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The Role of Tolvaptan in Autosomal Dominant Polycystic Kidney Disease

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The Role of Tolvaptan in Autosomal Dominant Polycystic Kidney Disease

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Faculdade de Medicina da Universidade do Porto, 15/03/2023

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The Role of Tolvaptan in Autosomal Dominant Polycystic Kidney Disease

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Abstract

Purpose: Autosomal Dominant Polycystic Kidney Disease (ADPKD) is the most common renal genetic disorder worldwide. It leads to the formation of multiple fluid-filled cysts in the kidneys, which can cause several health complications, including hypertension, chronic pain, hematuria, cyst infections, and nephrolithiasis. For years, treatment relied solely on supportive measures. Tolvaptan is a highly selective vasopressin V_2-receptor antagonist that was found to hamper renal cyst growth. Due to a pressing need to identify new targets to slow down or halt the disease's progression, research on tolvaptan has been developed. This review aims to highlight its therapeutic potential in managing ADPKD.

Methods: We conducted a search in MEDLINE to identify relevant articles on the use of tolvaptan in ADPKD. Titles and abstracts were screened, followed by a full-text assessment for eligibility in this review.

Results: We screened 38 articles by titles and abstracts and 28 full texts. In the end, 21 articles were eligible. We initially focused on two trials, TEMPO 3:4 and REPRISE, followed by related studies, and then, other relevant articles. These showed that tolvaptan slows kidney function decline and cyst growth, when compared to placebo, reflected by significantly slower rates of increase in total kidney volume and decrease in estimated glomerular filtration rate. It also reduced and/or delayed the appearance of ADPKD-related complications. The most common adverse effects found were aquaresis and hepatotoxicity, and were the cause of a significant number of discontinuations from the respective trials. However, clinical manifestations of these effects were easily reversible and manageable via down-titration or, worst case, suspension of tolvaptan treatment.

Conclusions: Tolvaptan is an effective option in the treatment of patients with ADPKD. Occurrence of adverse effects cannot be ignored and must be appropriately managed. However, the benefits of tolvaptan outweigh the risks, resulting in a better disease prognosis.

Keywords: Autosomal dominant polycystic kidney disease, Glomerular filtration rate, Safety profile, Tolvaptan, Total kidney volume.

Introduction

Autosomal Dominant Polycystic Kidney Disease (ADPKD) is the most common renal genetic disorder worldwide, affecting approximately 1 in 1000-2500 individuals (1-3). The disease is characterized by the formation of multiple fluid-filled cysts in the kidneys (and other organs), resulting from abnormal proliferation and growth of renal epithelial cells (1, 4). This condition can result in several health complications, including hypertension, chronic pain, hematuria, cyst infections, and nephrolithiasis (3, 5). In fact, it is responsible for approximately 10% of all cases of end-stage renal disease (ESRD) (2, 4, 6-8). Additionally, ADPKD can cause extrarenal symptoms such as hepatic and pancreatic cysts, intracranial aneurysms, abdominal hernias, and cardiac valve lesions (3, 5).

Mutations in either PKD1 (in 85% of cases) or PKD2 genes (in the remaining 15%) are responsible for the onset of the disease (1, 2, 5). These genes encode for transmembrane proteins, named polycystin-1 (PC-1) and polycystin-2 (PC-2), respectively, which interact with each other in a multifunctional signaling complex, responsible for the regulation of intracellular Ca^{2+} pathways, as well as development, maintenance, differentiation, and functionality of renal epithelial cells (2, 4, 9, 10). The production of altered polycystins results in a poorly differentiated phenotype of renal cells (hyperplastic cells), that give rise to the renal cysts (2, 4).

Tolvaptan is a highly selective vasopressin V_2-receptor antagonist (5, 11), initially developed for the treatment of secondary hyponatremia in adults with conditions like chronic heart failure, liver cirrhosis or the syndrome of inappropriate antidiuretic hormone secretion (SIADH) (12, 13). However, the observation of an association between increased adenosine-3′,5′-cyclic monophosphate (cAMP) production and fluid secretion in the lumen of cysts (14) has led to the hypothesis that tolvaptan could hamper renal cyst growth. This would be achieved via the inhibition of antidiuretic hormone-dependent production of cAMP (15, 16).

For many years, ADPKD treatment was mainly focused on supportive measures (2, 17). Therefore, there was a pressing need to identify novel therapeutic targets that could potentially slow down or halt the disease's progression, with tolvaptan-associated research being on the forefront of it (2).

Through this review, we aim to provide insight into this era of research, highlighting the latest discoveries related to the therapeutic action of tolvaptan in managing ADPKD, with special focus on the efficacy of tolvaptan treatment, while also addressing its safety profile.

Methods

To conduct this review, we performed a comprehensive search in the MEDLINE database, through the PubMed search engine, using the query ("Polycystic Kidney Diseases"[Mesh]) AND "Tolvaptan"[Mesh]. To narrow down the list of articles, we applied specific inclusion criteria, including the type of study (Clinical Trials, Randomized Controlled Trials, or Observational Studies), language (Portuguese or English), and the species in analysis (humans only). The articles obtained through this search were then screened by titles and abstracts. Subsequently, the full-text versions of the articles that passed the initial screening were retrieved and assessed for eligibility, for this review.

Results

Our search returned a total of 179 results. Out of these, 38 articles remained after application of the inclusion criteria, which were then screened by titles and abstracts. Nine were excluded as they focused heavily on a secondary drug/component that was not specifically related to tolvaptan and did not align with the objectives of this review. One additional article was excluded due to the lack of an abstract. After that, we assessed the remaining 28 full texts, and a total of 7 were excluded, as they didn't focus mainly on the effects of tolvaptan treatment: 4 investigated prognostic predictors, 2 aimed to find eligibility criteria for tolvaptan treatment and 1 was a guideline update. The remaining 21 articles were included and analyzed in this review. Fig. 1 illustrates the screening and selection process.

