10 years of Tolvaptan in ADPKD: A single center evaluation

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Research Article

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Abstract

Background

Tolvaptan is the only approved drug for the treatment of autosomal dominant polycystic kidney disease (ADPKD) and causes significant polyuria with secondary polydipsia. Up to now, there is no study that examines tolvaptan adherence and satisfaction with information about tolvaptan in ADPKD patients on tolvaptan long-term therapy.

Methods

This non-interventional study includes 12 ADPKD patients that were formerly enrolled in the Tolvaptan Efficacy and Safety in Management of Autosomal Dominant Polycystic Kidney Disease and Its Outcomes trial (TEMPO 3:4), in the subsequent extension trial (TEMPO 4:4) and have continued to use tolvaptan thereafter. Data were collected via questionnaires on patients' self-reported adherence (MARS-D: Medication Adherence Report Scale - German version) and satisfaction with the information received about tolvaptan (SIMS-D: Satisfaction with Information about Medicines Scale - German version). In addition, serum creatinine levels and clinical data were collected.

Results

The duration of tolvaptan treatment amounted to 10.2 ± 0.3 years at a daily dosage of 90.0 ± 28.6 mg. The evaluation of MARS-D demonstrated strong adherence to tolvaptan (range of possible score: 5–25; *median*: 23.5; *range* of individual results: 5). The analysis of SIMS-D showed a high level of satisfaction with the information received about the action and usage of tolvaptan (SIMS-D AU subscore; range of possible score: 0–9; *median*: 9, *range* of individual results: 1), but also revealed clearly measureable dissatisfaction regarding the information received about potential problems of tolvaptan in 42 % of the patients (SIMS-D PP subscore; range of possible score: 0–8; *median*: 8, *range* of individual results: 6). During treatment with tolvaptan, the mean eGFR decreased from 78.8 ± 15.9 ml/min/1.73 m^2 to 48.3 ± 19.4 ml/min/1.73 m^2 ($P < 0.0001$).

Conclusions

Although patients reported strong adherence to tolvaptan, even after 10.2 years of treatment, there was still dissatisfaction with the information received about potential problems with tolvaptan. Therefore, our data suggest conduction of at least one standardized patient survey on satisfaction with the information received about potential problems with tolvaptan in order to improve patient education regarding the use of tolvaptan in slowing ADPKD.

Trial registration:

German Clinical Trials Register; drks.de identification number: DRKS00019856

Background

Autosomal dominant polycystic kidney disease (ADPKD) is the most common inherited renal disorder and the fourth most frequent reason for renal replacement therapy in the world [1, 2]. It is characterized by the formation and continuous expansion of fluid-filled cysts in the kidneys, but extrarenal cysts, intracranial aneurysms, changes in cardiac valves and colonic diverticulosis are also possible. About 85 % of the patients have a mutation in the PKD1 gene and the majority of the others in the PKD2 gene that code for polycystin-1 and polycystin-2, respectively [3, 4]. The polycystins are located in the primary cilium, a hair-like sensor being attached to the surface of many mammalian cells including renal collecting duct principal cells [5]. In ADPKD models, both mutations attenuate ciliary calcium signaling and lead to an upregulation of cyclic adenosine monophosphate (cAMP) that stimulates proliferation and fluid secretion of the renal cyst tubular epithelial cells [6–8]. Vasopressin significantly increases intracellular cAMP of renal tubular epithelium in vitro [9] and the vasopressin V2 receptor antagonist OPC31260 (tolvaptan) has been shown to slow the progression of experimental ADPKD [10–12]. Subsequently, the clinical study program TEMPO (Tolvaptan Efficacy and Safety in Management of Autosomal Dominant Polycystic Kidney Disease and Its Outcomes) proved the efficacy and safety of tolvaptan in the treatment of ADPKD patients [13–15]. This led to the approval of tolvaptan for the treatment of adults at high risk for rapid progression of ADPKD. Considering the ubiquitous tolvaptan-induced diabetes insipidus renalis as an important side effect during continuous treatment with tolvaptan, patient adherence is strongly challenged but still required for successful long-term therapy. While a high degree of tolvaptan adherence became previously apparent in TEMPO and in the cohort of Edwards et al. [14, 16, 17], no study so far specifically targeted adherence of ADPKD patients after a decade of taking tolvaptan. The aim of our work was therefore the examination of tolvaptan adherence and satisfaction with information received about tolvaptan in our cohort of 12 ADPKD patients with 10 years of tolvaptan treatment. Data were collected via the German versions of the Medication Adherence Report Scale (MARS-D) and the Satisfaction with Information about Medicines Scale (SIMS-D) [18, 19]. The development of kidney function (assessed by the CKD-EPI eGFR formula), blood pressure and the incidence of complications related to renal cysts were also evaluated.

Methods

Design

This is a non-interventional, monocentric observation of long-term tolvaptan treated ADPKD patients using standardized questionnaires to investigate therapy adherence and satisfaction with information received about tolvaptan. The identification number of the study in the German register of clinical studies (drks.de) is DRKS00019856 (registered retrospectively at 16/01/2020). Our study was approved by the University of Dresden Ethics Committee (Bearbeitungsnummer/Processing number: EK 237062017). The investigation conforms to the principles outlined in the Declaration of Helsinki.

Subjects

From our cohort of tolvaptan-treated ADPKD outpatients, the study enrolled seven males and five females who participated in both the TEMPO 3:4 (3-years, multicenter, randomized, double-blind, placebo-controlled, phase 3 study; ClinicalTrials.gov Identifier NCT00428948) and the TEMPO 4:4 trial (2-years, open-label extension study; ClinicalTrials.gov Identifier NCT01214421) at the Dresden University Hospital. Only patients belonging to the verum group of TEMPO 3:4 were considered for the present work. Subsequently, all 12 patients received tolvaptan during the open-label evaluation period of TEMPO 4:4 and continued to receive the study drug until the market launch of tolvaptan in Germany in May 2015. The time period of the TEMPO studies is hereinafter referred to as the TEMPO period. After a short tolvaptan-free interval, all patients went on to receive tolvaptan as Jinarc® (Otsuka Pharma GmbH, Frankfurt am Main, Germany) at the same dosage as in the TEMPO studies in the nephrological outpatient clinic of the University Hospital Dresden. Enrollment into the current study took place after detailed information and written informed consent from the study participants. The time period between the start of Jinarc® and the time of the current study is hereinafter referred to as the Jinarc® period. During the Jinarc® period, regular nephrological check-ups took place every three months in the nephrological outpatient clinic of the University Hospital Dresden. Body weight, blood pressure, medical history and clinical status were recorded. According to the approval regulations of Jinarc®, the liver function tests were checked in addition to control of creatinine levels at every visit. The demand of a sufficient drinking habit as well as a low salt consumption was indicated during each consultation and if necessary, the antihypertensive medication was adjusted. All patients received an MRI for height-adjusted total kidney volume (HtTKV) determination using the Mayo algorithm [20].

