Autosomal dominant polycystic kidney disease (ADPKD) is the most common form of inherited kidney disease and represents the fourth most common cause of end-stage kidney disease (ESKD) in Western nations. ADPKD is a multisystem disease that is characterized by the progressive development of renal cysts, which results in urinary concentration abnormalities, increased kidney volume due to cyst formation, hypertension, haematuria, renal pain, urinary tract infections, and deterioration of renal function. Extra-renal manifestations include liver and pancreatic cysts, bowel diverticula, and increased risk of intracranial and other arterial aneurysms.

In most patients, ADPKD leads to an increase in total kidney volume (TKV) and a decline in estimated glomerular filtration rate (eGFR). Although the rate of renal function deterioration varies from person to person, approximately 70% of patients with ADPKD will progress to ESKD at a median age of 56 years. ESKD requires haemodialysis or renal transplantation, the costs of which are considerable.

In patients with ADPKD, TKV is used as a surrogate marker of kidney size. Kidney function (assessed by eGFR) is classified using chronic kidney disease (CKD) stages 1–5 (Table 1). The classification of ADPKD according to height-adjusted TKV and age predicts eGFR decline over time and progression to ESKD in ADPKD patients across a range of CKD stages.

<table>
<thead>
<tr>
<th>CKD stage</th>
<th>Description</th>
<th>eGFR (mL/min per 1.73m²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>G1</td>
<td>Normal or high</td>
<td>≥90</td>
</tr>
<tr>
<td>G2</td>
<td>Mildly decreased</td>
<td>60–89</td>
</tr>
<tr>
<td>G3a</td>
<td>Mild to moderately decreased</td>
<td>45–59</td>
</tr>
<tr>
<td>G3b</td>
<td>Moderately to severely decreased</td>
<td>30–44</td>
</tr>
<tr>
<td>G4</td>
<td>Severely decreased</td>
<td>15–29</td>
</tr>
<tr>
<td>G5</td>
<td>Kidney failure</td>
<td>&lt;15</td>
</tr>
</tbody>
</table>

Note: CKD is defined as either kidney damage or reduced kidney function for >3 months. Reduced kidney function is defined as eGFR <60 mL/min per 1.73 m² (GFR categories G3–G5). Kidney damage is defined as pathologic abnormalities or markers of damage, including abnormalities in blood or urine tests or imaging studies.

Burden of disease

European population- and registry-based studies have determined prevalence rates of between 2.41 and 3.96 per 10,000 people, which suggests that ADPKD is a rare disease in Western populations. ADPKD is, however, associated with a substantial level of disease burden.

Medical costs due to ADPKD have been demonstrated to be significant, with healthcare resource utilisation and expenditures being higher in CKD stages 4–5 than in CKD stages 1–3 and highest in ADPKD patients with ESKD. Additionally, indirect costs also increase with disease progression and lost wages due to reduced productivity have been demonstrated to be considerable in absolute terms.

Early-stage ADPKD is associated with substantial negative physical and emotional effects, which worsen with disease progression. In a multinational European study that assessed health-related quality of life (HRQOL) across all stages of the disease, overall HRQOL was generally highest in patients with CKD stages 1–3, followed by transplant recipients, patients with CKD stages 4–5, and patients on dialysis. These findings are consistent with a UK study in which kidney disease-related HRQOL declined and psychosocial risk increased with increasing disease progression in patients with ADPKD.