When dealing with the topic of tolvaptan's action on ADPKD, it is most appropriate to begin with the two largest clinical trials evaluating the efficacy and safety of tolvaptan on patients with ADPKD: TEMPO 3:4 (18) and REPRISE (19). Following these, studies that were based and/or expanded on TEMPO 3:4's findings were addressed (20-24), with a special parenthesis on Japanese side of investigations (25-28). Other important studies were also mentioned (29-34). Lastly, we delved upon some of the main adverse effects of tolvaptan, as presented in the analyzed studies (18-21, 24-26, 28-30, 34-38).

TEMPO 3:4

The Tolvaptan Efficacy and Safety in Management of Autosomal Dominant Polycystic Kidney Disease and Its Outcomes (TEMPO) 3:4 trial (18) was a phase 3, multicenter, randomized, double-blind, placebo-controlled, parallel-group study published in December 2012. The trial included 1445 eligible patients, aged between 18 and 50 years old, who had a diagnosis of ADPKD, a total kidney volume (TKV) of 750 ml or more, and an estimated creatinine clearance (CrCl) of at least 60 mL/min.

Participants were randomized in a 2:1 ratio to receive either tolvaptan or a placebo, in a 45-15 mg daily morning and afternoon dosage scheme, with escalation according to tolerability.

The primary outcome of this study was the yearly change rate in TKV, in percentage. In the span of three years, TKV showed an annual increase of 2.8% [95% confidence interval (CI): 2.5 to 3.1] when treated with tolvaptan, compared to an annual increase of 5.5% (95% CI: 5.1 to 6.0) when treated with a placebo. This means that tolvaptan administration resulted in a decrease of 2.7% per year in the rate of growth compared to the placebo group (95% CI, −3.3 to −2.1). That is a reduction of 49% in the TKV from the baseline to the post-treatment measurement. The positive impact of tolvaptan on TKV was consistent across all subgroups, including gender, age, initial TKV, baseline estimated CrCl level, and hypertension.

The main secondary outcome of the study was the rate of decline in kidney function. Tolvaptan administration resulted in a significantly lower increase in serum creatinine compared to the placebo group (0.16 mg/dl vs. 0.23 mg/dL, respectively). The estimated glomerular filtration rate (eGFR) decline rate was also positively influenced by tolvaptan, with a 2.72 mL/min/1.73 m^2 reduction, per year, in the tolvaptan group vs. 3.70 in the placebo group. Tolvaptan treatment resulted in an increased eGFR of 0.98 mL/min/1.73 m^2 per year, which means that tolvaptan was responsible for slowing the rate of decline in kidney function by 26%. The positive effects of tolvaptan were observed across all subgroups, except for patients younger than 35 and those without hypertension or a TKV inferior to 1500 mL.

Lastly, time to clinical progression of the disease, defined as the occurrence of different clinical findings, like kidney pain, worsening hypertension or albuminuria, was also evaluated. The use of tolvaptan resulted in a lower incidence of ADPKD-related events compared to placebo, as shown by the lower number of events observed per 100 person-years of follow-up in the tolvaptan group [44 vs. 50 events, respectively; hazard

ratio (HR): 0.87; 95% CI: 0.78 to 0.97; *p*=0.01]. This was mainly due to the positive effects of tolvaptan on the decline of kidney function and reducing kidney pain. However, there was no significant effect on hypertension or albuminuria events.

REPRISE

Five year later, Torres *et al* conducted a new randomized controlled trial on this area of research. The REPRISE trial (19) is a phase 3, randomized withdrawal, multicenter, placebo-controlled, double-blind trial published in November 2017. TEMPO 3:4 (18) enrolled patients with early-stage ADPKD and an estimated CrCl of ≥60 ml/min, but it revealed unexpected liver toxicity associated with tolvaptan use. In contrast, the REPRISE trial was designed to study the safety and efficacy of tolvaptan in patients with later-stage ADPKD and late-stage 2 to early-stage 4 chronic kidney disease (CKD), while also monitoring for potential liver toxicity more frequently. Between 2014 and 2016, 1496 eligible patients were randomly allocated in a 1:1 ratio to receive either tolvaptan or a placebo, for a period of 12 months. Eligible individuals had to be between 18 and 55 years old, with an eGFR ranging from 25 to 65 mL/min/1.73 m^2. Alternatively, patients who were between 56 and 65 years old were eligible if their eGFR was between 25 and 44 mL/min/1.73 m^2, but they also needed a historical record of a decline in eGFR greater than 2.0 mL/min/1.73 m^2 per year. Daily doses of tolvaptan were either 60 mg in the morning and 30 mg in the afternoon, or 90 mg in the morning and 30 mg in the afternoon.

The study's primary outcome was the difference in eGFR between the baseline and follow-up. At 1 year, the eGFR showed a lower mean [± standard deviation (SD)] change in the tolvaptan group when compared to the placebo group [-2.34±0.24 mL/min/1.73 m^2 (95% CI: −2.81 to −1.87) vs. -3.61±0.24 mL/min/1.73 m^2 (95% CI: −4.08 to −3.14), respectively]. Tolvaptan slowed down the decline in eGFR by 1.27 mL/min/1.73 m^2, compared to placebo (95% CI: 0.86 to 1.68; *p*<0.001). Subgroup

analyses showed that tolvaptan had a favorable impact on most patient groups, except for those who were older than 55 years, nonwhite, or had stage 2 CKD, where the effectiveness was not significant due to smaller sample sizes.

The secondary endpoint of the study was the gradient of eGFR change, calculated from individual slopes for each patient. After adjusting for the trial duration and acute effects of tolvaptan, the mean slopes of the eGFR change were lower in the tolvaptan group when compared to the placebo group (-3.16±0.14 mL/min/1.73 m^2 vs. -4.17±0.14 mL/min/1.73 m^2, respectively) with a significant difference in mean slopes of 1.01 mL/min/1.73 m^2 between the two groups (95% CI: 0.62 to 1.40; p<0.001). The subgroup analyses of the secondary endpoint were similar to the primary endpoint, with tolvaptan having a significantly beneficial effect in all subgroups except for smaller groups of patients who were older than 55 years, nonwhite, or had stage 2 CKD.