Measurements

Patient self-assessment of adherence and satisfaction with information about tolvaptan was carried out using the MARS-D and SIMS-D questionnaires. Both questionnaires were kindly provided by Professor Rob Horne (© Rob Horne, School of Pharmacy, University College London, Great Britain) and the Department of General Practice and Health Services Research and Department of Internal Medicine IV, Clinical Pharmacology and Pharmacoepidemiology, University Hospital Heidelberg, Heidelberg, Germany, and were filled out by the patients subsequently after enrollment into the study. The MARS-D [18] is the German version of the MARS (Medication Adherence Report Scale) [21] questionnaire and consists of five items describing non-adherent behavior. Patients were asked to score their own behavior regarding the frequency of the different aspects on the following response scales: ‘always’, ‘often’, ‘sometimes’, ‘rarely’ and ‘never’. Each item is scored with one (‘always’) to five points (‘never’), leading to a sum score ranging between 5 and 25, a higher score indicating higher adherence to the prescribed tolvaptan therapy. The SIMS-D [19] is the German version of the SIMS (Satisfaction with Information about Medicines Scale) [22] questionnaire and consists of 17 items. These specify the type of information that patients need for safe and accurate self-management of medication. Patients were asked to rate the drug information they had received on a 5-point scale: “too much,” “about right,” “too little,” “none received,” and “none needed.” Responses of the items of the SIMS-D: “too much,” “too little,” and “none received” are counted zero, “about right” and “none needed” are counted one. The evaluation of items 1 to 9 identifies satisfaction with information about “action and usage of medication” (AU subscale, range of possible score: 0–9), evaluation of items 10 to 17 identifies satisfaction with information about “potential problems of medication” (PP subscale, range of possible score: 0–8), a higher score indicating higher satisfaction with the information received about tolvaptan. The kidney function was estimated by the CKD-EPI eGFR formula (CKD-EPI eGFR) expressed as ml/min/1.73 m^2 [23]. During TEMPO 3:4 and TEMPO 4:4, the respective creatinine levels were measured at the Covance Central Laboratory Services-Geneva, Switzerland. The results of the creatinine measurements were taken from the TEMPO study files with the permission of Otsuka Pharmaceutical. The change in eGFR during the TEMPO period was calculated between the end of the tolvaptan dose-escalation period at week 3 of TEMPO 3:4 and the point of the last creatinine determination in TEMPO 4:4. During the Jinarc® period, the creatinine levels were measured at the Institute for Clinical Chemistry and Laboratory Medicine at the University Hospital Dresden, Germany. The change in eGFR during the Jinarc® period was calculated between the time three months after the first prescription of Jinarc® and the time of the current study. The change in eGFR over the entire period of treatment with tolvaptan was calculated between the end of the tolvaptan dose-escalation period at week 3 of TEMPO 3:4 and the time of the current study. The annual slope of eGFR was calculated for the TEMPO and the Jinarc® period. The difference between the annual slope of eGFR in the TEMPO and the Jinarc® period was calculated by subtracting the annual slope of eGFR during the TEMPO period from that of the Jinarc® period. Further clinical data on age, sex, prescribed drugs, arterial blood pressure values and complications related to renal cysts were taken from the documentation of the nephrological outpatient clinic and the TEMPO study files with the approval of Otsuka Pharmaceutical. The mean arterial blood pressure was estimated by doubling the diastolic blood pressure, adding the systolic blood pressure and dividing this composite sum by three. We were also interested whether blood pressure and number of antihypertensive drugs would change during the TEMPO and Jinarc® period. Accordingly, the change in mean arterial blood pressure, systolic blood pressure, diastolic blood pressure and the change in the number of antihypertensive drugs during the TEMPO period was calculated between the end of the tolvaptan dose-escalation period at week 3 of TEMPO 3:4 and

the point of the last creatinine determination in TEMPO 4:4. The change in mean arterial blood pressure, systolic blood pressure, diastolic blood pressure and the change in the number of antihypertensive drugs during the Jinarc® period was calculated between the time three months after the first prescription of Jinarc® and the time of the current study.

Statistical analysis

Statistical significance was defined as $P < 0.05$. Descriptive statistics on categorical data are presented with median, maximum, minimum and range (difference between the largest and smallest value). The sum scores of MARS-D, SIMS-D AU and SIMS-D PP are displayed in frequency diagrams. Metric data are presented as mean with standard deviation. The change in eGFR during the TEMPO period, the change in eGFR over the entire period of treatment with tolvaptan, and the change in the annual slope of eGFR between the TEMPO period and the Jinarc® period were analysed using the paired t-test after checking for normal distribution with the Kolmogorov-Smirnov test. The change in eGFR during the Jinarc® period was analysed using the Wilcoxon signed-rank test after checking for normal distribution with the Kolmogorov-Smirnov test. The correlations of the difference in the annual slope of eGFR between the TEMPO and the Jinarc® period with the change in mean arterial, systolic and diastolic blood pressure during the Jinarc® period were calculated by using the Pearson correlation.

Results

General characteristics of the 12 patients are represented in Table 1. The mean duration of tolvaptan treatment amounted to 10.2 ± 0.3 years. The mean tolvaptan daily dosage was 90 ± 28.6 mg. The mean change in kidney function over the entire period of treatment with tolvaptan amounted to -30.5 ± 10.4 ml/min/1.73 m^2 ($P < 0.0001$). During the entire observation period, none of the patients showed aberrant liver function tests potentially related to tolvaptan. In patient number 9, the blood pressure could not be adjusted appropriately due to multiple drug intolerance and the therapy with Jinarc® was stopped at the time of the current study due to CKD stage 5. Detailed characteristics of the 12 patients are represented in Table 3.

