PERSPECTIVE

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Is tolvaptan a promising ally in the treatment strategy of autosomal dominant polycystic kidney disease?

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ABSTRACT

Autosomal Dominant Polycystic Kidney Disease (ADPKD) is one of the most common monogenic diseases in humans. It is characterized by the development and progressive growth of bilateral renal cysts which destroy the normal renal tissue, leading to loss of function. As the disease progresses patients may need renal replacement therapy; ADPKD is responsible for 5 to 10% of all patients being on renal replacement therapy.

This article reviews the results of the recent clinical trials on the use of tolvaptan in ADPKD, discussing the recommended decision algorithm on behalf of the ERA-EDTA working groups of Inherited Kidney Disorders (WGIDKD) and European Renal Best Practice (ERBP). In addition, the review will focus on the eligibility criteria for treatment with tolvaptan and its potential adverse effects.

Key-Words: ADPKD; clinical trials; tolvaptan.

INTRODUCTION

Autosomal Dominant Polycystic Kidney Disease (ADPKD) is a multissystemic disease caused by inherited or acquired genetic mutations and is the most common hereditary kidney disease[1]. ADPKD is characterized by the formation and progressive enlargement of numerous bilateral renal cysts, which can lead to loss of renal function and eventually culminate in the need of dialysis or renal transplantation. ADPKD is an important cause of end-stage kidney disease (ESKD), and approximately 50% of these patients will require renal replacement therapy in their fourth to sixth decade.

Until recently, the treatment of ADPKD has been symptomatic, aiming at the reduction of cardiovascular morbidity and mortality associated with the manifestations of the disease. The management of these patients consisted of non-specific measures, including maintenance of ideal body weight, regular exercise, blood pressure control, restriction of salt and protein in the diet, avoiding NSAID abuse, promoting a high water intake and other general renoprotective measures, such as the blockage of the renin–angiotensin–aldosterone system (RAAS)[2].

The vasopressin V2 receptors are located in the basolateral membrane of epithelial cells of the distal tubule, connecting tubule and collecting ducts[3].The main function of these receptors is the regulation of the body's water by determining the level of water reabsorption throughout the aquaporin-2 water channels[4,5]. The arginine vasopressin (AVP), by binding to this receptor, activates adenylate cyclase, and consequently increases the levels of intracellular cAMP. This induces the phosphorylation of aquaporin-2 water channels that are

redistributed to the apical membrane, resulting in urine concentration and water reabsorption[6,7]. The circulating levels of AVP are increased in ADPKD patients, which have a positive impact on the levels of intracellular cAMP in collecting ducts. The cAMP then increases the proliferation of epithelial cells in renal cyst walls and the rate of fluid production into cysts. This understanding contributes to belief in the detrimental role played by AVP in ADPKD pathogenesis, especially in the processes involved in cytogenesis and cyst enlargement.

With improved physiopathological knowledge of this disorder, it was noticed that progressive cyst formation and growth lead, in the course of the ADPKD, to development of disease complications, such as hypertension, urinary calculi, cyst infection, flank pain, hematuria secondary to cyst hemorrhage and chronic kidney disease[8]. It has been widely accepted that the increase in cyst number and size in the natural course of the disease will produce derangements of the normal kidney architecture associated with deterioration of renal function over time. So, one rational intervention to halt disease progression is stopping or slowing cyst growth, and tolvaptan, a vasopressin antagonist, seems to contribute to the reduced growth of renal cysts and the rate of progression of chronic kidney disease. The use of tolvaptan, an arginine vasopressin V2 receptor (AVPR2) inhibitor, has shown results in slowing the progression of renal loss of function in patients with ADPKD and, therefore, several placebo-controlled large dimensions trials were developed and their outcomes published[9-11].

This article reviews the use of tolvaptan in the treatment of ADPKD patients, paying special attention to the recommendations of the ERA-EDTA Working Group on Inherited Kidney Disorders and European Renal Best Practice. The review will also examine the outcomes of the open-label trial Tolpatan Efficacy and safety in Management of Polycystic kidney disease and its Outcomes (TEMPO 3:4), the extension trial TEMPO 4:4, and the recently published data of the REPRISE trial.