The third and last endpoint of the study revolved around the hepatic safety of tolvaptan and will be discussed separately in the “Adverse Effects” section.

Related to TEMPO

The TEMPO 4:4 trial (20) was an open-label extension study that investigated the long-term safety and effectiveness of tolvaptan in patients who had completed TEMPO 3:4 (18). The study included 557 early-treated patients and 314 delayed-treated patients who were given tolvaptan in split-dose regimens of 45/15, 60/30, or 90/30 mg. The main focus of the study was to evaluate the difference in the change of TKV between early-treated and delayed-treated subjects from the baseline of TEMPO 3:4 to the 24th month of TEMPO 4:4. During the study, it was observed that the increase in TKV was 29.9% in early-treated subjects compared to 31.6% in delayed-treated subjects, with no significant difference between the two groups (p=0.38). However, there was a significant difference in relation to the effect of tolvaptan on slowing down the decline of renal function during

the additional 2-year study period, which was the secondary endpoint in this study. The delayed-treated group showed a decline of 3.15 mL/min/1.73 m^2 in eGFR (p<0.001), while the slopes of TKV during TEMPO 4:4 were higher in early-treated subjects when compared to delayed-treated subjects [6.16% vs. 4.96% per year, respectively, treatment difference of 1.011 (95% CI: 1.00 to 1.02; p=0.05)].

Torres *et al* (21) also went back on the results of TEMPO 3:4 (18) with a *post hoc* analysis to reevaluate the primary and secondary efficacy measures based on the stage of CKD at the start of the study. Tolvaptan usage demonstrated a significant reduction in the annualized growth of TKV across CKD1, CKD2, and CKD3, with reductions of 1.99%, 3.12%, and 2.61% per year, respectively (all p<0.001), and a beneficial effect on the decline of eGFR, with reductions of 0.40 (p=0.23), 1.13 (p<0.001), and 1.66 mL/min/1.73 m^2 per year (p<0.001), respectively. Furthermore, patients in the tolvaptan group experienced fewer ADPKD-related events compared to those in the placebo group in CKD1 (HR, 0.83; 95% CI, 0.70 to 0.98; p=0.03) and CKD3 (HR, 0.71; 95% CI, 0.57 to 0.89; p=0.003), but no significant difference was observed in CKD2 (HR, 1.02; 95% CI, 0.85 to 1.21; p=0.86).

Gansevoort *et al* (22) were concerned about the categorical classification of albuminuria as "albuminuria events" in TEMPO 3:4 (18), rather than considering it on a continuous scale. They believed this approach may have led to a decrease in sensitivity to identify changes induced by the treatment. Henceforth, in this *post hoc* analysis involving 1375 patients with ADPKD, albuminuria was assessed using the albumin-to-creatinine ratio (ACR) and measured from spot morning urine samples before tolvaptan administration. At the baseline, patients with elevated ACR demonstrated significantly higher TKV and lower eGFR compared to patients with lower ACR levels. This association persisted during the follow-up period, with higher baseline ACR levels being linked to a more rapid decline in eGFR (p<0.0001), but not TKV growth. Over the course of the 3-year trial, ACR increased in the placebo group and decreased in the tolvaptan-

treated group (+0.23 vs. -0.40 mg/mmol). The difference in ACR between the groups increased progressively, reaching a maximum of 24% at month 36 (p<0.001). The decrease in ACR was consistent across all subgroups examined and persisted even after discontinuation of the study drug. Notably, the beneficial effect of tolvaptan on TKV growth and eGFR decline was more pronounced in patients with higher baseline ACR levels.

Furthermore, Casteleijn *et al* (23) conducted a *post hoc* exploratory evaluation of the TEMPO 3:4 trial (18) to assess the impact of tolvaptan on kidney pain, defined, in this study, as "events with objective medical interventions". Out of the 1,445 patients included, 50.9% reported a history of kidney pain at the beginning of the study. History of urinary tract infections, presence of kidney stones or hematuria, and female gender (all p<0.001) were significantly associated with a history of kidney pain. Treatment with tolvaptan showed a significantly lower incidence of kidney pain events compared to placebo: 10.1% vs. 16.8% (p<0.001), with a risk reduction of 36% (HR 0.64; 95% CI 0.48-0.86). This reduction in pain events by tolvaptan was observed across all groups regardless of pain severity and was not influenced by predisposing factors (p>0.05).

Raina *et al* (24) also performed a *post hoc* analysis of the TEMPO 3:4 trial (18), this time aiming to better assess the use of tolvaptan in adolescents and young adults (AYA's) with ADPKD. The study analyzed 51 patients between the ages of 18 and 24 (29 in the tolvaptan group and 22 in the placebo group). During the 3-year study, the annual growth rate of TKV in AYA's subgroup (primary outcome) treated with tolvaptan was found to be 3.8% per year (95% CI: 3.8 to 5.2), while in the placebo group it was 6.5% per year (95% CI: 4.2 to 8.6). The use of tolvaptan resulted in a decrease of 2.7 percentage points per year (p=0.0491) compared to placebo, indicating a treatment effect of 41.2%.

Study Developments in Japan

With Japan being the first country in the world to approve tolvaptan for ADPKD treatment in 2014, Muto *et al* (25) made a subgroup analysis of Japanese patients enrolled in TEMPO 3:4 (18), aiming to better assess the safety and effectiveness of tolvaptan in the population of Japan. The primary and secondary outcomes of this study coincided with TEMPO 3:4's. In a study involving 177 patients in a period of 36 months, the results showed that the tolvaptan group (118 patients) had a lower annual rate of TKV change at 1.3% (95% CI: 0.4 to 2.1), compared to the placebo group (59 patients) with 5.0% (95% CI: 3.9 to 6.2; $p<0.001$). The tolvaptan group also had a smaller reduction in eGFR at -3.83 mL/min/1.73 m^2 compared to -5.05 mL/min/1.73 m^2 in the placebo group. This resulted in a treatment effect of +1.22 mL/min/1.73 m^2 (95 % CI 0.41–2.02; $p=0.003$).

