of ADPKD because of its success in animal models. If clinical trials can prove slowing of the disease progression, hemodialysis and kidney transplant for those patients may not be necessary. What is the effectiveness of tolvaptan as a treatment option for ADPKD to inhibit renal cyst progression?

Method: An exhaustive literature search was done using the following search engines, MEDLINE, CINAHL, EMBR, Web of Science, and the initial search used the following combined search terms as treatment, clinical trial, and polycystic kidney disease. The bibliographies of the articles were further searched for relevant sources. Articles with primary data evaluating ADPKD were included. Relevant articles were assessed for quality using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE). A search on the National Institute of Health (NIH) clinical trials site was done.

Results: Two studies met inclusion criteria and were included in this systematic review. The result of the 3 year study found tolvaptan to be significant in slowing down the total kidney volume (TKV), which is related to the cyst progression in kidneys. Cyst growth progressed more slowly in the tolvaptan treated patients than in the historical controls. The secondary objective of eGFR was also measured, but was not found to be significant in maintaining the filtration rate, even though the trend is more noticeable than in the control group. The other study was a 1-week administration of tovaptan where the result was analyzed post hoc. The post hoc blinded analysis of renal MRI showed a significant 3.1% reduction in the TKV from baseline after 1 week of tolvaptan with P-value

Conclusion: Tolvaptan showed a positive result on inhibition of renal cysts growth in patients with ADPKD, but it does not have a significant effect on the other outcomes, such as slowing progression of GFR, which measures kidney's failure and its progression to ESRD. Further studies such as TEMPO (an NIH phase 2 registered trial), may show more evidence of slowing down the disease progression and tolvaptan drug alteration may be necessary to reduce AEs and be more of an appropriate drug to treat ADPKD.

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The student author attests that this work is completely his/her original authorship and that no material in this work has been plagiarized, fabricated or incorrectly attributed.
Tolvaptan: a Possible Treatment for Autosomal Dominant Polycystic Kidney Disease

Ray J. Lin

A Clinical Graduate Project Submitted to the Faculty of the

School of Physician Assistant Studies

Pacific University

Hillsboro, OR

For the Masters of Science Degree, August 10, 2013

Faculty Advisor: Mark Pedemonte, PA-C
Clinical Graduate Project Coordinator: Annjanette Sommers, PA-C, MS
Biography

Ray Lin was born in Taipei, Taiwan and grew up in Los Angeles, California. He received a Bachelor of Architecture Design degree from California Polytechnic State University in San Luis Obispo, California, in 2000. He spent the next 9 years working in an architectural firm before deciding to pursue a career in the medical field. Prior to PA school he worked as a Medical Assistant at a dermatology clinic in Texas.
Abstract

**Background:** Autosomal-dominant polycystic kidney disease (ADPKD) is an inherited renal cystic disease that leads to end-stage renal disease. Patients who present with symptoms at an early age are more likely to live to develop end stage renal disease. Patients with ADPKD and renal failure are most commonly treated with hemodialysis. Tolvaptan is expected to be effective in the treatment of ADPKD because of its success in animal models. If clinical trials can prove slowing of the disease progression, hemodialysis and kidney transplant for those patients may not be necessary. What is the effectiveness of tolvaptan as a treatment option for ADPKD to inhibit renal cyst progression?

**Method:** An exhaustive literature search was done using the following search engines, MEDLINE, CINAHL, EMBR, Web of Science, and the initial search used the following combined search terms as treatment, clinical trial, and polycystic kidney disease. The bibliographies of the articles were further searched for relevant sources. Articles with primary data evaluating ADPKD were included. Relevant articles were assessed for quality using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE). A search on the National Institute of Health (NIH) clinical trials site was done.

**Results:** Two studies met inclusion criteria and were included in this systematic review. The result of the 3 year study found tolvaptan to be significant in slowing down the total kidney volume (TKV), which is related to the cyst progression in kidneys. Cyst growth progressed more slowly in the tolvaptan treated patients than in the historical controls. The secondary objective of eGFR was also measured, but was not found to be significant in maintaining the filtration rate, even though the trend is more noticeable than in the control group. The other study was a 1-week administration of tovaptan where the result was analyzed post hoc. The post hoc blinded analysis of renal MRI showed a significant 3.1% reduction in the TKV from baseline after 1 week of tolvaptan with P-value <0.001.