■ Tolvaptan efficacy and safety in management of autossomal dominant polycystic kidney disease and its outcomes (TEMPO 3:4)

A large phase 3, double-blind, randomized placebo-controlled clinical trial, Tolvaptan Efficacy and Safety in Management of Autossomal Dominant Polycystic Kidney Disease and Its Outcomes (TEMPO 3:4) included 1445 patients with ADPKD over a trial period of 3 years. The inclusion criteria were an estimated glomerular filtration rate (eGFR) ≥60 mL/min (estimated by the Cockcroft-Gault formula), a Total Kidney Volume (TKV) of ≥750 mL, measured by magnetic resonance imaging, and age between 18 and 50 years[10].

The patients were randomly assigned in a 2:1 ratio to receive twice-daily tolvaptan or a placebo. They received two different doses of the drug during the day (45/15 mg; 60/30 mg or 90/30 mg), remaining on the highest tolerated dose along the trial duration. The primary endpoint was the annual rate of change in TKV. The secondary endpoints included multiple ADPKD-related progression events (such as worsening kidney function, hypertension, albuminuria, kidney pain) and the rate of kidney function decline. According to the results of TEMPO 3:4, the use of tolvaptan in CDK 1-3 stages was associated with a reduction of the increase in TKV from 5.5% versus 2.8% per year compared to placebo ($p < 0,001$)[10].

The treatment effects were more notorious during the first year of treatment, in all subgroup analyses (gender, age, hypertension, kidney volume and eGFR at baseline). It is thought that the more pronounced change in TKV in the first year is due to an acute decrease in the secretion of cyst fluid. The authors believe that steady benefit of tolvaptan treatment in the second and third years was due to the inhibition of cyst cell proliferation, as demonstrated in animal and ex vivo human models. With respect to the secondary endpoint (ADPKD-related events), tolvaptan was also superior – 44 vs 55 events per 100 person-years of follow-up ($p=0.01$). In TEMPO 3:4, the slope of changes in kidney function (assessed by the serum creatinine level) showed that tolvaptan was associated with a reduction in the decline in eGFR from – 3.70 to -2.70 mL/min/1.3 m2 per year ($p< 0.001$)[10].

Authors found frequent adverse effects, affecting more than 97% of patients in this trial. Patients who received placebo had more ADPKD-related adverse effects, such as urinary infections, kidney pain, hematuria, whereas patients on tolvaptan had more adverse events related with aquaresis, such as thirst, polydipsia, polyuria and nocturia. In the tolvaptan group a more clinically important elevation of the aminotransferases, defined as a value more than 3 times the upper limit of normal range, was also noted. Two patients withdrew from the study because of liver enzyme elevation, but in both cases the levels normalized after drug interruption[10]. The trial drop-out was observed in both groups, and was higher in the tolvaptan group (23% vs

13.8% in the placebo group). Adverse events motivated the study drop-out of 15.4% of the patients in the tolvaptan group vs 5% in the placebo group. Overall, the TEMPO 3:4 trial demonstrated a beneficial role of tolvaptan in diminishing the rate of TKV growth and loss of eGFR in ADPKD patients[10,12].

■ Recommendations for the use of tolvaptan in autosomal dominant polycystic kidney disease: a position statement on behalf of the ERA-EDTA Working Group on Inherited Kidney Disorders and European Renal Best Practice.

Until recently, treatment of ADPKD was only symptomatic[2]; however, the therapeutic paradigm changed with the publication of the TEMPO 3:4 trial. In May 2015, based on the outcomes of the TEMPO 3:4 trial, the European Medicines Agency (EMA) approved the use of tolvaptan for treatment in ADPKD; Japan, Canada, Switzerland and Korea also approved its utilization[10].