Years later, Muto *et al* (26) returned with a *post hoc* evaluation on the efficacy of tolvaptan. Patients included in this new analysis were those whose efficacy parameters were measured, at year 2, in the TEMPO Extension Japan Trial (TEMPO-EXTJ), which furthered the investigation on tolvaptan's effects in the Japanese population for, approximately, 3 additional years. Patients who successfully completed TEMPO 3:4 (18) at Japanese trial sites were given the opportunity to enroll in TEMPO-EXTJ, where everyone got access to the treatment. In patients treated with tolvaptan in the TEMPO 3:4 and TEMPO-EXTJ trials, the annual slope of eGFR was -3.480 mL/min/1.73 m^2 in TEMPO 3:4, and -3.417 mL/min/1.73 m^2 in TEMPO-EXTJ. The approximately 3.6 month off-treatment interval between the two trials did not appear to have a significant effect on the eGFR slope. However, in patients who received a placebo in TEMPO 3:4 before starting tolvaptan in TEMPO-EXTJ, the eGFR slope was significantly less steep from TEMPO 3:4 (-4.287 mL/min/1.73 m^2) to TEMPO-EXTJ (-3.364 mL/min/1.73 m^2), with a difference of 0.923 ($p=0.0441$).

Horie *et al* (27) also made a *post hoc* analysis of Japanese patients enrolled in the TEMPO 3:4 trial (18), investigating the potential interrelation between the effects of tolvaptan on TKV and renal function. In the 147 Japanese patients from the TEMPO 3:4 trial that were included in this analysis, 55 received placebo whilst 92 received tolvaptan. Among the tolvaptan-treated patients, 37 were categorized as “responders”, exhibiting a net decrease in TKV from baseline to year 3, while 55 were categorized as “non-responders”, showing a net increase in TKV. During the follow-up period, the mean changes in TKV were 16.99% in the placebo group, -8.33% in the responder group, and 13.95% in the non-responder group. For eGFR, the mean changes were -12.61 mL/min/1.73 m^2 in the placebo group, -8.47 in the responder group, and -8.58 in the non-responder group. Compared to the placebo group, both the responder and non-responder groups demonstrated a significant slowing of eGFR decline (p<0.05).

Mochizuki *et al* (28) performed a real-world, post-marketing surveillance aimed to assess the long-term safety and efficacy of tolvaptan in Japanese patients with ADPKD, in actual clinical practice. This study analyzed the baseline characteristics of 1630 patients who, following administration of tolvaptan, showed a significant annual percentage decrease in TKV, from 1.68% to 2.73% per year (p<0.0001). Similarly, the change in eGFR showed improvement, with the rate shifting from -3.31 to -2.28 mL/min/1.73 m^2 per year, after initiating tolvaptan treatment (p=0.0403).

Other Studies

Even before TEMPO 3:4 (18), Higashihara *et al* (29) prospectively analyzed the measurements of TKV and eGFR in two 3-year studies of tolvaptan. This study included 63 subjects with ADPKD, who were randomly matched in a 1:2 ratio to historical controls based on factors such as gender, hypertension, age, and baseline TKV or eGFR. At baseline, the TKV was similar between the control (1422 ml) and the tolvaptan group

(1635 ml), as was the eGFR, at 62 ml/min/1.73 m², for both groups. However, over the course of the study, the control group showed an increase in TKV by 5.8% per year, while the tolvaptan group demonstrated a much lower increase of 1.7% per year [p<0.001, estimated ratio of geometric mean 0.96 (95% CI, 0.95 to 0.97)]. The corresponding annualized decline in eGFR was greater in the control group at -2.1 ml/min/1.73 m² per year compared to -0.71 in the tolvaptan group [p<0.01, linear mixed model group difference 1.1 ml/min/1.73 m² per year (95% CI, 0.24 to 1.9)].

Regarding short-term effects of tolvaptan, Irazabal *et al* (30) investigated 20 patients with ADPKD, before and after 1 week of daily split-dose treatment, to determine the renal mechanisms involved and to assess the dependence on underlying renal function of the antagonist effects of tolvaptan. This treatment resulted in a significant reduction in GFR, but no correlation was observed between baseline GFR and the percentage change in GFR caused by tolvaptan. Additionally, blinded *post hoc* analysis of renal MRI's revealed that tolvaptan significantly reduced TKV by 3.1% and individual cyst volume by 1.6%, at just 1 week of treatment. Initial analysis of this small cohort suggested that these effects were more prominent in patients with preserved renal function and larger cysts. No correlation was found between changes in TKV and body weight or estimated body water. Boertien *et al* (31) examined the short-term renal hemodynamic effects of tolvaptan in patients with ADPKD divided by 3 groups, at different stages of CKD: Group A with a GFR of >60, Group B with a GFR of 30-60, and Group C with a GFR <30 ml/min/1.73 m². Measurements were taken before treatment, after 3 weeks of tolvaptan administration (up titrated to 90/30 mg/day, split dose), and 3 weeks after the last dose. The main efficacy variables studied did not show significant differences between the three study groups (except for smaller increases in urine volume in Group C). However, the results showed that minor and reversible, statistically significant decreases in GFR occurred in Groups A and B, suggesting that tolvaptan may cause short-term, minor drops in GFR, in individual patients.