**Conclusion:** Tolvaptan showed a positive result on inhibition of renal cysts growth in patients with ADPKD, but it does not have a significant effect on the other outcomes, such as slowing progression of GFR, which measures kidney’s failure and its progression to ESRD. Further studies such as TEMPO (an NIH phase 2 registered trial), may show more evidence of slowing down the disease progression and tolvaptan drug alteration may be necessary to reduce AEs and be more of an appropriate drug to treat ADPKD.

**Keywords:** Tolvaptan, treatment, clinical trial, polycystic kidney disease.
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Table I: GRADE Quality of Assessment and Summary of Findings

List of Abbreviations

ADPKD  Autosomal Dominant Polycystic Kidney Disease
ARPKD  Autosomal Recessive Polycystic Kidney Disease
AE     Adverse Events
cAMP   Cyclic Adenosine Monophosphate
CRISP  Consortium of Radiologic Imaging Studies of Polycystic Disease
eCCr   Estimated creatinine clearance
eGFR   Estimated glomerular filtration rate
ESRD   End-stage renal disease
GFR    Glomerular filtration rate
GRADE  Grading of Recommendations, Assessment, Development and Evaluations
HF     Heart Failure
LMM    Linear Mixed Model
MDRD   Modification of Diet in Renal Disease
MRI    Magnetic resonance imaging
NNT    Number Needed to Treat
RDC    Ravine’s diagnostic criteria
RRT    Renal replacement therapy
SIADH  Syndrome of Inappropriate Antidiuretic hormone Hypersecretion
TEMPO  Tolvaptan Efficacy and Safety in Management of Autosomal Polycystic Kidney Disease and Its Outcome
TKV    Total kidney volume
Tolvaptan: a Possible Treatment for Autosomal Dominant Polycystic Kidney Disease.

BACKGROUND

Autosomal-dominant polycystic kidney disease (ADPKD) is an inherited renal cystic disease that leads to end-stage renal disease. This disease occurs worldwide and in all races with a prevalence estimated to be between 1:400 and 1:1000 and affects males more than females at ratios of 1.2-1.3:1 for the early incidence rates of ADPKD which will progress to end-stage renal disease (ESRD) in Japan, Europe and the United States. According to National Kidney Foundation (NKF) guidelines, ESRD is indicated when glomerular filtration rate (GFR) falls below a value of 15 ml/min per 1.73m$^2$ with the need for permanent renal replacement therapy (RRT). A patient with a value between 15-29 ml/min will need to prepare to receive RRT as treatments. ADPKD is genetically heterogeneous with 2 genes identified: PKD1 and PKD2. Autosomal-recessive polycystic kidney disease (ARPKD) is less common than ADPKD, but together with nephrophthaisis is the leading cause of ESRD in childhood. Virtually all individuals who inherit PKD1 or PKD2 eventually develop renal cysts that are visible by ultrasononographic imaging studies. The age at which affected individuals have clinical manifestations such as renal failure or hypertension is variable. Patients with PKD1 present with symptoms at a younger age than those with PKD2. In one study the median age of patients who presented with renal failure was 54 and 74 years for those with PKD1 and PKD2, respectively. However, early onset disease has been described with both mutations. Patients who present with symptoms at an early age are more likely to live to develop end stage renal disease. In one study, patients diagnosed before the age of
30 had a mean renal survival of 10 years less than those diagnosed after the age of thirty. Currently there is no effective therapy for these diseases. Patients with ADPKD and renal failure are most commonly treated with hemodialysis. Such patients have equivalent or perhaps better overall outcomes with any renal replacement therapy compared to non-ADPKD patients. Although beneficial, each hemodialysis session is not cheap to the patients and impacts their qualities of life greatly. The mean total cost of each maintenance hemodialysis session was estimated to be $297 USD with mean total annual cost of dialysis per patient estimated to be $46,332 USD. The earlier ADPKD progresses to ESRD, the higher the cost to an individual. Time taken away from the patients with hemodialysis impacts their livelihood, and the added cost of continued hemodialysis impacts our healthcare system. Advances in the understanding of cytogenesis and availability of genetically related animal models provide unique opportunities to develop effective treatments. If the progression of ADPKD can be slowed to reach ESRD at a much later stage in life, not only will the patient benefit, but the impact on the cost of our healthcare support systems will be dramatic.