Adherence to tolvaptan

The MARS-D questionnaire showed a high degree of adherence to tolvaptan with a median count of 23.5 points (*range*: 5 points). 3 of the 12 patients (25 %) answered that they never forget the intake of tolvaptan and 9 patients (75 %) that they rarely forget the intake of tolvaptan. 6 patients (50 %) never suspended the intake of tolvaptan and 6 patients (50 %) rarely suspended the intake of tolvaptan. 8 patients (67 %) never skipped a single dose of tolvaptan on purpose, 3 patients (25 %) rarely skipped a single dose of tolvaptan on purpose and 1 patient (8 %) sometimes skipped a single dose of tolvaptan on purpose. 11 patients (92 %) never changed the dosage of tolvaptan and never took less tolvaptan than prescribed whereas 1 patient (8 %) rarely changed the dosage of tolvaptan and rarely took less tolvaptan than prescribed. The descriptive values of the MARS-D are shown in Table 2. The MARS-D sum score for each patient is shown in Table 3. The distribution of the MARS-D sum score is displayed in Fig. 1a.

Satisfaction with information received about tolvaptan

The evaluation of SIMS-D AU showed a high level of satisfaction with information received about the action and usage of tolvaptan (*median sum score*: 9, *range*: 1). 9 patients (75 %) were completely satisfied with the information received about the action and usage of tolvaptan (9 points each) and 3 patients (25 %) had a sum score of 8 points (Fig. 1b). 11 of the 12 patients (92 %) rated the information received on what tolvaptan is called, what tolvaptan is for, what tolvaptan does, how tolvaptan works, how long tolvaptan will take to act, how to use tolvaptan and how to get a further supply of tolvaptan as “about right” and 1 patient (8 %) as “none needed”. 8 patients (67 %) rated the information received on how to tell if tolvaptan works as “about right”, 2 patients (17 %) as “none needed”, 1 patient (8 %) as “too little”, and 1 patient (8 %) as “none received”. 10 patients (83 %) rated the information received on how long they will need tolvaptan as “about right”, 1 patient (8 %) as “to little”, and 1 patient (8 %) as “none needed”.

The analysis of the SIMS-D PP revealed some dissatisfaction regarding the information received about potential problems with tolvaptan (*median sum score*: 8 points, *range*: 6 points). 7 patients (58 %) were completely satisfied with the information received about potential problems of tolvaptan (8 points each) but 5 patients (42 %) had a respective sum score of only 2, 3, 4, 4 and 6 points (Fig. 1c). 10 patients (83 %) rated the information received on whether tolvaptan has any unwanted side effects and what they should do if they experience unwanted side effects as “about right”, 1 patient (8 %) as “none needed”, and 1 patient (8 %) as “to little”. 10 patients (83 %) rated the information received on what they should do if they forget to take a dose of tolvaptan as “about right”, 1 patient (8 %) as “none needed”, and 1 patient (8 %) as “to little”. 9 patients (75 %) rated the information received on whether they can drink alcohol whilst taking tolvaptan as “about right”, 1 patient (8 %) as “none needed”, 1 patient (8 %) as “too little”, and 1 patient (8 %) as “none received”. Only 7 patients (58 %) rated the information received about the risk of getting tolvaptan-related side effects as “about right”, 1 patient (8 %) as “none needed”, 3 patients (25 %) as “too little”, and 1 patient (8 %) as “none received”. Again, only 7 patients (58 %) rated the information received on whether tolvaptan interferes with other medicines as “about right”, 1 patient (8 %) as “none needed”, and 4 patients (33 %) as “too little”. Also, only 7 patients (58 %) rated the information received on whether tolvaptan will make them feel drowsy as “about right”, 1 patient (8 %) as “none needed”, 3 patients (25 %) as “too little”, and 1 patient (8 %) as “none received”. Likewise, only 7 patients (58 %) rated the information received on whether tolvaptan will affect their sex life as “about right”, 1 patient (8 %) as “none needed”, 2 patients (17 %) as “too little”, and 2 patients (17 %) as “none received”. The descriptive values of the SIMS-D AU and SIMS-D PP sum scores are shown in Table 2. The SIMS-D AU and SIMS-D PP sum score for each patient is shown in Table 3.

Change in kidney function during tolvaptan long-term treatment

Patient number 12 underwent surgical cyst deroofing of the liver after the end of TEMPO 4:4 in 2015 and had to spend two weeks in the intensive care unit due to complications and acute renal failure. This patient (marked as # 12 in Fig. 2) had a 15.5 ml/min/1.73 m^2 reduced eGFR after this event and was therefore excluded from the calculation of the change in eGFR. During the entire treatment with tolvaptan, the mean eGFR of the remaining 11 patients decreased from 78.8 ± 15.9 ml/min/1.73 m^2 after the dose-escalation period at week 3 in TEMPO 3:4 to 48.3 ± 19.4 ml/min/1.73 m^2 at the time of the current study ($P < 0.0001$). There was also a significant decrease of the mean eGFR from week 3 in TEMPO 3:4 to 62.7 ± 17.8 ml/min/1.73 m^2 at the end of TEMPO 4:4 (TEMPO peroid, $P < 0.0001$; Fig. 2a). Three months after the first prescription of Jinarc®, the mean eGFR amounted to 61.74 ± 19.3 ml/min/1.73 m^2 and decreased also significantly to the time of the current study (Jinarc® period, Fig. 2a, P = 0.001). Patients number 9 and 10 had the worst kidney function at the end of the TEMPO and the Jinarc® period and therefore, were probably in the most progressive stage of ADPKD (marked with # 9 and # 10 in Fig. 2). Patient number 12 was prescribed Jinarc® in 2016 at a stable general condition and was therefore re-included for the calculation of the annual slope of eGFR. The mean annual slope of eGFR was − 2.7 ± 1.3 ml/min/1.73 m^2 per year during the TEMPO period and − 4.5 ± 2.6 ml/min/1.73 m^2 per year during the Jinarc® period ($P = 0.08$; Fig. 2b) where patients number 1 to 4 (marked with # 1, # 2, # 3 and # 4 in Fig. 2) experienced a pronounced decrease. In fact, there was a correlation of the difference in the annual slope of eGFR between the TEMPO and the Jinarc® period with the change in mean arterial ($r = 0.60$; $P = 0.04$), systolic ($r = 0.72$; $P = 0.01$; Fig. 2c) but not diastolic blood pressure during the Jinarc® period ($r = 0.23$; $P = 0.47$). The respective arterial blood pressure values and total number of anti-hypertensive drugs of each patient are listed in Table 3.