One of the major constraints on ADPKD studies is how to evaluate progression and how to determine who are eligible for treatment with tolvaptan. A hierarchical decision algorithm was published by the European Renal Association-European Dialysis and Transplant Association (ERA-EDTA) Working Group of Inherited Kidney Disorders (EGIKD) and European Renal Best Practice (ERBP) for the use of tolvaptan in patients with ADPKD[13]. The recommendations suggested that tolvaptan can be used in ADPKD patients aged between 18 and 50 years old, with CKD stages 1-3a (eGFR of > 45 mL/min/1,73m^2) and who have or are likely to have a rapidly progressing disease. In TEMPO 3:4, the inclusion criterion was an eGFR ≥ 60 mL/min/1.73 m^2, using the Cockcroft-Gault formula; however it is known that tubular creatinine secretion overestimates GFR by approximately 20%. Therefore, TEMPO 3:4 included 17% of patients with an eGFR, determined by the CDK-EPI equation, of less than 60 mL/min/1.73 m^2. A post-hoc analysis revealed that in this subcategory of patients, the efficacy of tolvaptan treatment was similar or slightly better than in patients with higher eGFR[10,12].

According to this consensus, tolvaptan should not be started in patients aged 30–40 years with CKD stage 1, or in patients aged 40 to 50 years with CKD 1 or 2, because these patients, with a relatively high eGFR for their age group, will unlikely have a rapid disease progression[10,12].

An important definition present in this consensus is that a rapid disease progression can be defined as a confirmed annual eGFR decline of at least 5mL/min/1.73 m^2, in a one-year period; and /or at least 2.5 mL/min/1.73m^2 per year over a period of five years. However, we should take into account the limited value of eGFR changes during the early stages ADPKD in predicting disease progression, because eGFR can remain stable for a relatively long time before progressing toward ESRD[10,12,14,15].

Another proposed definition of rapid progressive disease is based on the TKV increase per year. A patient may have a rapid progressive disease if he has an increase greater than 5% in TKV per year on repeated measurements, preferably 3 or more measurements at 6-month intervals with the use of magnetic resonance or CT scan, although MRI is preferred to spare radiation exposure[13,16].

The Consortium for Radiologic Imaging Studies of Polycystic Kidney Disease (CRISP) demonstrated that TKV increases in the early stages, before the increase in serum creatinine, predict a subsequent decline in renal function. However it was noted that TKV and its association with renal function decline had an important inter-individual variability, specially related to patient age and stature. Accordingly, an ESRD risk perdition tool, where TKV is adjusted for height and age, was developed by Irazabal *et al*, based on data of 509 patients from the Mayo Clinic Translational PKD Center. The patients were categorized radiologically as typical (suggesting the possibility of rapid progression) and atypical. The typical group was then subcategorized based on height-adjusted TKV, ranges for age (1A; 1B; 1C; 1D and 1E groups), with the objective to predict the rate of eGFR decline and the risk of progression to ESRD. The consensus recommends the use of Mayo classification of ADPKD, and states that classes 1C-1E are at increased risk of rapid disease progression and consequently suitable for treatment. On the other hand, atypical patients have a low probability of development of a rapid progression[13,16,17].

Because of the limited availability and cost of MRI, ultrasound has been used to measure kidney volume, although its results are operator- and machine-resolution dependent. The CRISP study proposed that a kidney length of 16.5cm in a patient younger than 45 years old qualified the patient as having a rapid disease progression, and this recommendation was also included in ERA-EDTA guidelines[13,18].

Concerning genetic information and its impact on predicting the risk of rapid progression, the consensus

suggests that patients at higher risk are those with a truncating PDK1 mutation conjugated with early onset of clinical symptoms and total score of > 6 points in a PRO-PKD scale (a scale used to assess the prognosis in ADPKD patients, based on clinical and genetic information)[13,19]. The consensus also proposes that patients with a family history, with two first-degree family members reaching ESRD before the age of 58 years, may be at risk of rapid disease progression, and therefore the need for treatment should be reassessed every 3–5 years[13,20,21].

Conjugating all these markers of progression, the authors suggest the use of a hierarchical algorithm to assess which patients have or are likely to have a rapid progression. The algorithm starts with the most consistent markers of progression, finishing with the less definitive indicators. Patients with possible rapid progression should be re-evaluated for treatment every 3–5 years[13].

The consensus also takes the safety profile of tolvaptan into consideration. As seen in TEMPO 3:4, one serious reported adverse effect was the potential for liver toxicity. The simultaneous increase in transaminases and bilirubin was considered a high risk signal, and the European Medicines Agency (EMA) advised monitoring liver function monthly in the first 18 months of treatment and every 3 months thereafter. All documented liver function tests abnormalities associated with tolvaptan treatment in ADPKD patients were reversible after drug cessation. A higher incidence of gout was also observed in patients treated with tolvaptan in the TEMPO 3:4 trial (2.9% vs 1.4% with placebo), so until their data is available, it is recommended to restrict the simultaneous use of diuretics[13,22,23].