So what causes cysts to form in ADPKD? Within our kidneys polycysteins and fibrocystein/polyductin are multifunctional proteins with numerous interacting partners that are essential in maintaining the differentiated phenotype of the tubular epithelium. Reduction in one of these proteins below a critical level induces changes in protein trafficking and targeting, cell-matrix and cell-to-cell interactions, proliferation and apoptosis, planar polarity, and fluid secretion that result in the nitration and growth of cysts. In theory, increased collection duct permeability to water and concentrated urinary osmolality above that of plasma, causes cyst growth which is “clamped” by
The treatment of patients with ADPKD includes non-specific measures that are applicable to all ESRD patients, such as strict blood pressure control, dietary protein restriction, a low salt diet, and statins, which may prevent progression of disease and reduce cardiovascular mortality.

Currently there are some new treatments that are being explored. Treatment such as Small-molecule cystic fibrosis transmembrane conductance regulator (CFTR) inhibitors and V$_2$-receptor antagonists show promising effects of slow cyst growth in laboratory animals. There are no published clinical trials performed for CFTR inhibitors at this time but there are a few trials that were recently completed for V$_2$-receptor antagonists.

Tolvaptan is an orally effective nonpeptide arginine vasopressin (AVP) V$_2$-receptor antagonist. It inhibits not only the binding of AVP, but also the AVP-induced production of cyclic adenosine monophosphate (cAMP). In addition, tolvaptan has no intrinsic V$_2$ receptor agonistic effect. There is clear evidence that cAMP plays a major role in cystogenesis. The AVP V$_2$-receptor pathway is a major pathway for cAMP accumulation in the renal collecting ducts. The V$_2$-receptor antagonists could be useful in the treatment of PKD. The FDA approved its current use for treatment of clinically significant hypervolemic or euvolemic hyponatremia. Tolvaptan showed marked aquaresis in healthy and diseased animals. In rat models with acute and chronic hyponatremia, tolvaptan improved organ water retention and increased survivability. Miyazaki et al showed tolvaptan reduced cardiac preload without unfavorable effects on renal functions, systemic hemodynamics, and circulating neurohormones in dogs with heart failure (HF). Furthermore, in animal models of human polycystic kidney disease,
use of tolvaptan showed a decrease in kidney weight as well as in cyst and fibrosis volume.\textsuperscript{18}

The purpose of this study is to explore the effectiveness of a possible treatment that is in current clinical trials. Tolvaptan is indicated as a useful therapy in hyponatremia, HF and other diseases that are accompanied by volume overload. Furthermore, tolvaptan is also expected to be effective in the treatment of ADPKD. If clinical trials can prove slowing of the disease progression, the need for hemodialysis and kidney transplant for those patients may not be necessary. Therefore this review aims to determine the effectiveness of tolvaptan as a treatment option for inhibiting renal cyst growth in people with ADPKD.

METHODS

An exhaustive literature search was done using the following search engines, MEDLINE, CINAHL, EMBR, Web of Science, and the initial search used the following combined search terms as treatment, clinical trial, and polycystic kidney disease. The bibliographies of the articles were further searched for relevant sources. Articles with primary data evaluating ADPKD were included. A search on the National Institute of Health (NIH) clinical trials site was conducted. Relevant articles were assessed for quality using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE).\textsuperscript{27}

RESULTS

The results returned from MEDLINE revealed 55 relevant articles, CINAHL 3, and EBMR 2. Only 2 articles from this search met inclusion criteria with clinical trials of
tolvaptan for the purpose of treatment in ADPKD. These articles include one randomized controlled trial\textsuperscript{13} and one blinded post hoc analysis.\textsuperscript{15} Both studies were funded by Otsuka Pharmaceutical Development & Commercialization Inc. In addition, the search of the NIH clinical trial database revealed one currently registered completed trial of a Phase 2, multi-center, open-label study to determine long-term safety, tolerability, and efficacy of split-dose oral regimens of tolvaptan tablets in a range of 30 to 120 mg/d in patients with autosomal dominant polycystic kidney disease which will not be included as part of the review since it is not fully analysed.\textsuperscript{26}

