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Autosomal dominant polycystic kidney disease: the role of tolvaptan in slowing rate of kidney function decline

Making Education Easy 2019

Independent commentary by Professor Carol Pollock

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This publication is intended as an educational resource for healthcare professionals. The review will discuss the role of tolvaptan in the clinical management of autosomal dominant polycystic kidney disease. Tolvaptan is currently the only approved pharmacological treatment which has been proven to be effective in slowing the rate of kidney function decline in patients with autosomal dominant polycystic kidney disease.[1,2]

Introduction

Autosomal dominant polycystic kidney disease (ADPKD) is an inherited disease, characterised by the development and progression of renal cysts, leading to increased kidney volume, reduced renal function and eventual progression towards end-stage kidney disease (ESKD).[3-5]

ADPKD is an autosomal dominant disorder, thus individuals at risk have a 50% chance of inheriting the disease.[3,6] It is genetically heterogeneous, with two causative genes identified: *PKD1*, which encodes polycystin 1 (PC-1) and accounts for 85% of cases; and *PKD2*, which encodes polycystin 2 (PC-2) and accounts for 15% of cases.[3] Mutations in *PKD1* versus *PKD2* lead to more severe disease, with average ages at ESKD of 58.1 versus 79.7 years, respectively.[3] More severe disease is also observed in ADPKD cases associated with truncating versus non-truncating mutations of *PKD1* (the former account for 65% of *PKD1* mutations).[3] The disease is associated with a variety of phenotypes, determined by the identity of the affected locus (*PKD1* vs *PKD2* mutation), the allelic variant (truncating, non-truncating, or hypomorphic), timing of gene inactivation, mosaicism, and genetic background. Affected family members may have discordant disease severity, suggesting a role for both genetic and environmental modifiers. However, approximately 10-15% of ADPKD cases occur in individuals with no family history of ADPKD.[3,7]

ADPKD patients with typical symmetric, bilateral, diffuse cyst distribution are categorised as class 1 (approximately 90% of patients), whereas patients with atypical, asymmetric, or segmental cyst distribution are categorized as class 2.[8] Class 1 patients can be further divided into subclasses A to E (based on TKV and age).[8] As for all patients with chronic kidney disease (CKD), kidney function in patients with ADPKD is classified by CKD stages 1-5.[8]

Over time, total kidney volume (TKV) increases and kidney function declines in patients with ADPKD. The physical signs and symptoms include hypertension, acute and chronic pain, urinary tract infections, increasing abdominal girth and extra-renal manifestations such as mitral valve disease, cerebral aneurysms, diverticular disease and potential complications related to cysts in other organs, dominantly the liver.[3] While the rate of disease progression varies from person to person, up to 70% of ADPKD patients will progress to ESKD, between their fourth and seventh decade of life.[9]

The disease is currently diagnosed radiologically using computed tomography (CT), magnetic resonance imaging (MRI) or ultrasound. The Modified Pei-Ravine criteria are the current accepted criteria for diagnosis.[10,11] Genetic testing may be performed but is not currently used routinely for diagnosis. Estimated Glomerular Filtration Rate (eGFR) is used to measure kidney function.

The prevalence of ADPKD is approximately 3.3 to 4.0 per 10,000 in the general population.[12,13] About 4% of Australian patients with chronic kidney disease have ADPKD.[14] ADPKD imposes a large financial burden on medical resources and the community (through loss of productivity) and a heavy financial, emotional and psycho-social burden on individuals and families.[9,15,16]

Focus on tolvaptan

Tolvaptan (JINARC) is a selective vasopressin type 2 receptor antagonist that blocks vasopressin's actions in the collecting duct of the kidney. Tolvaptan is currently the only approved treatment with proven effectiveness in slowing the rate of kidney function decline in patients with ADPKD.[1,2] Other pharmacological therapies are only used to control the general complications of CKD and have no specific effect in slowing renal functional decline in patients with ADPKD, e.g. antihypertensives for blood pressure management, antibiotics for urinary tract infections, and analgesics for pain.[3,17,18] As in all patients with ESKD, dialysis and kidney transplantation are used as renal replacement therapies.[3]