When initiating therapy with tolvaptan, a variable acute reversible decrease in eGFR is expected, depending on baseline eGFR. The initial dose of tolvaptan should be 45 mg in the morning and 15 mg in the afternoon and it should be up-titrated to 60/30 mg or 90/30 mg when tolerated. In TEMPO 3:4, the rate of withdrawal was around 23% during the 3-year trial and 7.4 % of the patients treated with tolvaptan discontinued the drug because of aquaresis effects. In order to avoid this problem, the authors recommend discussing the adverse effects and impact on lifestyle with patients, and also counselling them to an adequate fluid intake, in order to maintain water homeostasis and to avoid increaseed vasopressin reflex[10,13,24]. Taking into account the beneficial effects of tolvaptan in slowing the increase in TKV and the decline of kidney function demonstrated in TEMPO 3:4, over a period of 3 years, the EMA and the working group consider it is important to evaluate the treatment efficacy and safety beyond 3 years. At the date of publication of this consensus, the authors were awaiting the long-term treatment data developed after TEMPO 3:4.

TEMPO 4:4

In order to assess a long-term analysis of the safety and efficacy of tolvaptan on TKV and in eGFR, the TEMPO 3:4 trial was extended for two more years (TEMPO 4:4). Of the 1445 patients randomized to TEMPO 3:4, 60.3% were also enrolled in TEMPO 4:4. The trial group included 557 patients who received prior tolvaptan (early-treated group) and 314 who received prior placebo (delayed group)[25]. The results showed that TKV growth was 29.9% in early-treatment patients and 31.6% in the delayed-treated group, which was not statistically significant between groups. The TKV increase in both groups was lower than the estimated growth (40%) in untreated patients, according to the authors. The fact that the tolvaptan effect on TKV is greatest in the first year of treatment and the imbalances of the randomization could have contributed to the inability to demonstrate the early treatment advantage on TKV achieved in TEMPO 3:4[25].

TEMPO 4:4 data showed that the effect of tolvaptan on slowing renal function decline seen in TEMPO 3:4 was maintained. The eGFR slopes were similar in both study groups (early and delayed-treatment patients) with -3.26 vs -3.14 mL/min/1.73 m2 per year. Despite the larger number of patients on active treatment, TEMPO 4:4 has several limitations as it didn't take into account the changing treatment effect of tolvaptan over time and its effects on the rate of TKV growth, the loss of randomization from TEMPO 3:4 or the highly variable intervals between the two studies. Therefore, this trial didn't demonstrate a strong and sustained beneficial difference in TKV growth with tolvaptan. However it showed that tolvaptan has a sustained disease-modifying effect on eGFR in ADPKD patients and that the tolvaptan safety profile was similar in TEMPO 4:4 and in TEMPO 3:4. (10, 25)

These findings were encouraging, but also emphasized the need to develop a randomized, double-blind, long-duration trial to respond to questions about the real effects of tolvaptan in a long-duration therapy.

■ Replicating Evidence of Preserved Renal Function: An Investigation of Tolvaptan Safety and Efficacy (REPRISE)

The REPRISE trial is a phase 3, randomized withdrawal, placebo-controlled, doubled-blind trial that was undertaken under the aegis of the Food and Drug Administration (FDA), aimed at patients in more advanced stages of CKD than those included in the TEMPO 3:4 trial[26]. The trial, unlike TEMPO 3:4, had an 8-week pre-randomization period, to guarantee that each patient could take tolvaptan without dose-limiting adverse effects. The main objective of this phase was to reduce withdrawals associated with aquaresis adverse events[26].

This trial included 1337 ADPKD patients, aged 18 to 55 years with eGFR of 25–65 mL/min/1.73m^2 and patients 56 to 65 years old with eGFR of 25–44 mL/min/1.73m^2. Patients in this older group also had to have evidence of an annual decline of more than 2 mL/min/1.73m^2. Patients were then randomized into balanced groups to receive tolvaptan or placebo for a period of 12 months. Patients in the tolvaptan group received two doses of the drug per day (45/15 mg; 60/30 mg or 90/30 mg), remaining on the highest tolerated dose for the trial duration[26].