In contrast, Edwards *et al* (32) had the objective to determine if the reduction achieved through tolvaptan administration is long-lasting, accumulative, and capable of delaying the necessity for kidney replacement therapy. A cohort of 97 patients who received tolvaptan for at least one year (mean 6 years, SD: 4.6 ± 2.8; range: 1.1-11.2) was analyzed, which demonstrated lower eGFR slopes compared to historical controls, both from baseline (mean ± SD: 22.20 ± 2.18 ml/min/1.73 m² per year) and from month 1 (mean ± SD: 21.97 ± 2.44 ml/min/1.73 m² per year) (both $p<0.001$). They also had a lower risk of experiencing a 33% reduction in eGFR compared to controls [risk ratio 0.63 (95% CI, 0.38 to 0.98) from baseline; risk ratio 0.53 (95% CI, 0.31 to 0.85) from month 1]. The annualized eGFR slopes of patients treated with tolvaptan remained consistent throughout the follow-up period, and the differences between observed and predicted eGFRs at the last follow-up increased with the duration of treatment.

Bennett *et al* (33) utilized the ADPKD-Outcomes Model (OM), a validated tool for predicting disease progression, to evaluate the potential long-term advantages of tolvaptan therapy in patients with ADPKD. The predictions generated by the ADPKD-OM, based on the TEMPO 3:4 trial (18), were then compared to aggregated data from the TEMPO 4:4 extension trial (20) and the REPRISE study (19). After validation, the ADPKD-OM was applied to estimate the potential benefit of tolvaptan therapy on the time to ESRD in various ADPKD populations. In simulated patients with ADPDK-OM (matching the baseline characteristics of the overall TEMPO 3:4 trial population), tolvaptan therapy was predicted to extend the average age of onset of ESRD by five years, compared to the natural progression of the disease (57 years vs. 52 years, respectively). Subgroup and sensitivity analyses revealed that the delay in reaching ESRD was most pronounced in patients with CKD stage 1 at baseline (6.6 years), followed by CKD 2 and 3 subgroups (4.7 and 2.7 years, respectively).

Finally, in a very recent study, Mekahli *et al* (34) investigated the safety and effectiveness of tolvaptan in children and adolescents with ADPKD, aiming to address

the potential treatment of disease progression during childhood, and thus prevent irreversible kidney damage. In this 1-year, double-blind, randomized trial involving 91 participants (66 aged 12-17 and 25 aged 7-11 years old), tolvaptan demonstrated, when compared to placebo, a greater reduction in spot urine osmolality, at week 1 [least squares mean reduction -390 mOsm/kg vs. -90 mOsm/kg (p<0.001)], and a greater reduction (from baseline) in urine specific gravity [least squares mean reduction 0.009 vs. 0.002 (p<0.001)]. Additionally, participants aged 12-17 years old also had a smaller increase in height-adjusted TKV with tolvaptan, compared with placebo, after 12 months [2.6% vs. 5.8% (p<0.05)].

Adverse Effects

Patients who were given tolvaptan experienced a higher frequency of adverse events associated with increased aquaresis, leading to symptoms like thirst, pollakiuria, polyuria, nocturia, and polydipsia (18-21, 25, 30, 36, 37). These observations are consistent with tolvaptan's mechanism of action in inhibiting the effects of antidiuretic hormone (ADH) and are a consequence of the elimination of electrolyte-free water (25, 29, 34). Conversely, those given a placebo displayed more frequent adverse events linked to ADPKD, such as kidney pain, hematuria, urinary tract infections, and back pain (18, 19, 21). It is also worth noting that most discontinuations were a result of adverse events associated with the aquaretic effects of tolvaptan, rather than being related to the progression of ADPKD (18, 19, 21, 25). According to TEMPO 3:4 (18), the tolvaptan group experienced a higher rate of discontinuations due to adverse events compared to the placebo group (15.4% vs. 5.0% of patients), with approximately 8% being attributed to aquaresis. Despite that, tolerability was often achieved via down-titration of tolvaptan dosage (34, 36).

Shoaf *et al* (36) investigated further the idea of an optimal starting regimen for tolvaptan treatment, which they found out to be the split-dose regimen 45/15 mg, demonstrating both effectiveness and tolerability in suppressing urine osmolality (Uosm, selected as the biomarker to assess the inhibition of tolvaptan) below 300 mOsm/kg for 24 hours, in over 50% of the participants. This was the regimen chosen as the initial treatment plan for the TEMPO 3:4 trial. Uptitration to higher regimens, like 90/30 mg, achieved Uosm suppression in 85% of the tested subjects, but was often unsuccessful due to poorer tolerability, resulting in the aquaretic adverse events discussed. Subjects who consented to uptitrate had, in general, lower baseline eGFR.

Another important effect was hepatotoxicity, with a higher percentage of patients administered tolvaptan experiencing hepatic enzyme abnormalities. Investigators analyzed this further in REPRISE (19) and reported elevations in alanine aminotransferase (ALT) levels exceeding three times the upper limit of the normal range in 38 patients (5.6%) receiving tolvaptan, whereas only 8 patients (1.2%) in the placebo group had such elevations. Among the tolvaptan group (681 patients), 10.9% reported hepatic adverse events, while in the placebo group (685 patients), only 5.3% experienced similar events, with serious hepatic adverse events occurring in 4.6% and 0.6%, respectively. These findings were consistent among various studies (18, 20, 21, 25, 28, 37), with some even reporting cases that met Hy's law criteria (serum ALT levels exceeding three times, along with bilirubin levels exceeding two times the upper limit of the normal range), like TEMPO 3:4 (18) and TEMPO 4:4 (20). However, this was a rare occurrence, since abnormal bilirubin levels were not as frequent as elevations in ALT (19). More importantly, all patients reporting liver function abnormalities experienced complete resolution after discontinuation of the drug (18-20, 24, 25, 37).

Certain articles (18, 28, 34) also documented cases where hypernatremia reached potentially clinically significant levels, in a few patients. However, these

occurrences were not categorized as severe, nor did they result in any serious adverse events.