Tolvaptan is approved in Australia for slowing the progression of cyst development and renal insufficiency in ADPKD in adults with CKD stage 1 to 3 at the time of initiation of treatment and evidence of rapidly progressing disease.[19] Tolvaptan may be used alongside other treatments for the various signs and symptoms found in ADPKD, e.g. antihypertensives for management of hypertension.[19] Tolvaptan has been PBS listed, starting January 2019.

Other countries have also approved the use of tolvaptan for the treatment of ADPKD including the US[20], Japan, Canada[21], South Korea, Switzerland, and the European Union (EU)[22].

The approval of tolvaptan calls for the development of widely accepted treatment guidelines for using it in patients with ADPKD, and there are currently none, including in Australia. The most recent Australian guidelines on the diagnosis and management of ADPKD were published in 2016, before the approval of tolvaptan.[23]

In the EU, on behalf of the European Renal Association – European Dialysis and Transplant Association (ERA-EDTA) Working Groups of Inherited Kidney Disorders and European Renal Best Practice, Gansevoort et al. provided recommendations for starting tolvaptan and which patients should be treated with the drug.[24] In the EU, tolvaptan is indicated for slowing the progression of cyst development and renal insufficiency of ADPKD in adults with CKD stage 1–4* at the time of initiation of treatment and with evidence of rapidly progressing disease. The recommendation suggests clarifying the CKD stage and age at which tolvaptan can be initiated as well as the definition of rapidly progressive disease. Therefore, the recommendation provides a decision tree for patients most likely to benefit from the use of tolvaptan (see **Figure 1**). In addition, this algorithm helps to screen out patients less likely to show clinical benefit from the use of tolvaptan but should be re-evaluated in 3-5 years. Gansevoort et al. also highlighted the consideration of factors other than eligibility before the initiation of therapy, such as contraindications, adverse events, patient motivation and lifestyle factors, and patient's global risk profile.