Given the link between disease progression and increasing treatment-related costs and declining patient HRQOL, it has been proposed that the value of medical interventions that can slow the progression of the ADPKD should be considered.
Tolvaptan in the Management of Autosomal Dominant Polycystic Kidney Disease

Tolvaptan

**Mechanism of action**

Arginine vasopressin (AVP) is an antidiuretic hormone that stimulates intracellular cyclic adenosine monophosphate (cAMP) production by binding to V2 receptors in the collecting ducts and distal nephron of the kidney. V2 receptor antagonists such as AVP play a fundamental role in the regulation of cyst development and renal insufficiency in adult ADPKD patients with CKD stages 1–3 at treatment initiation and evidence of rapidly-progressing disease. Speculation about the use of tolvaptan has been developed by European and Canadian expert groups. Factors used to identify rapidly progressive ADPKD that is likely to result in ESKD include: TKV/age, rate of change of TKV, eGFR/age, rate of decline of eGFR, genotype, and family history. The following is a summary of the pharmacological properties of tolvaptan as well as relevant prescribing information. The Jnarc Product Information should be consulted for detailed information about its use, including dosage adjustments, contraindications, special warnings, precautions, drug interactions, and use in special patient populations.

**Dosage and administration**

Tolvaptan is administered orally usually at a starting dosage of 60 mg/day, administered in two divided doses of 45 mg in the morning (≥30 min before the morning meal) and 15 mg approximately 8 hours later (with or without food). The dosage should be increased to 90 mg/day (60 mg + 30 mg) and then to a target dosage of 120 mg/day (90 mg + 30 mg), with intervals of ≥1 week between titrations. Patients should be maintained on the highest tolerable dosage of tolvaptan.

**Treatment with tolvaptan**

Treatment with tolvaptan must be initiated and monitored by a physician experienced in the management of ADPKD and who has a full understanding of the risks associated with tolvaptan therapy including potential hepatic toxicity and monitoring of the adequacy of vasopressin inhibition and dehydration secondary to the aquaretic effects of tolvaptan. Due to the aquaretic effect of tolvaptan, patients must have access to fluids (e.g. water) and be able to drink sufficient quantities in response to the first signs of thirst.

**Pharmacokinetics**

Tolvaptan is rapidly absorbed following oral administration, with peak plasma concentrations ($C_{\text{max}}$) being reached about 2 hours after dosing. The mean absolute bioavailability of tolvaptan is approximately 56%. The $C_{\text{max}}$ is increased when tolvaptan is co-administered with a high-fat meal. Although the clinical relevance of this finding is unclear, it is recommended that the morning dose be administered in the fasting state.

Tolvaptan is metabolized in the liver primarily by cytochrome P450 (CYP) 3A isoenzymes and is eliminated almost entirely by non-renal routes, as indicated by <1% of the dose being excreted unchanged in the urine. Tolvaptan is a weak CYP3A4 substrate and does not appear to have any inhibitory activity for CYP3A. The terminal elimination half-life of tolvaptan is about 8 hours.

**Drug interactions**

Concomitant use of medicines that are moderate or strong CYP3A inhibitors increases tolvaptan exposure. Hence, the dosage of tolvaptan should be reduced if the drug is used concurrently with moderate (e.g. fluconazole, diltiazem) or strong (e.g. ketoconazole, ritonavir) CYP3A4 inhibitors. Concomitant use of medicines that are potent CYP3A inducers will reduce tolvaptan exposure and efficacy. Therefore, the co-administration of tolvaptan and strong CYP3A inducers (e.g. rifampicin, carbamazepine, St John’s Wort) should be avoided cautiously. Tolvaptan is a substrate and competitive inhibitor of the transporter P-glycoprotein (P-gp). Exposure to the P-gp substrate digoxin was increased when digoxin was concurrently used with tolvaptan. Patients co-administered tolvaptan and digoxin or other P-gp substrates with narrow therapeutic windows (e.g. dabigatran) should be managed cautiously.

Tolvaptan is a potential inhibitor of the OATP1B1, OATP1B3, OCT3, BCRP and OCT1 transporters. Co-administration of tolvaptan with substrates of OATP1B1 and OATP1B3 (e.g. rosuvastatin and pitavastatin), OAT3 (e.g. methotrexate, ciprofloxacin), BCRP (e.g. sulfasalazine), or OCT1 (e.g. metformin) requires patients that be managed cautiously and evaluated for excessive effects of such medications. Because tolvaptan is capable of blocking vascular vasopressin V2-receptors involved in the release of coagulation factors from endothelial cells, the ability of vasopressin analogues to prevent or control bleeding may be attenuated when given concurrently with tolvaptan. The co-administration of tolvaptan with vasopressin analogues (e.g. desmopressin) is not recommended.