**The 3-Year Study**

This study\textsuperscript{13} is a Phase 2 clinical trial where consenting ADPKD patients were enrolled in two multicenter open-label tolvaptan-treatment studies in North America and Japan. For the North American study, eligibility requirements were men or women age >18 years fulfilling Ravine’s diagnostic criteria,\textsuperscript{20} prior participation in a phase 1 tolvaptan ADPKD trial, and willingness to adhere to contraceptive precaution. Ravine’s diagnostic criteria (RDC) is explained by the authors as (explanation from study). Exclusion criteria included inability to comply with study procedures, estimated glomerular filtration rate (eGFR) <30ml/min per 1.73 m\textsuperscript{2}, anticipation of renal replacement therapy within 1 year, and active treatment that would affect endpoint measurements. The Japanese study was similar except for participants were enrolled at age 20 years without upper limit and also had further exclusion that included subjects with serum creatinine \(\geq\) 2.5mg/dl, uncontrolled hypertension, systolic BP <90 mmHg, serious cardiac or hepatic disease, or a history of significant bleeding or bleeding tendency. A total of 63 subjects started the regimen of tolvapan at various split-doses
depending on the tolerance of each patient and 12 subjects were lost prior to the end of the study which lasted 36 months 6 of whom withdrew due to adverse events (AE). The remaining 6 were unaccounted for.13

The primary objective of this trial was to confirm the long-term safety and tolerability of tolvaptan. Subject safety was assessed by regular monitoring of adverse events, directed physical examination, vital signs, laboratory, and electrocardiogram measurement. The secondary objective of this trial was to acquire pilot efficacy data by assessing changes in urine osmolality, total kidney volume (TKV), estimated glomerular filtrate, and hypertension status. Control data were gathered from participants in the Consortium of Radiologic Imaging Studies of Polycystic Disease (CRISP) and Modification of Diet in Renal Disease (MDRD) studies.17,29 The first control subject was matched to the first tolvaptan-treated subject and then the second control was matched to the second tolvaptan-treated subject, and so on until all had one match similar to the treated subject. The process then proceeded in again, selecting a second similar control subject for the tolvaptan-treated subject who was last matched until all had two control matches for every study subject. Therefore, a total of 102 control match subjects were included in this study for comparison.13

The result of this study13 found tolvaptan to be significant in slowing down the total kidney volume (TKV), which is related to the cyst progression in kidneys. Cyst growth progressed more slowly in the tolvaptan treated patients than in the historical controls. Eighty-one percent of subjects completed 3 years of treatment. Although all of the participants experienced AEs and six participants withdrew from the study because of AEs, most were mild to moderate in severity. The author stated that tolvaptan had a
strong effect on TKV growth, consistent with a potent effect on cyst growth. The growth of cysts appears to resume beyond 6 months but at a much slower rate than in the control group. The secondary objective of eGFR was also measured, but was not found to be significant in maintaining the filtration rate, even though the trend is more noticeable than in the control group. The mean change in eGFR over 3 years of treatment with tolvaptan was marginally less than in the control group even though the tolvaptan group had larger kidney size at baseline. The authors recognized this study has limitations. Twelve of 51 of the tolvaptan-treated patients were Japanese whereas both of the matched-control patient cohorts were predominantly Caucasian with only approximately 1% Asian. Another limitation is that controls were not studied concurrently.\textsuperscript{13}

Lastly, only 8 out of 51 study subjects were not receiving antihypertensive therapy at the beginning of the study and by the end, 3 became hypertensive during the 3 years of treatment.\textsuperscript{13}