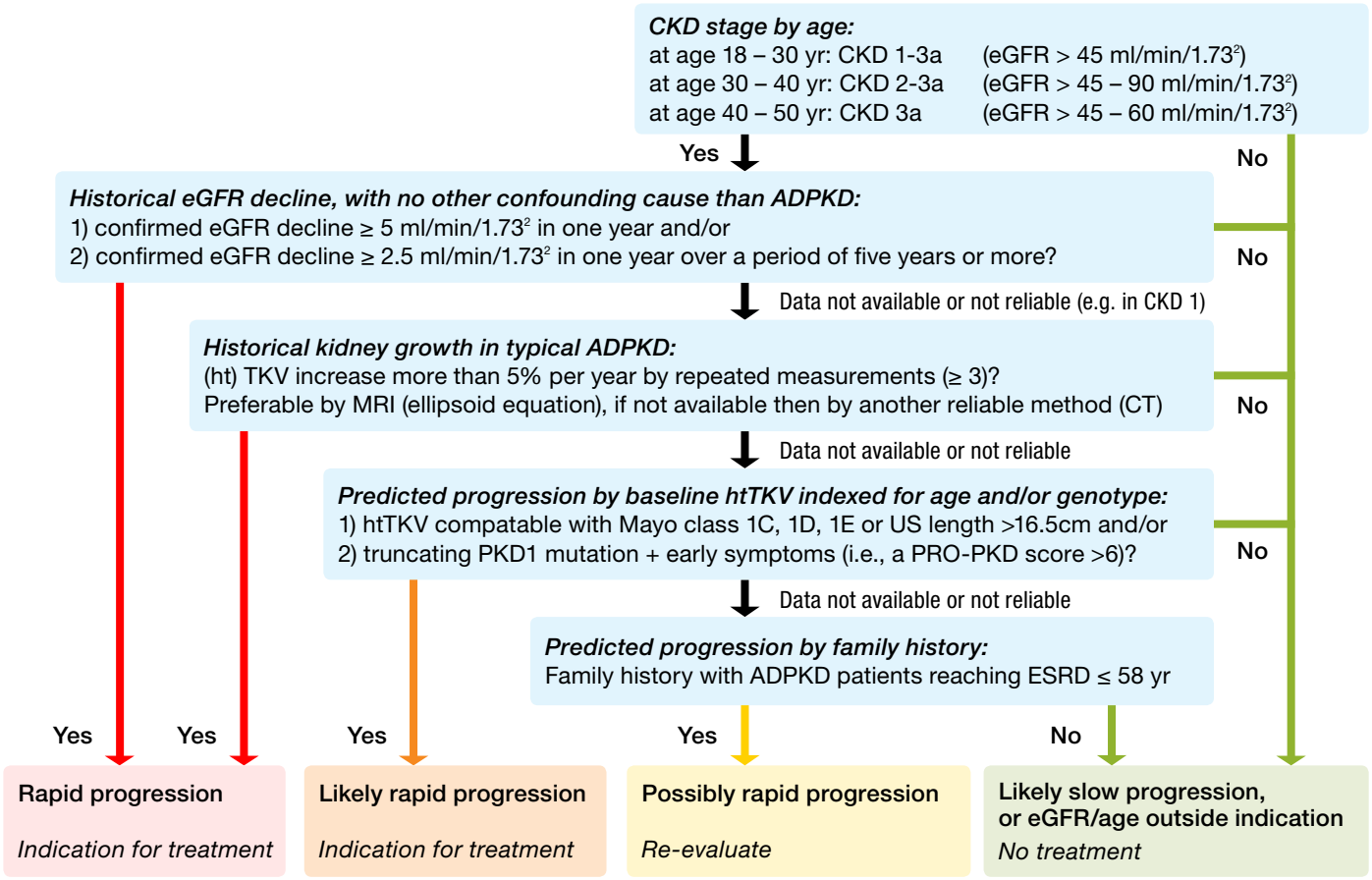


Figure 1. Algorithm to assess indications for initiation of tolvaptan treatment in ADPKD[24]
Please see Gansevoort et al.[24] for more information.

Key clinical studies of tolvaptan in ADPKD

TEMPO 3:4

TEMPO 3:4 was a phase 3, multicentre, double-blind, placebo-controlled, 3-year trial, which randomly assigned 1445 patients with ADPKD in a 2:1 ratio to receive tolvaptan or placebo.[1] Patients were 18 to 50 years of age with a TKV of 750 mL or more and an estimated creatinine clearance of ≥60 mL per minute. The primary outcome was the annual rate of change in TKV. Secondary endpoints included a composite of time to clinical progression (defined as worsening kidney function, kidney pain, hypertension and albuminuria) and rate of kidney function decline.

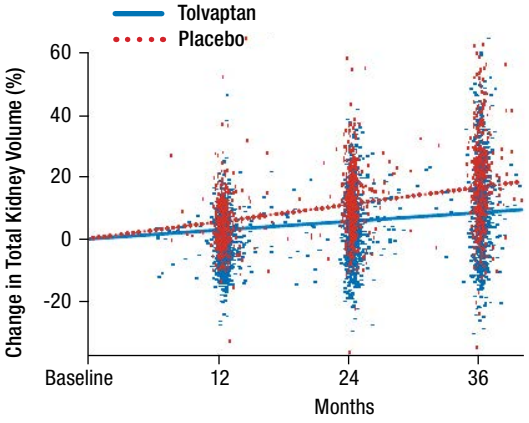
The increase in TKV in the tolvaptan group was 2.8% per year versus 5.5% per year in the placebo group (P<0.001) (see **Figure 2**). The composite endpoint of time to clinical progression favoured tolvaptan over placebo with lower rates of worsening kidney function and kidney pain. Tolvaptan was associated with a slower decline in kidney function (reciprocal of the serum creatinine level, -2.61 $[mg/mL]^{-1}$ per year vs -3.81 $[mg/mL]^{-1}$ per year; P<0.001) (see **Figure 3**).