Urological events during treatment with tolvaptan

7 patients (58 %) reported urological complications since the beginning of TEMPO 3:4. 1 patient (8 %) described a single occasion of flank pain. 1 patient (8 %) suffered flank pain during a renal cyst infection. 1 patient (8 %) described three events of flank pain. 1 patient (8 %) reported two events of flank pain and a single episode of macrohematuria. 1 patient (8 %) had flank pain twice a year and 1 patient (8 %) had flank pain four times a year. 1 patient (8 %) suffered from weekly flank pain. The urological events of each patient are shown in Table 3.

Discussion

Although tolvaptan has specific side effects and is not primarily essential for survival, a high degree of adherence to tolvaptan therapy became apparent in the pivotal TEMPO 3:4 and TEMPO 4:4 trials in patients with ADPKD [14, 16]. Therefore, we wanted to examine the adherence and the satisfaction with information received about tolvaptan in our ADPKD patients with 10 years of tolvaptan treatment. To the best of our knowledge, our group of 12 ADPKD patients, with a mean tolvaptan treatment duration of 10.2 years, is the largest reported cohort up to now in this regard. The mean daily dosage of 90 mg tolvaptan corresponded to the average dosage of 95 mg per day in the verum group of TEMPO 3:4 [14] and a median Irazabal-classification of 1D was indicative for the presence of rapidly progressive ADPKD [20]. People with ADPKD are often highly motivated patients because they know the scenario of end-stage renal failure from their relatives. Nevertheless, non-adherence in patients usually increases over time of medication intake with a considerable side effect profile and may hereby challenge the long-term treatment effects of tolvaptan. Nevertheless, the MARS-D sum score of the patients amounted to 23.5 points (maximum possible score: 25 points), thus demonstrating the consistently high degree of tolvaptan adherence even after 10.2 years of treatment. This result is in line with Edwards et al. who reported on a group of ADPKD patients in whom only 1 in 39 patients with more than five years of tolvaptan treatment (group average tolvaptan treatment period: 7.6 years) discontinued tolvaptan due to an adverse event [17]. Interestingly, 50 % of the patients stated that they rarely suspend the intake of tolvaptan and one third of the patients stated that they rarely or sometimes skip a single dose of tolvaptan on purpose. Maybe, this can be partly explained by occasional changes in patients' condition such as diarrhea, fever or lack of access to water. Moreover, due to the permanent polyuria and polydipsia, it is understandable to skip a single dose of tolvaptan on purpose in everyday issues such as important personal or business appointments, shift changes, flights or long-distance freeway journeys. Since patients deal with diseases differently, they also need different information about prescribed medications on an individual basis [22, 24]. Therefore, examination of satisfaction with the information received about tolvaptan could open up the possibility of adapting this information to the individual needs of ADPKD patients. The evaluation of the SIMS-D AU resulted in an average of 9 points (maximum possible score: 9 points) with a range of only 1 point, and thus indicated a high level of satisfaction with the information received about the action and usage of tolvaptan. However, there was a single patient who, even after taking tolvaptan for 10 years, stated that he had not received any information about how to recognize the effects of tolvaptan. As mentioned above, the provision of information by doctors should aim to meet the preferences of the individual patient, but of course every patient should receive a certain minimum amount of basic information. In contrast to the SIMS-D AU, the evaluation of the SIMS-D PP revealed a clearly measureable level of dissatisfaction regarding the information received about potential problems with tolvaptan in 42 % of the patients. Although the overall score of the SIMS-PP amounted to the maximum possible score of 8 points, there was a rather big range of 6 points. In fact, one third of the patients were dissatisfied with the information received about the risk of tolvaptan-related side effects such as drowsiness, sex life impairment, or potential drug interactions. This result suggests that concerns about tolvaptan-related side effects are common in ADPKD patients, even after 10 years of tolvaptan treatment. Notwithstanding, a lack of information about side effects is certainly a missed opportunity to reassure patients, while patients who are concerned anyway may become even more dissatisfied with their situation. Recently, Joly et al. reported on baseline results from the ACQUIRE study (ClinicalTrials.gov Identifier NCT02848521) that collects ADPKD-specific health-related quality of life and treatment satisfaction data in 385 ADPKD patients (45 % of them with tolvaptan treatment) [25]. In ACQUIRE, the mean "global treatment satisfaction" was scored 58, 68, and 67 for CKD stage 1, 2, and 3 with the abbreviated Treatment Satisfaction Questionnaire for Medication (TSQM-9, score *range*: 0 to 100) [26]. However, the TSQM-9 neither examines satisfaction with the medical information received nor influence of drug side effects on treatment satisfaction like the original TSQM [27]. Nevertheless, and in accordance with our results from the SIMS-D