The 1-Week Study

In this particular 1 week duration study,\textsuperscript{15} the result of TKV was a blinded post hoc analysis. Post hoc hypotheses based on subgroup analysis often arise from exploration of a data set in which many such hypotheses are considered.\textsuperscript{11} The original purpose of the study was to clarify the potential renal mechanisms to see whether the antagonist effects were dependent on underlying renal function in 20 patients with ADPKD before and after 1 week of daily split-dose treatment. Participating ADPKD patients were previously diagnosed base on Ravine’s criteria, 18-60 years of age and selected to represent a wide range of disease severity with estimated creatinine clearance (eCCr) by the Cockcroft-Gault equation \( \geq 30\text{ml/min} \). A total 20 participants (10
caucasian males and 10 caucasian females) were enrolled in the study. Exclusion criteria included concurrent diseases that could interfere with the conduct of the study or the interpretation of the results. This was a single center, sequential, multiple-dose study of the effect of split-dose tolvaptan tablets on ADPKD patients. Subjects were given enough tablets for 7 days with 45 mg on awakening and 15mg 8 hrs later on study days 1-6. On day 7, subjects administered tolvaptan 45mg on awaking at home and administered additional 15mg 8hrs later at the study facility. On day 8, subjects were given 45mg doses at the study facility then followed by measurement of renal clearance, renal blood flow by MRI, and chemistry and hematology parameters.\(^{15}\)

The goal of this study\(^{15}\) was to check various effects of tolvaptan on laboratory parameters. Changes in TKV were not an initial focus for this study since it had been believed that it would take months to detect the effects due to inhibition of cell proliferation or fluid secretion. The post hoc blinded analysis of renal MRI showed a significant 3.1% reduction in the TKV from baseline after 1 week of tolvaptan with P-value <0.001. In order to determine whether the reduction in kidney volume was due to changes in the cyst volume, individual cyst size was measured in 9 patients. To protect against bias, the MRI scan was blinded to the examiner by de-identified patients and the removal of the date of examination. In 8 of the 9 patients, the mean cyst volume was lower following administration of tolvaptan and in 3 of them the change was statistically significant. The researches suggest that early decrease in TKV, is likely attributable to changes in cyst fluid secretion.\(^{15}\)

The result also showed the administration of tolvaptan increases urine flow, and free water clearance, and induced an 8.6% reduction in GFR. However, there was no
correlation between percent changes in GFR and GFR value at baseline with a P-value = 0.398. It is unlikely that relative concentration of plasma volume accounts for the 8.6% reduction in GFR, since no significant change in blood hemoglobin or serum protein or albumin concentration was detected.  

**DISCUSSION**

Tolvaptan is currently approved in the US and EU for the treatment of hyponatremia in euvolemic and hypervolemic states and syndrome of inappropriate antidiuretic hormone hypersecretion (SIADH). The drug was designed for patients with disorders such as HF, liver cirrhosis, impaired renal function, and SIADH due to excess water retention. It has recently realized that it might be effective in the treatment of PKD due to its mechanism of actions. Several recent studies show tolvaptan to be effective in animal models in demonstrating that vasopressin stimulates renal cytogenesis by increasing intracellular cAMP, which promotes transepithelial fluid secretion and stimulates cyst-derived cell proliferation in vitro. Therefore, tolvaptan is expected to become a useful drug in the treatment of PKD. The two clinical trials, the 3-year and 1-week studies do suggest such an effective mechanism in significantly slowing down renal cysts progression in ADPKD patients. However, there are many limitations that still result in this drug not being being fully utilized in a clinical setting. These limitations include but are not limited to clinical trial sample size, the number of adverse events, and the length treatment and follow up.