A post hoc analysis was performed to reassess the primary and secondary efficacy endpoints by CKD stage at baseline,[25] which suggested clinically similar beneficial effects of tolvaptan in ADPKD across CKD stages 1–3.

Tolvaptan treatment was associated with an increased risk of derangement of liver function, with serious adverse events of alanine aminotransferase (ALT) elevation and aspartate aminotransferase (AST) elevation both experienced by 0.9% of patients in the tolvaptan group and 0.4% of patients in the placebo group.[1] Two patients had laboratory and clinical evidence of potentially serious drug-induced liver injury, meeting Hy's law criteria (serum ALT level of >3 times the upper limit of the normal range and bilirubin level of >2 times the upper limit of the normal range). There were also more events relating to aquaresis in the tolvaptan group than placebo group, most commonly thirst (55.3% patients vs 20.5% patients), polyuria (38.3% vs 17.2%) and nocturia (29.1% vs 13.0%). Tolvaptan was also associated with a higher rate of discontinuation from treatment (23% vs 14% with placebo). There were fewer ADPKD-related events in the tolvaptan group including serious adverse events of pyelonephritis (0.5% vs 1.0% with placebo), renal-cyst infection (0.6% vs 0.8%) and renal-cyst haemorrhage (0.3% vs 0.8%).

*Please note, tolvaptan is not approved in Australia for CKD stage 4.

Total Kidney Volume



Treatment Effect for Total Kidney Volume

Subgroup	Absolute Treatment Effect	Relative Treatment Effect	Annual Slope		P Value
	Difference in annual slope %/yr	%	Tolvaptan %/yr	Placebo %/yr	
Sex					
Male		37.3	4.15	6.62	<0.001
Female		71.1	1.24	4.29	<0.001
Age					
<35 yr		28.0	4.37	6.06	0.02
≥35 yr		58.2	2.23	5.34	<0.001
Hypertension					
Yes		50.5	3.01	6.09	<0.001
No		51.2	1.62	3.32	0.008
Estimated creatinine clearance					
<80 ml/min		57.2	2.27	5.32	<0.001
≥80 ml/min		47.5	2.92	5.56	<0.001
Total kidney volume					
<1500 ml		48.8	2.24	4.37	<0.001
≥1500 ml		51.1	3.29	6.74	<0.001
All patients		49.2	2.80	5.51	<0.001

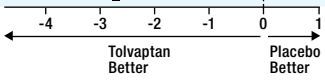
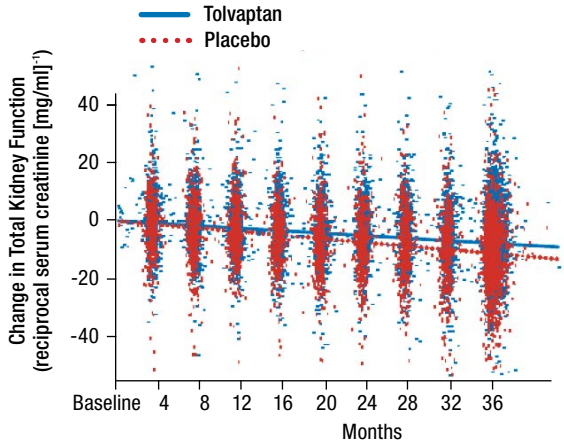


Figure 2. Total kidney volume in the TEMPO 3:4 trial[1]