PP subscale, a “two-thirds rating” of "global treatment satisfaction" indicates the need for improvement in the care of patients with ADPKD. Of course, the required monthly check intervals after starting tolvaptan for a total of 18 months are very favorable in order to detect possible side effects such as hypohydration or an increase in hepatic enzymes. But during this period, not only the titration of the maximum tolerated dosage of tolvaptan, but also a standardized survey of the patients about their satisfaction with tolvaptan and the information received about it should be performed at least once. As the SIMS takes into account individual differences by eliciting the patients’ own views about the medication information received, it could be used as a measurement tool in clinical practice to evaluate the individual information needs to facilitate optimal patient satisfaction with tolvaptan [22]. Unexpectedly, the mean annual slope of eGFR accelerated from − 2.7 ± 1.3 ml/min/1.73 m^2 per year during the TEMPO period to -4.5 ± 2.6 ml/min/1.73 m^2 per year during the Jinarc® period. Recently, Yu et al. have shown that the long-term decline of eGFR in ADPKD patients accelerated in later life and was associated with the baseline Irazabal-subclass [28]. However, this association was not absolutely constant in our small cohort of tolvaptan-treated ADPKD patients, and a detailed examination revealed that an acceleration in the annual slope of eGFR could be observed especially in individuals whose drug therapy for arterial hypertension had to be intensified during the Jinarc® period. For this purpose, the inhibition of the renin-angiotensin-aldosterone system (RAAS) was primarily maximized, to which these patients probably reacted particularly sensitively and therefore possibly showed a decrease in eGFR, as has already been reported by Schrier et al. in this context [29]. Accordingly, there was also a significant correlation of the difference in the annual slope of eGFR between the TEMPO and the Jinarc® period with the change in mean arterial and systolic blood pressure during the Jinarc® period. In view of the small size of our study population, this effect, which probably only occurred in a few patients, may nevertheless have led to a bias in the annual slope of eGFR. Considering the mean annual slope of eGFR of -2.72 ml/min/1.73 m^2 per year in TEMPO 3:4 [14] and − 3.14 to -3.26 ml/min/1.73 m^2 per year in TEMPO 4:4 [15], the reasons for the poorer course in the mean annual slope of eGFR during the Jinarc® period were therefore probably the progression of ADPKD and a bias due to the intensification of blood pressure therapy in individual patients. The small number of patients, the monocentricity, only one examination during the trial and the fact that adherence was self-reported, are noteworthy limitations of our study. As a self-reported study, there may be differences between the actual behavior of patients and what they reported in the MARS-D and future adherence-studies in this population may need to combine a self-reported measure with other techniques like pill counting.

Conclusions

Although the patients reported strong adherence to tolvaptan, even after 10.2 years of treatment, there was clearly measurable dissatisfaction with the information received about tolvaptan’s side effect profile in 42 % of the patients. We therefore conclude that at least one standardized patient survey on satisfaction with the information received about potential side effects of tolvaptan should be conducted during any tolvaptan treatment in order to improve patient education regarding the use of tolvaptan in slowing ADPKD. This outcome should encourage further trials to define the role of the SIMS questionnaire in this context.

Abbreviations

AU: Action and usage of medication subscale of SIMS-D

ADPKD: Autosomal dominant polycystic kidney disease

cAMP: Cyclic adenosine monophosphate

CKD: Chronic kidney disease

CKD-EPI: Chronic kidney disease epidemiology collaboration

eGFR: Estimated glomerular filtration rate

HtTKV: Height-adjusted total kidney volume

MARS-D: Medication Adherence Report Scale - German version

PKD1: Polycystic kidney disease 1

PKD2: Polycystic kidney disease 2

PP: Potential problems of medication subscale of SIMS-D

SIMS-D: Satisfaction with Information about Medicines Scale - German version

TEMPO: Tolvaptan Efficacy and Safety in Management of Autosomal Dominant Polycystic Kidney Disease and Its Outcomes trial

TSQM-9: Abbreviated Treatment Satisfaction Questionnaire for Medication

Declarations

Ethics approval and consent to participation

The study protocol was approved by the University of Dresden Ethics Committee (Bearbeitungsnummer/Processing number: EK 237062017). The investigation conforms to the principles outlined in the Declaration of Helsinki. The patients were of legal age and able to consent. Enrollment into the study took place after detailed information and written informed consent.

Availability of data and materials

The datasets generated and analyzed during the current study are available from the corresponding author upon reasonable request and with permission of Otsuka Pharmaceutical.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

H.S. and C.H. conception and design of research; H.S., A.P. and P.G. patient care; H.S. analyzed data; H.S. and C.H. interpreted results; H.S. prepared figures; H.S. drafted manuscript; H.S., P.G., and C.H. edited and revised manuscript

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References

1. Chapman AB, Devuyst O, Eckardt KU, Gansevoort RT, Harris T, Horie S, et al. Autosomal-dominant polycystic kidney disease (ADPKD): Executive summary from a Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference. Kidney International. 2015;88:17–27.
2. Torres VE, Harris PC, Pirson Y. Autosomal dominant polycystic kidney disease. Lancet. 2007;369:1287–1301.
3. Hughes J, Ward CJ, Peral B, Aspinwall R, Clark K, Millán JLS, et al. The polycystic kidney disease 1 (PKD1) gene encodes a novel protein with multiple cell recognition domains. Nature Genetics. 1995;10:151–160.
4. Mochizuki T, Wu G, Hayashi T, Xenophontos SL, Veldhuisen B, Saris JJ, et al. PKD2, a gene for polycystic kidney disease that encodes an integral membrane protein. Science. 1996;272:1339–1342.
5. Praetorius HA, Spring KR. A PHYSIOLOGICAL VIEW OF THE PRIMARY CILIUM. Annual Review of Physiology. 2005;67:515–529.
6. Hanaoka K, Guggino WB. cAMP regulates cell proliferation and cyst formation in autosomal polycystic kidney disease cells. Journal of the American Society of Nephrology. 2000;11:1179–1187.
7. Yamaguchi T, Pelling JC, Ramaswamy NT, Eppler JW, Wallace DP, Nagao S, et al. cAMP stimulates the in vitro proliferation of renal cyst epithelial cells by activating the extracellular signal-regulated kinase pathway. In: Kidney International. Blackwell Publishing Inc.; 2000. p. 1460–1471.
8. Ta CM, Vien TN, Ng LCT, DeCaen PG. Structure and function of polycystin channels in primary cilia. Cellular Signalling. 2020;72:109626.
9. Yasuda G, Jeffries WB. Regulation of cAMP production in initial and terminal inner medullary collecting ducts. Kidney International. 1998;54:80–86.
10. Gattone VH, Wang X, Harris PC, Torres VE. Inhibition of renal cystic disease development and progression by a vasopressin V2 receptor antagonist. Nature Medicine. 2003;9:1323–1326.
11. Torres VE, Wang X, Qian Q, Somlo S, Harris PC, Gattone VH. Effective treatment of an orthologous model of autosomal dominant polycystic kidney disease. Nature Medicine. 2004;10:363–364.
12. Wang X, Gattone V, Harris PC, Torres VE. Effectiveness of vasopressin V2 receptor antagonists OPC-31260 and OPC-41061 on polycystic kidney disease development in the PCK rat. Journal of the American Society of Nephrology. 2005;16:846–851.