Concerning polyuria, Casteleijn *et al* (35) conducted a study to examine the impact of tolvaptan-induced polyuria on ureter diameter in patients with ADPKD, since prolonged polyuria can lead to the dilation of the ureters, potentially resulting in a loss of renal function. They found that this increase in ureter diameter did not happen, suggesting that tolvaptan is a safe therapy from a urological point of view. On other hand, Kramers *et al* (38) proposed that the osmolar excretion plays a crucial role in determining urine volume in patients using tolvaptan, which impedes urine concentration. Therefore, by limiting osmolar intake, it may be possible to mitigate tolvaptan-induced polyuria, providing patients with greater control over aquaretic side effects and enhancing the overall tolerability of these drugs.

Torres *et al* (37) also conducted a long-term, phase 3 study on the safety profile of tolvaptan. No significant safety issues were observed during the extension of this study, but it raised awareness to a possible heightened risk of developing skin malignancies, in patients with ADPKD, especially those with deteriorating kidney function. The results also clarified that adverse effects of tolvaptan are more pronounced during the first 18 months, in newly-treated patients. Regular monthly monitoring of liver function during this time window of treatment allows for early detection and appropriate management of any transaminase elevations, which may lead to higher tolerance rates in the long run. Besides closer monitoring of symptoms and hepatic function (19, 25, 28), more adjustment time to tolvaptan (20, 26), lower dosages (34, 36) and sufficient water intake (28) are known to positively affect tolerability to treatment.

All the findings stated in this section were consistent among pediatric and young adult patients (24, 34).

Conclusion

In conclusion, the articles analyzed in this review support the idea that tolvaptan is an effective option when treating patients with ADPKD. Tolvaptan slowed the rate of kidney function decline and cyst growth, when compared to placebo. This was reflected in the values of eGFR and TKV, which seemed to decrease and increase, respectively, at profoundly milder rates, resulting in a better disease prognosis.

However, regarding safety of usage, treatment with tolvaptan is not without its adverse effects, mainly aquaresis and hepatotoxicity. Despite not outweighing its benefits, these effects influenced tolerability to the drug. Nonetheless, it should be emphasized that both aquaretic effects and liver enzyme abnormalities were reversible, via down-titration or discontinuation of the treatment. Other potential effects were not studied in detail, nor manifested enough to be considered statistically significant.

In the future, further research would be beneficial to delve deeper into the potential long-term effects and safety profile of tolvaptan, especially after real-world application. This would provide a more comprehensive understanding of its benefits and risks, allowing for more informed clinical decision-making. Additionally, exploring strategies to mitigate or manage the adverse effects associated with tolvaptan could improve its overall tolerability and patient compliance. Researching the best supportive measures to the success of tolvaptan treatment, like the impact of different diets, with varying water and salt intakes, could be of interest. At the same time, monitoring of adverse effects also proved to be an effective strategy, therefore, it would be important to find the ideal monitoring scheme for treated patients.

To our knowledge, tolvaptan is not currently used in Portuguese clinical practice, and it is our hope that this review provides a new insight and, ultimately, contributes to the evaluation and potential adoption of tolvaptan as part of the treatment armamentarium for ADPKD patients in the Portuguese healthcare system.

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Informed Consent and Ethics: Not applicable.

Author contributions

FS: conceptualization, methodology, results analysis, writing - original draft.

LC: conceptualization, supervision, writing – review and editing.

Both authors approved the final version.