**Special populations**

Dosage adjustments are not required in patients with renal impairment or mild or moderate hepatic impairment (Child-Pugh classes A and B). However, the benefits and risks of tolvaptan should be evaluated in patients with severe hepatic impairment and their liver enzymes should be monitored regularly (see Hepatotoxicity section).

**Contraindications**

Tolvaptan should not be used in patients with elevated liver enzymes and/or other signs or symptoms of liver impairment prior to commencement of treatment that meet requirements for permanent discontinuation of tolvaptan. Volume depletion, hypernatraemia, anuria, inability to feel or respond to thirst, pregnancy, breastfeeding, and patient non-adherence with monthly liver enzyme testing are other reasons that preclude use of tolvaptan.

**Hepatotoxicity**

Tolvaptan has been associated with idiosyncratic hepatic toxicity characterised by elevations of blood alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels, with rare cases of concomitant elevations in bilirubin-total (BT) levels. To mitigate the risk of liver injury, regular monitoring of liver enzymes and bilirubin should be performed prior to starting tolvaptan, monthly for 18 months, and every 3 months thereafter. At the onset of symptoms or signs consistent with hepatic injury or if clinically significant abnormal ALT or AST increases are detected during treatment, tolvaptan administration must be immediately interrupted and repeat tests including ALT, AST, BT, and alkaline phosphatase (AP) must be obtained as soon as possible (ideally within 48-72 hours). Testing must continue at increased time frequency until symptoms/signs/laboratory abnormalities stabilise or resolve, at which point tolvaptan may be cautiously re-initiated.

Tolvaptan is contraindicated in patients with elevated liver enzymes and/or signs or symptoms of liver injury prior to initiation of treatment that meet the following requirements for permanent discontinuation:

- ALT or AST >8-times upper limit of normal (ULN).
- ALT or AST >5-times ULN for >2 weeks.
- ALT or AST >3-times ULN and BT >2-times ULN or International Normalized Ratio (INR) >1.5.
- ALT or AST >3-times ULN with persistent symptoms of hepatic injury noted above.
In case of abnormal baseline levels of liver enzymes below the limits for permanent discontinuation, treatment with tolvaptan should only be started if the potential benefits of treatment outweigh the potential risks and liver function testing is continued with an increased time frequency. 20

Clinical efficacy and tolerability

Treatment with tolvaptan significantly reduced cyst burden and slowed disease progression over 3 years of follow-up in ADPKD patients with early-stage CKD in the pivotal large-scale TEMPO 3:4 trial, 21 which led to the first marketing approval for tolvaptan in 2015 (by the European Medicines Agency). 22 The results of the TEMPO 3:4 trial were confirmed in the subsequent TEMPO 4:4 trial, 23 which was an open-label, 2-year extension trial. The effects of tolvaptan on disease progression have also been assessed in a retrospective analysis of long-term administration of tolvaptan with follow-up for ≤11.2 years. 22 Additionally, the REPRIS trial evaluated tolvaptan in patients with more advanced CKD than in TEMPO 3:4, 24 with the results indicating that tolvaptan may be effective over a broad range of CKD stages.

In terms of tolerability, TEMPO 3:4, TEMPO 4:4, and REPRIS trials showed that the most common adverse events of tolvaptan are linked to its aquaretic mechanism of action, including thirst, polyuria, nocturia, and polydipsia as a result of the excretion of electrolyte-free water. 21 22 23 24 25 26 Rare cases of idiosyncratic hepatitis (which reversed on interruption or discontinuation of tolvaptan) were also observed (See Hepatotoxicity section).