The sample size in the 3-year study began at 63 study subjects, of whom 12 (19%) withdrew from the study. Although the size was considered decent, greater numbers of study subjects will be necessary in order to calculate more precise statistical
values. The 3-year study\textsuperscript{13} showed statistical significance of in how tolvaptan slowed progression in TKV, other secondary outcomes may become clearer with a larger sample size. The authors revealed that 6 of those lost to follow up withdrew due to AEs, but do not account for the other 6. The reasons behind the losses may be important in ensuring full transparency in a study funded primarily by Otsuka Pharmaceutical Development & Commercialization Inc. who developed the drug. Another limitation of this study was the lack of a concurrent control group during the 3 year period. The control data were pulled from CRISP and MDRD to match the study subjects. The authors did not clarify how the controls were matched to the study subjects, although later comments in the results indicate that it was not a racial match as Caucasian controls were matched with Japanese study subjects. Neither was it a consideration of kidney size as it was later found that the matched controls started off with unequal kidneys. Another problem with matching seems to be that all of the treatment group were treated for 3 years and the controls appear to have been selected from data in historical files only at the end of the study. Although the data is useful for comparison in this study, the concurrent control group would have eliminated doubts of other situational or environmental factors affecting the outcome of the results, and how the controls were match to the study subjects. The authors also report an 81\% completion rate which sounds like a positive result, however, this is misleading as this also means that there was a 19\% loss to follow up, which is rather a high number. In the other study,\textsuperscript{15} which only lasted 1 week, the sample size of 20 participants is not only small but also lacks diversity. All patients in that study were Caucasian and accordingly the result are only generalizable to such a population group. No control group was utilized concurrently with this study.
In the 3-year study\textsuperscript{13} of tolvaptan all the AEs that occurred associated with the drug were well documented. Higashihara et al\textsuperscript{13} identified that the most prominent AEs were thirst, abnormally frequent urination, renal pain and upper urinary tract infection with higher occurrences at higher split dosage (90/30 mg/d) of tolvaptan. AEs were accounted for in all subjects participated in the study, and included renal impairment, acute renal failure, benign pituitary tumor, transient ischemic attack, eye swelling, and subarachnoid hemorrhage with fatal outcome.\textsuperscript{13} Since one may have had a fatal outcome, very little information was given as to this specifics although as it was included in the list of AEs, this seems to be an acknowledgement that it was drug related. In the 1-week study\textsuperscript{15} of tolvaptan, the common AEs were similar to those of the 3-year study\textsuperscript{13}, which included polyuria, polydipsia, nocturia and dry mouth. It is reasonable to assume that the less serious AEs referred to in the 1-week study\textsuperscript{15} were because the patient were only given tolvaptan for 8 days. If the patient had taken long term tolvaptan, the AEs may have mimicked those of the longer study up to and including fatal outcomes. These studies demonstrated that the AEs from tolvaptan were moderately tolerated by most patients. The loss to follow up due to AEs in the 3-year study\textsuperscript{13} demonstrated serious limitations of in clinical administration of this drug. A further study in greater sample size is necessary to better define the size of population it would affect.

Tolvaptan showed significant difference in slowing progression of renal cysts during the 3 year span of the study. However, other secondary outcomes may require longer period of time to achieve a significant result. For example, the GFR measurement shows tolvaptan was able to maintain GFR during the study period, however, the mean changes did not result in a P-value that render the data significant. The mean change
measurements of patients on tolvaptan show smaller changes in GFR according to Table 4 in the 3-year study by Higashihara et al. The significance of the GFR changes may not be apparent without a much longer study period. A longer study period involving tolvaptan is necessary to measure the secondary outcomes of disease progression to ESRD.

Tolvaptan is continually studied as a treatment option for ADPKD. A design of Tolvaptan Efficacy and Safety in Management of Autosomal Dominant Polycystic Kidney Disease and Its Outcome (TEMPO) study was recently completed in February 2012 but is not yet available. It will be interesting to see the results of this new study. This TEMPO study seeks to determine whether tolvaptan inhibits TKV growth in patients with ADPKD whether such changes meaningfully affect the clinical course of the disease. The study design is a retrospective, 3 year, multicenter, double-blinded, placebo-controlled trial of tolvaptan with approximately 1,445 patients with ADPKD enrolled between March 2007 and January 2009. This randomized trial is the largest clinical study of proposed ADPKD intervention to date. The outcome of this study may better justify tolvaptan’s effect on renal cysts growth and GFR.

**CONCLUSION**

Although tolvaptan has a positive result on inhibition of renal cysts growth in patients with ADPKD, it does not have a significant effect on the other outcomes, such as slow progression of GFR, which measures kidney’s failure and its progression to ESRD. Tolvaptan does not have sufficient evidence in clinical setting for the use of treatment for ADPKD at this time, perhaps further studies such as TEMPO, will show more evidence of slowing down the disease progression. Furthermore, tolvaptan drug alteration may be
necessary to reduce AEs and become a more appropriate drug to treat ADPKD.
References


27. Available at: http://gradeworkinggroup.org/


### TABLES

Table 1: GRADE Quality of Assessment and Summary of Findings: What is the effectiveness of tolvaptan as a treatment option for autosomal dominant polycystic kidney disease to inhibit renal cyst progression?

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+ Lack of appropriate description of case and control matching
++ Small and isolated sample
*= unit of ml/min/1.73 m2
**= participant became hypertensive