Kidney Function



Treatment Effect for Kidney Function

Subgroup	Absolute Treatment Effect	Relative Treatment Effect	Annual Slope		P Value
	Difference in annual slope ([mg/ml]-1)	%	Tolvaptan (mg/ml)-1	Placebo	
Sex					
Male		32.1	-2.37	-3.49	<0.001
Female		30.7	-2.85	-4.11	0.02
Age					
<35 yr		26.5	-1.93	-2.62	0.19
≥35 yr		30.6	-2.84	-4.09	<0.001
Hypertension					
Yes		35.0	-2.72	-4.19	<0.001
No		9.6	-2.09	-2.31	0.69
Estimated creatinine clearance					
<80 ml/min		32.0	-3.69	-5.43	0.01
≥80 ml/min		29.7	-2.21	-3.14	0.001
Total kidney volume					
<1500 ml		21.7	-1.97	-2.52	0.10
≥1500 ml		36.6	-3.24	-5.11	<0.001
All patients		31.6	-2.61	-3.81	<0.001

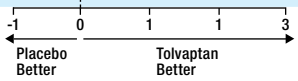


Figure 3. Kidney function in the TEMPO 3:4 trial[1]

Expert commentary on TEMPO 3:4

TEMPO 3:4 was undertaken in a relatively young patient population with preserved renal function but large kidneys predictive of an increased risk of future ESKD. The study demonstrated a reduction in the rate of cyst growth in the kidneys and a slowing of the rate of decline in eGFR in tolvaptan treated patients over 3 years versus the placebo treated patients. Important additional clinical benefits were observed in a reduction of urinary infection, haemorrhage into a cyst and in kidney pain. The more immediate benefit was further pronounced in patients most likely to have more rapid progression, namely those over 35 years, those with complications such as hypertension and those with larger kidneys.

Liver toxicity (elevations in transaminases of greater than 3 times the upper limit of normal) occurred in 0.9% versus 0.4% in placebo group. An independent analysis estimated that long-term tolvaptan therapy was associated with a risk of liver failure in one in 4,000 ADPKD patients.[26] Additional side effects were generally as expected with the use of an aquaretic agent i.e. polyuria, polydipsia and thirst. It should be noted that patients with poorly controlled diabetes were excluded from the TEMPO 3:4 study given the potential for tolvaptan to increase hepatic glucose output and worsen glycaemic control. Although not contraindicated in patients with concomitant diabetes mellitus, patients should be monitored for a deterioration in glycaemic control. The results of TEMPO 3:4 led to the approval of tolvaptan for the use of patients with ADPKD in Canada, South Korea, Japan and various countries in Europe including Norway, Scotland and Switzerland.

TEMPO 4:4

TEMPO 4:4 was an open-label extension study in patients (both had received prior tolvaptan and prior placebo) who had participated in Tempo 3:4, designed to provide an additional two years' data on the long-term safety and efficacy of tolvaptan in ADPKD.[27]

871 (60.3%) patients from the TEMPO 3:4 study participated in this study. The primary endpoint was the change in TKV from TEMPO 3:4 baseline to TEMPO 4:4 Month 24 in prior tolvaptan ("early tolvaptan) versus prior placebo ("late tolvaptan") subjects. Secondary endpoints included changes in eGFR.

Changes in TKV from TEMPO 3:4 baseline to TEMPO 4:4 Month 24 were 29.9% and 31.6% (early tolvaptan and late tolvaptan, respectively) and the difference between early tolvaptan and late tolvaptan treatment was not significant ($P = 0.38$). There was a persistent effect of tolvaptan on eGFR (difference of 3.15 mL/min/1.73 m^2; $P < 0.001$), and non-inferiority in eGFR slopes between early and late tolvaptan treatment. The safety profile was similar to that observed in TEMPO 3:4. One delayed-treated subject met the criterion for Hy's Law and recovered completely after discontinuation of tolvaptan.

The study demonstrated that the eGFR benefit, achieved at the end of TEMPO 3:4 in the prior tolvaptan subjects, was maintained for an additional two years in TEMPO 4:4, supporting a sustained disease-modifying effect of tolvaptan on eGFR. The authors noted that the trial had several limitations that may account for the lack of a sustained rate of slowing in TKV increases over time, including loss of randomisation and baseline imbalances due to the study being an extension from TEMPO 3:4.