The following Study summaries provide more details of the TEMPO 3:4, TEMPO 4:4, and REPRIS trials as well as the retrospective analysis of long-term administration of tolvaptan.

Tolvaptan in patients with autosomal dominant polycystic kidney disease 26

Authors: Torres VE et al.

Methods: The Tolvaptan Efficacy and Safety in Management of Autosomal Dominant Polycystic Kidney Disease and Its Outcomes (TEMPO) 3:4 trial was a multicentre, randomized, double-blind, phase III trial in which adult patients with ADPKD (TKV ≥750mL and eGFR ≥60mL) were randomly assigned (in a 2:1 ratio) to receive tolvaptan (at the highest of three twice-daily dose regimens able to be tolerated) or placebo for three years. The annual rate of change in TKV was the primary endpoint while a composite of time to clinical progression (defined as worsening kidney function, kidney pain, hypertension, and albuminuria) and rate of kidney function decline were sequential secondary endpoints.

Results: Of the 1445 patients randomised to treatment, 961 received tolvaptan and 484 received placebo. TKV increased at a rate of 2.8% per year in the tolvaptan group (95% CI: 2.5 to 3.1) versus 5.5% per year in the placebo group (95% CI: 5.1 to 6.0; p<0.001). The composite endpoint analysis showed fewer ADPKD-related events per 100 person-years of follow-up with tolvaptan than with placebo (44 vs 50 events; HR: 0.87; 95% CI: 0.78 to 0.97; p=0.001). Figure 1 and kidney pain (5 events per 100 person-years of follow-up in the tolvaptan group vs 5 in the placebo group [HR: 0.39; 95% CI: 0.26 to 0.57; p=0.001]). Figure 1 and kidney pain (5 events per 100 person-years of follow-up in the tolvaptan group vs 7 in the placebo group [HR: 0.64; 95% CI: 0.47 to 0.89; p=0.007]). Figure 2). The rate of kidney function decline from the end of dose escalation to month 36 was slower with tolvaptan than with placebo (reciprocal of the serum creatinine level, –2.61 [mg/mL] 1 per year vs –3.81 [mg/mL] 1 per year; p<0.001). Although fewer ADPKD-related adverse events occurred in the tolvaptan group than in the placebo group, tolvaptan-treated patients experienced more events related to aquarexia and hepatic adverse events unrelated to ADPKD, which contributed to a higher discontinuation rate (23% vs 14% in the placebo group). In a post hoc analysis of the hepatic events in TEMPO 3:4, elevations of ALT >3-times ULN and AST >2×ULN were seen in 4.4% of patients receiving tolvaptan and 1.0% of patients receiving placebo. 25

Comment: 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 to 2.1 mL/min per 1.73 m 2 versus 6.3 mL/min per 1.73 m 2 in 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 more pronounced in patients more likely to have more rapid progression, namely those aged >35 years, those with complications such as hypertension, and those with larger kidneys. Liver toxicity (elevations in transaminasines of >3 times the ULN) occurred in 0.9% of tolvaptan-treated versus 0.4% of placebo-treated patients (p=0.05). An independent analysis estimated that long-term tolvaptan therapy was associated with a risk of liver failure in one in 4,000 ADPKD patients. 25 Additional side effects were generally expected with the use of an aquaretic agent, i.e. polyuria, polydipsia, and thirst. It should be noted that patients with poorly-controlled diabetes mellitus 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, Korea, Japan, and various countries in the European Union including Norway, Scotland, and Switzerland.