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Figures

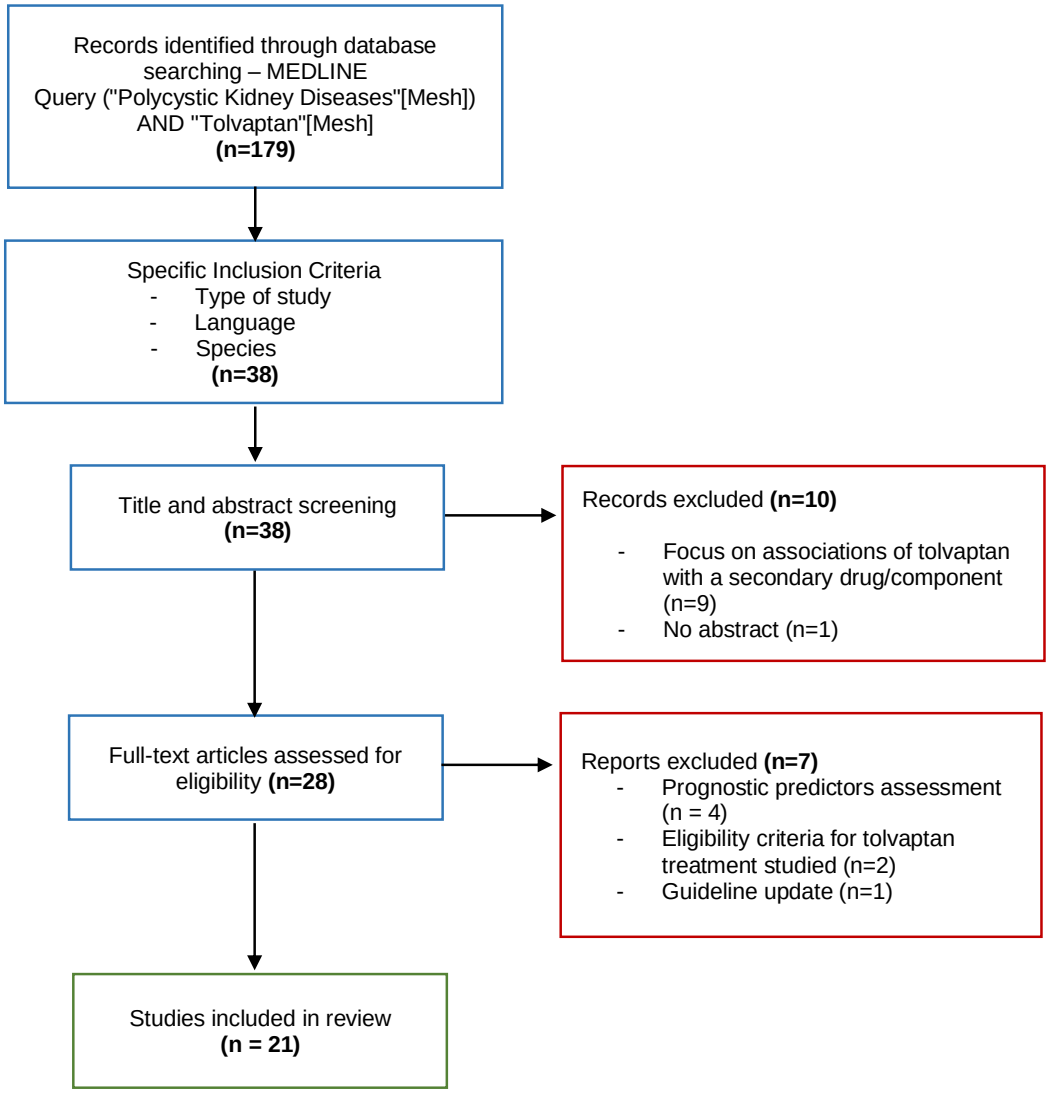

Fig. 1 – Flow diagram of the studies' screening and selection.

Reporting guidelines

Scale for the Assessment of Narrative Review Articles – SANRA

1) Justification of the article's importance for readership

- Page 6: "The disease is characterized by the formation of multiple fluid-filled cysts in the kidneys (and other organs), resulting from abnormal proliferation and growth of renal epithelial cells (1, 4). This condition can result in several health complications, including hypertension, chronic pain, hematuria, cyst infections, and nephrolithiasis (3, 5)."
- Page 7: "For many years, ADPKD treatment was mainly focused on supportive measures (2, 17). Therefore, there was a pressing need to identify novel therapeutic targets that could potentially slow down or halt the disease's progression, with tolvaptan-associated research being on the forefront of it (2)."

2) Statement of concrete aims or formulation of questions

- Page 7: "Through this review, we aim to provide insight into this era of research, highlighting the latest discoveries related to the therapeutic action of tolvaptan in managing ADPKD, with special focus on the efficacy of tolvaptan treatment, while also addressing its safety profile."

3) Description of the literature search

- Page 8: "To conduct this review, we performed a comprehensive search in the MEDLINE database, through the PubMed search engine, using the query ("Polycystic Kidney Diseases"[Mesh]) AND "Tolvaptan"[Mesh]. To narrow down the list of articles, we applied specific inclusion criteria, including the type of study (Clinical Trials, Randomized Controlled Trials, or Observational Studies),

language (Portuguese or English), and the species in analysis (humans only). The articles obtained through this electronic search were then screened by titles and abstracts. Subsequently, the full-text versions of the articles that passed the initial screening were retrieved and assessed for eligibility, for this review."

4) Referencing

- Page 6: "Mutations in either PKD1 (in 85% of cases) or PKD2 genes (in the remaining 15%) are responsible for the onset of the disease (1, 2, 5). These genes encode for transmembrane proteins, named polycystin-1 (PC-1) and polycystin-2 (PC-2), respectively, which interact with each other in a multifunctional signaling complex, responsible for the regulation of intracellular Ca^{2+} pathways, as well as development, maintenance, differentiation, and functionality of renal epithelial cells (2, 4, 9, 10)."
- Page 19: "Conversely, those given a placebo displayed more frequent adverse events linked to ADPKD, such as kidney pain, hematuria, urinary tract infections, and back pain (18, 19, 21). It is also worth noting that most discontinuations were a result of adverse events associated with the aquaretic effects of tolvaptan, rather than being related to the progression of ADPKD (18, 19, 21, 25)."

5) Scientific reasoning

- Page 9: "The Tolvaptan Efficacy and Safety in Management of Autosomal Dominant Polycystic Kidney Disease and Its Outcomes (TEMPO) 3:4 trial (18) was a phase 3, multicenter, randomized, double-blind, placebo-controlled, parallel-group study published in December 2012. The trial included 1445 eligible patients, aged between 18 and 50 years old, who had a diagnosis of ADPKD, a total kidney volume (TKV) of 750 ml or more, and an estimated creatinine

clearance (CrCl) of at least 60 mL/min. Participants were randomized in a 2:1 ratio to receive either tolvaptan or a placebo, in a 45-15 mg daily morning and afternoon dosage scheme, with escalation according to tolerability."

- Page 11: "Five year later, Torres *et al* conducted a new randomized controlled trial on this area of research. The REPRISE trial (19) is a phase 3, randomized withdrawal, multicenter, placebo-controlled, double-blind trial published in November 2017. […] Between 2014 and 2016, 1496 eligible patients were randomly allocated in a 1:1 ratio to receive either tolvaptan or a placebo, for a period of 12 months."

- Page 14: Furthermore, Casteleijn *et al* (23) conducted a *post hoc* exploratory evaluation of the TEMPO 3:4 trial (18) to assess the impact of tolvaptan on kidney pain, defined, in this study, as "events with objective medical interventions". Out of the 1,445 patients included, 50.9% reported a history of kidney pain at the beginning of the study.

6) Appropriate presentation of data

- Page 10: "The primary outcome of this study was the yearly change rate in TKV, in percentage. In the span of three years, TKV showed an annual increase of 2.8% [95% confidence interval (CI): 2.5 to 3.1] when treated with tolvaptan, compared to an annual increase of 5.5% (95% CI: 5.1 to 6.0) when treated with a placebo. This means that tolvaptan administration resulted in a decrease of 2.7% per year in the rate of growth compared to the placebo group (95% CI, −3.3

to −2.1). That is a reduction of 49% in the TKV from the baseline to the post-treatment measurement."