The primary endpoint of the trial was the change in eGFR from pre-treatment baseline levels to follow-up assessment, with adjustment for the exact duration that each patient participated in the trial, and then interpolated to 1 year. In the tolvaptan group, the change from baseline in eGFR was -2.34 mL/min/1.73m^2 and in the placebo group -3.61 mL/min/1.73m^2. When comparing placebo with tolvaptan, the results show that tolvaptan promoted a slower decline in eGFR with a difference of 1.27 mL/min/1.73m^2 ($p<0.0001$). A subgroup analysis showed a beneficial effect of tolvaptan in subgroups (gender, baseline eGFR, CKD stages 3A, 3B and 4), but did not evidence a clearly beneficial effect of tolvaptan in the smaller subgroups of patients with CDK stage 2, over 55 years old and in non-white patients[26].

The secondary endpoint was a comparison of the efficacy of tolvaptan treatment versus placebo in reducing the decline of annualized eGFR slope across all measured values in the study. In the tolvaptan group the mean slopes of the change in eGFR was -3.16 mL/min/1.73m^2 and – 4.17 mL/min/1.73m^2 in the placebo group, a difference of 1.,01 mL/min/1.73m^2 between the two groups ($p<0.001$). Similarity with the primary endpoint outcomes, there was no beneficial effect of tolvaptan in 3 subclasses of patients (CDK stage 2, over 55 years old and non-white)[26]. A subgroup analysis suggests that tolvaptan is less effective in patients over 55 years old. It was expected that these patients would have a more advanced disease at this age, but because this is not completely true, these patients needed to have an eGFR of 25 to 44 mL/min/1.73m^2 and evidence of a decline in EGFR superior to 2 mL/min/1.73m^2 per year. However, this category of patients had a slower decline in renal function than youngers patients who had similar CKD stages. Therefore, the authors proposed that this subcategory of patients had a slow progressive disease, and consequently, it is more difficult to demonstrate a beneficial effect to treatment with tolvaptan[26].

The safety profile of tolvaptan in this study, despite the participation of patients with more advanced stages of ADPKD, was comparable to that observed in the TEMPO 3:4 trial. In this study, 5.6 % of patients in the tolvaptan group had an increase in alanine aminotransferase 3 times the upper limit of normal (vs 1.2% of the patients in the placebo group). None of the patients exhibited total bilirubin greater than two times the upper normal limit value. In all cases, the elevated hepatic function tests normalized after interruption or discontinuation of the treatment. Monthly monitoring was suggested as a possible good way to early identify hepatic adverse effects and to interrupt the treatment early[10,23,26].

The rate of discontinuation of the trial was 9.5% in the tolvaptan group and 2.2 % in the placebo group and it was mainly associated with aquaresis adverse events in 2.1% of the patients in the tolvaptan group. This diverged from the TEMPO 3:4 trial probably because of the pre-randomized period which allowed the participation of patients who were able to take tolvaptan with tolerable levels of adverse effects[10,26].

Overall, the trial data emphasized the significant benefit in the reduction of eGFR decline in patients treated with tolvaptan. However, the study had some limitations, such as the creation of an ideal test group by removing the patients who could not tolerate the side effects of tolvaptan, the selection of patients according to eGFR, disregarding other important markers such as TKV or genotype. Again, the short duration of the trial limited assessment of the beneficial effect and the occurrence of adverse events over a long period of time[26].

CONCLUSION

Considering the clinical trial results, it seems reasonable to say that tolvaptan will play a central role in ADPKD treatment. So far, the consensus, based on actual evidence, suggests treatment of a certain group of patients, based on their risk of progression. However, there are still some questions that must be clarified. Further studies with a longer follow-up time are needed to understand precisely what subclasses of patients benefit from the treatment; to estimate if the adverse events observed in the trials will become more problematic and to understand the long-term effectiveness of the treatment. Additionally, the value of the TKV and its importance in patients with more advanced disease needs to be assessed to improve even more the selection criteria of the best candidates to fully benefit from this therapy.

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