Expert commentary on TEMPO 4:4

Tempo 4:4 enrolled patients who had participated in Tempo3:4 in an open label extension study. Hence it was not a randomised trial and given 60% of patients were rolled over into the study it wasn't powered to address a primary renal endpoint. It was designed to assess ongoing efficacy and safety. Similar benefits were seen in those who received delayed tolvaptan therapy with a slowing in the rate of progression of eGFR, similar to that observed in patients initially treated in the TEMPO 3:4 trial. The safety profile was replicated in the TEMPO 4:4 study.

REPRISE

REPRISE was a phase 3, randomised withdrawal, multicentre, placebo-controlled, double-blind trial in patients with later stage ADPKD.[2] After an 8-week pre-randomisation period designed to assess each patient's ability to take tolvaptan without dose-limiting side effects, 1370 patients with ADPKD were randomly assigned in a 1:1 ratio to receive tolvaptan or placebo for 12 months. Patients were 18 to 55 years of age with an eGFR of 25 to 65 mL/min/1.73 m^2 of body surface area or 56 to 65 years of age with an eGFR of 25 to 44 mL/min/1.73 m^2 and a proven decline in eGFR of >2 mL/min/1.73 m^2 per year. Patients in the older age group also had to have a rate of renal function decline of ≥2 mL/min/1.73 m^2 per year. The primary endpoint was the annualised change in the eGFR.

Patients receiving tolvaptan experienced a slower annualised rate of kidney function decline compared to placebo. The change from baseline in the eGFR was −2.34 mL/min/1.73 m^2 in the tolvaptan group, as compared with −3.61 mL/min/1.73 m^2 in the placebo group (difference, 1.27 mL/min/1.73 m^2; $P < 0.001$). Prespecified subgroup analyses showed a beneficial effect of tolvaptan across subgroups that were defined according to sex, baseline eGFR, stage of chronic kidney disease (except for stage 2), and geographic region, as well as in subgroups of patients who were 55 years of age or younger and patients who were white, but not in the smaller subgroups of patients who were older than 55 years of age, who were nonwhite, or who had chronic kidney disease of stage 2.

Regarding secondary endpoints, the mean slopes of the change in the eGFR at 1 year were −3.16 mL/min/1.73 m^2 in the tolvaptan group, as compared with −4.17 mL/min/1.73 m^2 in the placebo group (difference, 1.01 mL/min/1.73 m^2; $P < 0.001$).

Elevations in the alanine aminotransferase level (to >3 times the upper limit of the normal range) occurred in 38 of 681 patients (5.6%) in the tolvaptan group and in 8 of 685 (1.2%) in the placebo group. Elevations in the aminotransferase level were reversible after stopping tolvaptan. No elevations in the bilirubin level of more than twice the upper limit of the normal range were detected.

Expert commentary on REPRISE

REPRISE was undertaken as the FDA required additional data in patients with more significant renal impairment and across a broader age range. According to various criteria patients were enrolled up to 65 years of age and down to an eGFR of 25 mL/min/1.73 m^2. Patients were only enrolled if they could tolerate the aquaretic effects of tolvaptan during a pre-randomisation period. Pleasingly tolvaptan was effective in slowing the rate of decline in renal function by approximately 1.3 mL/min/1.73 m^2 per year in this population with more significant renal dysfunction, similar to that observed in patients with relatively preserved renal function enrolled in Tempo3:4. Subgroup analyses demonstrated patients over the age of 55 are less likely to demonstrate a benefit in slowing the rate of decline in renal function compared to younger patients. Equal benefit was observed in patients enrolling into the study with an eGFR of greater than or less than 45 mL/min/1.73 m^2. Indeed, the patients with stage 3 and 4 CKD appeared to derive greater benefit than did patients with stage 2 CKD. It should be noted that an acute reversible drop in eGFR can be expected after the commencement of tolvaptan, which is primarily due to inhibition of tubuloglomerular feedback, resulting in afferent arteriolar vasoconstriction and an accompanying decrease in both intraglomerular pressure and in single nephron GFR. Volume depletion is not considered to play a significant role in the expected acute reduction in eGFR as body weight did not alter. Such reductions in eGFR occur with blockade of the renin-angiotensin system and with the use of the sodium-glucose linked transport blockers, which we now recognise as being renoprotective. Derangement in liver function tests was again observed leading to recommendations for regular liver function testing in patients prescribed tolvaptan.