- Page 10 and 11: "Lastly, time to clinical progression of the disease, defined as the occurrence of different clinical findings, like kidney pain, worsening hypertension or albuminuria, was also evaluated. The use of tolvaptan resulted in a lower incidence of ADPKD-related events compared to placebo, as shown by the lower number of events observed per 100 person-years of follow-up in the tolvaptan group [44 vs. 50 events, respectively; hazard ratio (HR): 0.87; 95% CI: 0.78 to 0.97; *p*=0.01]."

- Page 13: Torres *et al* (21) also went back on the results of TEMPO 3:4 with a *post hoc* analysis to reevaluate the primary and secondary efficacy measures based on the stage of CKD at the start of the study. Tolvaptan usage demonstrated a significant reduction in the annualized growth of TKV across CKD1, CKD2, and CKD3, with reductions of 1.99%, 3.12%, and 2.61% per year, respectively (all *p*<0.001), and a beneficial effect on the decline of eGFR, with reductions of 0.40 (*p*=0.23), 1.13 (*p*<0.001), and 1.66 mL/min/1.73 m^2 per year (*p*<0.001), respectively. Furthermore, patients in the tolvaptan group experienced fewer ADPKD-related events compared to those in the placebo group in CKD1 (HR, 0.83; 95% CI, 0.70 to 0.98; *p*=0.03) and CKD3 (HR, 0.71; 95% CI, 0.57 to 0.89; *p*=0.003), but no significant difference was observed in CKD2 (HR, 1.02; 95% CI, 0.85 to 1.21; *p*=0.86).

Instructions for Authors

Portuguese Journal of Nephrology and Hypertension

Aims and Scope

Portuguese Journal of Nephrology and Hypertension is the official organ of the Portuguese Society of Nephrology and is published quarterly. Supplementary issues on selected themes may also be published at the discretion of the Editor-in-Chief.

The Journal publishes articles on clinical or laboratory topics of relevance to nephrology, dialysis, transplantation and hypertension. Papers relating to basic immunology, physiology, genetics and epidemiology are accepted when kidney related.

Portuguese Journal of Nephrology and Hypertension publishes Editorials and in-depth Reviews, Original Articles, Short Communications, Technical Notes, Case Reports and Letters. Articles are accepted and published in English. Manuscripts submitted to the Portuguese Journal of Nephrology and Hypertension will be sent for peer review on the understanding that the author(s) have not published the material elsewhere.

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Content types

The Portuguese Journal of Nephrology and Hypertension publishes: 1) Editorials; 2) Review Articles; 3) Original Articles; 4) Case Reports; 5) Letters to the Editor; 6) Nephropathology Quiz; 7) Top article.

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Editorials are usually invited, but authors may propose a paper for the Editor-in-Chief's consideration. They may have up to 2000 words and a maximum of 2 tables or figures. A maximum of 5 references is generally recommended.

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An original article must focus on relevant clinical investigation or basic research, and is limited to 4000 words including an abstract with up to 300 words. The order of the text should be as follows: Introduction, Subjects and Methods (any statistical method must be detailed in this section), Results and Discussion. A maximum of 50 references is generally recommended.

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Letters must contain information related to an article published in the Journal or may concern a topic of current interest in Nephrology. Letters (maximum of 3 authors) are limited to 500 words and 1 table or figure. A maximum of 5 references is generally recommended.

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These articles, by invitation of the Editors, must contain a commentary concerning an international paper published in the last 3 months. These manuscripts are limited to 1500 words and 20 references.

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- Funding: All sources of funding should be declared. Authors should declare the role of study sponsors, if any, in the collection, analysis and interpretation of data; in the writing of the manuscript; and in the decision to submit the manuscript for publication. If the study sponsors had no such involvement, the authors should so state.

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When reporting experiments on human subjects, it is mandatory to indicate whether the procedures were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975 (revised in 2015) and, in the case of renal transplant, the Declaration of Istanbul.

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References must be numbered consecutively in the order in which they are cited in the text. Each reference should give the name and initials of all authors unless they are more than six, when only the first three should be given followed by et al. Authors’ names should be followed by the title of the article, journal abbreviations according to the style used in Index Medicus, the year of publication, the volume number and the first and last page numbers. For papers in the course of publication, “in press” replaces the date; the journal name must be given in the references. Manuscripts that are unpublished, in preparation, or submitted, and personal communications should not be cited in the reference list but may appear parenthetically in the text. References to books should contain the author(s) name(s) and initials, the title of the book, followed by place of publication, publisher, year, and relevant pages. Websites must be referenced by the following order: title, URL and access date.

Examples:

1. Journals:

Hogan J, Mohan P, Appel GB. Diagnostic tests and treatment options in glomerular disease: 2014 update. Am J Kidney Dis 2014;63(4):656-666

2. Books:

Morris Peter, Knechtle Stuart. Kidney Transplantation - Principles and Practice. 7th Edition. Saunders, 2014:72

3. Website:

Substitutive Renal Therapy of Chronic Renal Disease in Portugal.
Available at https://www.spnefro.pt/tratamento_da_doenca_renal_terminal/2013
Accessed October 6, 2013.

4. Published Meeting Abstract:

Jorge Silva, Jorge Antunes, Telmo Carvalho, Pedro Ponce. Efficacy of preventing hemodialysis catheter infections with citrate lock (Encontro Renal abstract SE001). Port J Nephrol Hypert 2011; 25(1):56

Tables: Tables should supplement, not duplicate, the information in the main text. References to tables should be made in order of appearance in the text and should be in Roman numerals in brackets, e.g. (Table II). Each table should be typed on a separate sheet and have a brief heading describing its contents.

Figures: All illustrations (transparencies, photographs, diagrams, graphs, etc.) should be labelled consecutively in Arabic numerals (Fig. 1, 2...), according to their relative positions in the text. If a figure has been published before, the original source must be acknowledged and written permission from the copyright holder must be submitted with the material.