13. Higashihara E, Torres VE, Chapman AB, Grantham JJ, Bae K, Watnick TJ, et al. Tolvaptan in autosomal dominant polycystic kidney disease: Three years' experience. Clinical Journal of the American Society of Nephrology. 2011;6:2499–2507.
14. Torres VE, Chapman AB, Devuyst O, Gansevoort RT, Grantham JJ, Higashihara E, et al. Tolvaptan in Patients with Autosomal Dominant Polycystic Kidney Disease. New England Journal of Medicine. 2012;367:2407–2418.
15. Torres VE, Chapman AB, Devuyst O, Gansevoort RT, Perrone RD, Dandurand A, et al. Multicenter, open-label, extension trial to evaluate the long-term efficacy and safety of early versus delayed treatment with tolvaptan in autosomal dominant polycystic kidney disease: the TEMPO 4:4 Trial. Nephrology Dialysis Transplantation. 2018;33:477–489.
16. Devuyst O, Chapman AB, Shoaf SE, Czerwiec FS, Blais JD. Tolerability of Aquaretic-Related Symptoms Following Tolvaptan for Autosomal Dominant Polycystic Kidney Disease: Results From TEMPO 3:4. Kidney International Reports. 2017;2:1132–1140.
17. Edwards ME, Chebib FT, Irazabal M V, Ofstie TG, Bungum LA, Metzger AJ, et al. Long-Term Administration of Tolvaptan in Autosomal Dominant Polycystic Kidney Disease. Clinical journal of the American Society of Nephrology : CJASN. 2018;13:1153–1161.
18. Mahler C, Hermann K, Horne R, Ludt S, Haefeli WE, Szecsenyi J, et al. Assessing reported adherence to pharmacological treatment recommendations. Translation and evaluation of the Medication Adherence Report Scale (MARS) in Germany. Journal of evaluation in clinical practice. 2010;16:574–579.
19. Mahler C, Jank S, Hermann K, Horne R, Ludt S, Haefeli WE, et al. Psychometric properties of a German version of the "Satisfaction with Information about Medicines Scale" (SIMS-D). Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research. 2009;12:1176–1179.
20. Irazabal M V., Rangel LJ, Bergstralh EJ, Osborn SL, Harmon AJ, Sundsbak JL, et al. Imaging classification of autosomal dominant polycystic kidney disease: A simple model for selecting patients for clinical trials. Journal of the American Society of Nephrology. 2015;26:160–172.
21. Butler JA, Peveler RC, Roderick P, Horne R, Mason JC. Measuring compliance with drug regimens after renal transplantation: Comparison of self-report and clinician rating with electronic monitoring. Transplantation. 2004;77:786–789.
22. Horne R, Hankins M, Jenkins R. The Satisfaction with Information about Medicines Scale (SIMS): A new measurement tool for audit and research. Quality in Health Care. 2001;10:135–140.
23. Levey AS, Stevens LA, Schmid CH, Zhang Y, Castro AF, Feldman HI, et al. A new equation to estimate glomerular filtration rate. Annals of Internal Medicine. 2009;150:604–612.
24. Enlund H, Vainio K, Wallenius S, Poston JW. Adverse drug effects and the need for drug information. Medical Care. 1991;29:558–564.
25. Joly D, Doll H, Sánchez-Covisa J, O'reilly K, Wang-Silvanto J. FP051BASELINE RESULTS FROM ACQUIRE: A STUDY MEASURING QUALITY OF LIFE, AND TREATMENT PREFERENCE AND SATISFACTION OF AUTOSOMAL DOMINANT POLYCYSTIC KIDNEY DISEASE PATIENTS IN EUROPE. Nephrology Dialysis Transplantation. 2019;34 Supplement_1.
26. Bharmal M, Payne K, Atkinson MJ, Desrosiers MP, Morisky DE, Gemmen E. Validation of an abbreviated Treatment Satisfaction Questionnaire for Medication (TSQM-9) among patients on antihypertensive medications. Health and Quality of Life Outcomes. 2009;7:1–10.
27. Atkinson MJ, Sinha A, Hass SL, Colman SS, Kumar RN, Brod M, et al. Validation of a general measure of treatment satisfaction, the Treatment Satisfaction Questionnaire for Medication (TSQM), using a national panel study of chronic disease. Health and Quality of Life Outcomes. 2004;2:1–13.
28. Yu ASL, Shen C, Landsittel DP, Grantham JJ, Cook LT, Torres VE, et al. Long-term trajectory of kidney function in autosomal-dominant polycystic kidney disease. Kidney International. 2019;95:1253–1261.
29. Schrier RW, Abebe KZ, Perrone RD, Torres VE, Braun WE, Steinman TI, et al. Blood Pressure in Early Autosomal Dominant Polycystic Kidney Disease. New England Journal of Medicine. 2014;371:2255–2266.

Tables

Table 1
General characteristics of the patients

n **(race)**	**12 (caucasian)**
Female (%)	5 (41.7)
Mean age in years (SD)	49.8 (6.6)
Mean HtTKV in mL/m (SD)	1023.0 (303.9)
Mean age at Kidney-MRI in years (SD)	44.4 (6.5)
Median of Irazabal-subclasses *	1D
Prevalence of arterial hypertension in %	100
Mean age at first diagnosis of arterial hypertension in years (SD)	32.6 (9.1)
Mean number of antihypertensive drugs (SD)	2.6 (1.2)
Angiotensin-converting-enzyme inhibitor or -receptor blocker in %	100
Mean tolvaptan daily dosage in mg/d (SD)	90.0 (28.6)
Mean duration of [years (SD)]	
Cumulative tolvaptan therapy	10.2 (0.3)
Tolvaptan therapy in TEMPO 3:4	3.0 (0.0)
Tolvaptan therapy in TEMPO 4:4	3.8 (0.3)
Jinarc® therapy	3.4 (0.2)
Tolvaptan interruption between end of TEMPO 4:4 and first prescription of Jinarc®	0.6 (0.2)

HtTKV (height-adjusted total kidney volume), MRI (Magnetic Resonance Imaging), SD (standard deviation), * Irazabal et al. [20].