Long-term administration of tolvaptan

This study from the Mayo Clinic with follow-up for up to 11.2 years (mean 4.6 years) showed a sustained reduction in the annual rate of eGFR decline in patients treated with tolvaptan compared with controls and an increasing separation of eGFR values over time between the two groups.[28]

One hundred and twenty-eight patients with ADPKD were eligible to enter open-label extension studies. Ninety-seven patients treated with tolvaptan for ≥ 1 year (mean 4.6 years, up to 11.2 years) were analysed for efficacy using three approaches: (1) comparison of eGFR slopes and outcome (33% reduction from baseline eGFR) to controls; (2) Stability of eGFR slopes with duration of follow-up; and (3) comparison of observed and predicted eGFRs at last follow-up.

Patients treated with tolvaptan had lower eGFR slopes from baseline (mean -2.20 mL/min/1.73 m^2 per year) and from month 1 (mean -1.97 mL/min/1.73 m^2 per year) compared with controls (mean -3.50 mL/min/1.73 m^2 per year; $P < 0.001$), and lower risk of a 33% reduction in eGFR (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). Annualized eGFR slopes of patients treated with tolvaptan did not change during follow-up and differences between observed and predicted eGFRs at last follow-up increased with duration of treatment.

Among 108 patients included in the tolerability and safety analysis, none was lost to follow-up. Eight discontinued the drug because of adverse events related to tolvaptan. One of 39 patients with a follow-up extending beyond 5 years discontinued tolvaptan because of an adverse event thought to be likely related to the drug (fatigue).

Expert commentary on long-term administration of tolvaptan

Loss of efficacy of any drug over time is clearly of concern to patients, clinicians and regulators. These longer-term studies have demonstrated that the initial observed differences in the rate of slowing of eGFR in tolvaptan treated patients are sustained in follow up studies of these patients for up to 11.2 years (average 4.6 years) with an increasing separation of eGFR values between the groups over time. Hence although the absolute differences in eGFR over a year appear to be modest, the cumulative benefits are great and can substantially delay the time to commencement of renal replacement therapy. If extrapolated, a reduction in the decline of renal function of 1.2 mL/min/1.73 m^2 per year gives an additional 36 mL/min of glomerular function at the end of 30 years. Clearly this may be the difference between life dependent on or independent of renal replacement therapy.

Expert's concluding comments

Strategies to control the progression of CKD have to date been generically applied to the CKD population. Targets are to control blood pressure, control blood sugar levels where relevant, and reduce albuminuria with an additional focus on reducing cardiovascular morbidity and mortality. Uncommon inflammatory diseases require immunosuppression. Tolvaptan is unique in that it provides specific targeted therapy to the subset of CKD patients with ADPKD. Importantly, it has been shown to be renoprotective in patients across the range of CKD stages 2-4. Its use should be broadly considered in patients in whom eGFR is declining, whose kidneys are enlarging and who have a family history of early commencement of dialysis. Although genetic tests to predict those at risk of progressive disease are not currently widely available, they may be more accessible in the future and then be also used as an aid to guide instigation of therapy.

Patients should be forewarned of the inevitable aquaretic effects of tolvaptan and also be advised of the need for mandatory surveillance of liver function.

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