Table 2
Descriptive values of MARS-D and SIMS-D sum scores

Questionnaire (score *range*)		***Median***	***Minimum***	***Maximum***	***Range***
MARS-D (5–25)		23.5	20	25	5
SIMS-D	AU (0–9)	9	8	9	1
	PP (0–8)	8	2	8	6

MARS-D: Medication Adherence Report Scale - German version, SIMS-D: Satisfaction with Information about Medicines Scale - German version / AU: Action and Usage subscale / PP: Potential Problems subscale.

Table 3
Detailed characteristics of the patients

Patient number	1	2	3	4	5	6	7	8	9	10	11	12
Sex (age at study in years)	m (49)	m (45)	m (47)	m (41)	m (53)	m (56)	m (50)	f (37)	f (60)	f (53)	f (54)	f (52)
HtTKV in mL/m at age (years) with Irazabal-subclass *	1155 (45) 1D	778 (41) 1C	1155 (43) 1D	1095 (35) 1D	712 (47) 1C	1207 (51) 1C	1309 (45) 1D	1461 (31) 1E	599 (55) 1B	1132 (45) 1D	483 (49) 1B	1192 (46) 1D
Tolvaptan daily split dosage (mg/mg)	60/30	90/30	90/30	90/30	45/15	60/30	90/30	45/15	45/15	90/30	45/15	45/15
Duration of (months)												
Cumulative tolvaptan therapy	119	117	119	129	123	122	126	119	124	121	125	119
TEMPO period	78	79	79	84	81	83	84	80	87	78	84	78
Jinarc® period	41	38	40	45	42	39	42	39	37	43	41	41
Gap between TEMPO and Jinarc® period	8	11	10	5	7	7	7	7	8	5	7	9
CKD-EPI eGFR (ml/min/1.73 m^2)												
Week 3 in TEMPO 3:4	91.1	76.2	73.2	94.0	79.2	83.5	105.7	84.1	58.2	49.6	72.5	68.6
End of TEMPO 4:4	70.2	66.8	67.2	84.7	68.0	63.8	79.9	71.6	29.0	30.7	57.8	46.0
Month 3 with Jinarc®	69.0	65.4	67.0	87.7	63.3	59.7	78.8	75.1	26.2	27.0	59.9	30.5
Time of study with Jinarc®	39.9	46.3	50.3	66.1	57.8	53.4	75.3	60.0	9.9 ‡	18.7	53.9	21.0
Difference between week 3 in TEMPO 3:4 and time of study with Jinarc®	-51.2	-29.9	-22.9	-27.9	-21.4	-30.1	-30.4	-24.1	-48.3	-30.9	-18.6	-47.6
Annual slope of CKD-EPI eGFR (ml/min/1.73 m^2 per year)												
TEMPO period	-3.5	-1.8	-0.9	-1.3	-1.7	-2.9	-5.1	-1.9	-4.2	-3.0	-2.2	-4.1
Jinarc® period	-10.0	-7.2	-5.6	-6.2	-2.0	-2.4	-1.3	-5.3	-5.8	-2.8	-2.0	-3.3
Difference between TEMPO period and Jinarc® period	-6.5	-5.4	-4.7	-4.9	-0.3	0.5	3.8	-3.4	-1.6	0.2	0.2	0.8
Systolic/diastolic arterial blood pressure (mmHg), mean arterial blood pressure (mmHg) and [total number of anti-hypertensive drugs]												
Week 3 in TEMPO 3:4	124/82 96 [2]	126/87 100 [2]	122/86 98 [0]	130/87 101 [1]	145/86 106 [1]	117/76 90 [3]	128/84 99 [1]	123/85 98 [1]	164/87 113 [3]	125/80 95 [2]	122/76 91 [2]	120/70 87 [1]
End of TEMPO 4:4	149/83 105 [3]	142/97 112 [2]	143/90 108 [0]	131/83 99 [1]	138/77 97 [1]	128/78 95 [4]	133/79 97 [1]	122/86 98 [1]	166/78 107 [3]	124/90 101 [2]	122/72 89 [2]	123/77 92 [4]

HtTKV (height-adjusted total kidney volume); * Irazabal et al. [20]; ‡ end of tolvaptan.

Patient number	1	2	3	4	5	6	7	8	9	10	11	12
Month 3 with Jinarc®	154/88	161/93	154/91	148/95	137/78	144/85	131/87	129/91	161/88	125/84	132/80	135/85
	110	116	112	113	98	105	102	104	112	98	97	102
	[3]	[2]	[0]	[1]	[1]	[4]	[1]	[1]	[3]	[3]	[3]	[3]
Time of study with Jinarc®	121/79	125/82	134/91	138/94	131/83	137/85	130/80	129/89	167/81	118/84	135/83	134/77
	93	96	105	109	99	102	97	102	110	95	100	96
	[4]	[3]	[1]	[2]	[2]	[5]	[1]	[1]	[3]	[3]	[3]	[3]
Difference between week 3 in TEMPO 3:4 and end of TEMPO 4:4	25/1	16/10	21/4	1/-4	-7/-9	11/2	5/-5	-1/1	2/-9	-1/10	0/-4	3/7
	9	12	10	-2	-9	5	-2	0	-6	6	-2	5
	[1]	[0]	[0]	[0]	[0]	[1]	[0]	[0]	[0]	[0]	[0]	[3]
Difference between month 3 with Jinarc® and time of study with Jinarc®	-33/-9	-36/-11	-20/0	-10/-1	-6/5	-7/0	-1/-7	0/-2	6/-7	-7/0	3/3	-1/-8
	-17	-20	-7	-4	1	-3	-5	-2	-2	-3	3	-6
	[1]	[1]	[1]	[1]	[1]	[1]	[0]	[0]	[0]	[0]	[0]	[0]
Urological events during treatment with tolvaptan												
Flank pain	3	0	1	2	0	weekly	0	0	1	0	2 / year	4 / year
Macrohematuria	0	0	0	1	0	0	0	0	0	0	0	0
Renal cyst infection	0	0	0	0	0	0	0	0	1	0	0	0
Sum score of questionnaires (score *range*)												
MARS-D (5–25)	23	24	24	25	20	21	23	24	24	24	22	23
SIMS-D AU (0–9)	9	9	9	8	9	8	9	9	9	9	9	8
SIMS-D PP (0–8)	8	8	6	2	8	4	8	8	8	3		

HtTKV (height-adjusted total kidney volume); * Irazabal et al. [20]; ‡ end of tolvaptan.

Figures

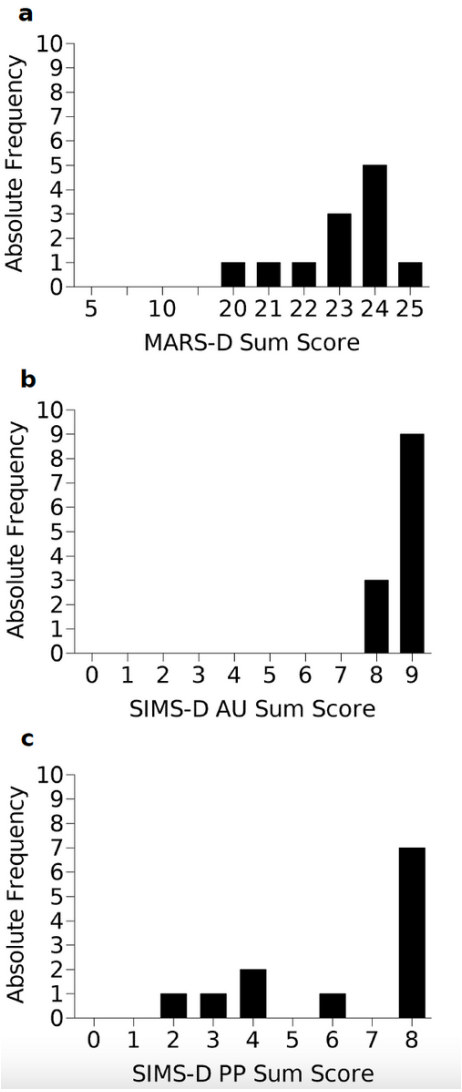

Figure 1

Distribution of the sum scores of the questionnaires. The abscissa scale corresponds to the respective score range. a: MARS-D (Medication Adherence Report Scale - German version). b: SIMS-D AU (Satisfaction with Information about Medicines Scale, Action and Usage subscale - German version). c: SIMS-D PP (Satisfaction with Information about Medicines Scale, Potential Problems subscale - German version).

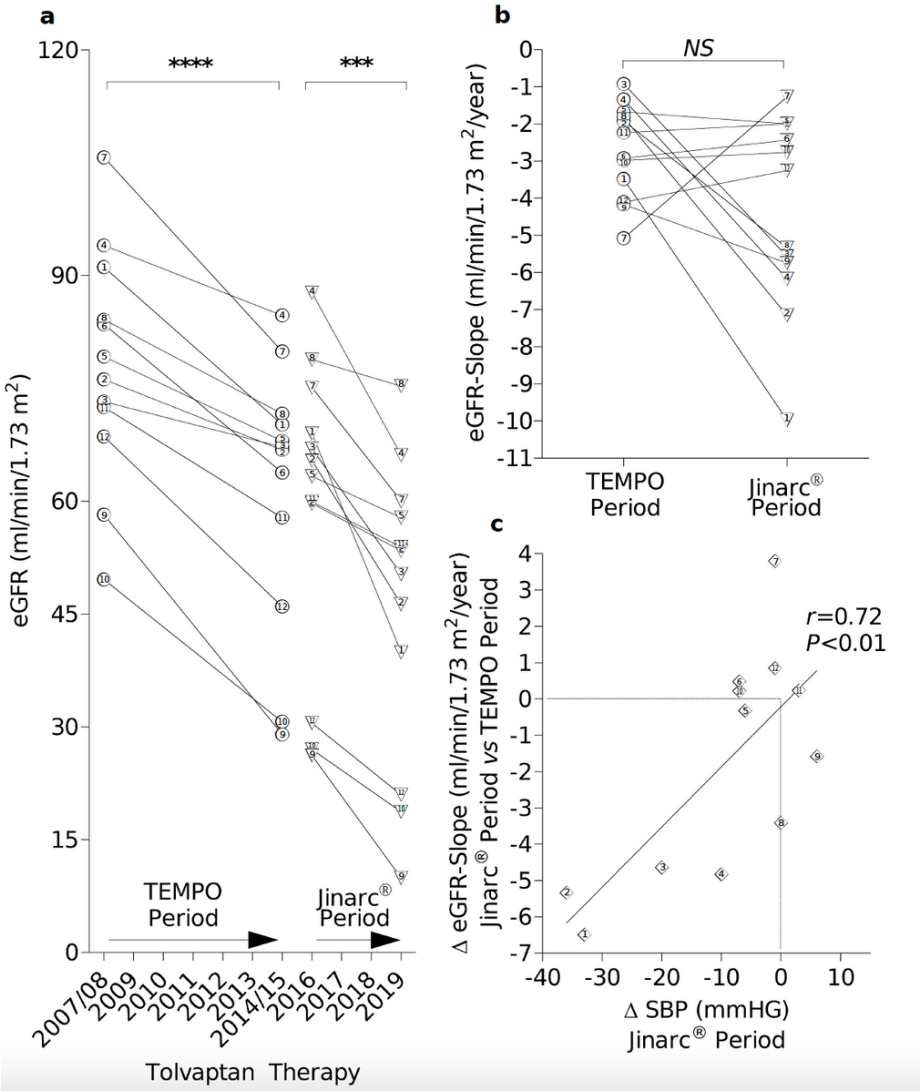

Figure 2

Change in kidney function during tolvaptan long-term treatment. The numbers correspond to the individual patients. a: Change of eGFR in the TEMPO period between week 3 after dose-escalation of tolvaptan in TEMPO 3:4 and the end of TEMPO 4:4 (****: P < 0.0001) and in the Jinarc® period between month 3 with Jinarc® and the time of the current study (***: P = 0.001). b: Annualized eGFR-slope during the TEMPO period and the Jinarc® period (P = 0.08, NS). c: Pearson correlation of the difference in the annual slope of eGFR between the Tempo and the Jinarc® period with the change in mean systolic blood pressure (SBP) during the Jinarc® period (r = 0.72; P < 0.01).