A. Risk of worsening kidney function

Hazard ratio, 0.39 (95% CI, 0.26–0.57)  
P<0.001 by Cox model

B. Risk of clinically-significant pain

Hazard ratio, 0.64 (95% CI, 0.47–0.89)  
P=0.007 by Cox model

Figure 1. Effect of tolvaptan on the time to multiple events of worsening kidney function (A) and kidney pain (B) associated with ADPKD. 26

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Figure 2. Cumulative event hazard associated with clinical progression in the TEMPO 3:4 trial for patients aged ≥35 years. Placebo: 0.37; tolvaptan: 0.28; HR: 0.74 (95% CI, 0.61–0.90). 21

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Figure 3. Effect of Tolvaptan on the Time to Multiple Events Associated with Autosomal Dominant Polycystic Kidney Disease (ADPKD).
Multicenter, open-label, extension trial to evaluate the long-term efficacy and safety of early versus delayed treatment with tolvaptan in autosomal dominant polycystic kidney disease: the TEMPO 4:4 Trial

Authors: Torres VE et al.

Methods: TEMPO 4:4 was an open-label extension trial that was designed to provide an additional two years of data on the long-term efficacy and safety of tolvaptan in patients who had completed TEMPO 3:4. The disease-modifying effects of tolvaptan on TKV and eGFR end-points were assessed, including change from baseline over the combined duration of TEMPO 3:4 (3 years) and TEMPO 4:4 (2 years) and non-inferiority of slopes during TEMPO 4:4.

Results: Of the 1445 patients randomized to treatment in TEMPO 3:4, 871 (60.3%) enrolled in TEMPO 4:4 (557 early-treated [i.e. prior tolvaptan] patients and 314 delayed-treated [i.e. prior placebo] patients). Changes in TKV from TEMPO 3:4 baseline to TEMPO 4:4 month 24 were 29.9% in early- and 31.6% in delayed-treated patients. Adjusting for baseline covariates improved the TKV treatment difference at month 24 in TEMPO 4:4 from -1.70% to -4.15% between the groups (and increased the p value from p=0.38 to p=0.04). The effect of tolvaptan on slowing renal function decline in TEMPO 3:4 was maintained for an additional 2 years in TEMPO 4:4 (3.15 mL/min per 1.73m²; p<0.001). TKV slopes in TEMPO 4:4 were higher in early- versus delayed-treatment groups (6.16% vs 4.96% per year; treatment difference, 1.01%; p=0.05). eGFR slopes were similar in early- and delayed-treated subjects (-3.26 vs -3.14 mL/min per 1.73m²). The tolerability profile of tolvaptan in TEMPO 4:4 was similar to its tolerability profile in TEMPO 3:4, including a similar frequency of transaminase elevations >3-times ULN (2.5% with early- and 3.8% with delayed-treatment).

Comment: TEMPO 4:4 enrolled patients who had participated in TEMPO 3:4 in an open-label extension study. Hence, it wasn’t 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.

Tolvaptan in later-stage autosomal dominant polycystic kidney disease

Authors: Torres VE et al.

Methods: The Replicating Evidence of Preserved Renal Function: An Investigation of Tolvaptan Safety and Efficacy in ADPKD (REPRISE) trial was a multicentre, randomized withdrawal, double-blind, placebo-controlled, phase III trial that assessed the efficacy and safety of tolvaptan in more advanced ADPKD and with more frequent hepatic safety monitoring. Adult patients with ADPKD who were either 18–55 years of age with an eGFR of 25–65 mL/min per 1.73m² or 56–65 years of age with an eGFR of 25–44 mL/min per 1.73m² were randomly assigned in a 1:1 ratio to receive tolvaptan or placebo for 12 months after they had completed an 8-week pre-randomization period that included sequential placebo and tolvaptan run-in phases during which the ability of the patients to take tolvaptan without dose-limiting side effects was assessed.

Results: A total of 1370 patients who entered the single-blind tolvaptan period and did not have adverse effects that prevented their continuation in the trial were randomly assigned to receive tolvaptan (n=683) or placebo (n=687). Mean changes in eGFR from baseline to follow-up were -2.54 mL/min per 1.73m² (95%CI: -2.81 to -2.27) in tolvaptan-treated patients versus -2.81 mL/min per 1.73m² (95%CI: -3.05 to -2.57) in placebo-treated patients (treatment difference, 0.27 mL/min per 1.73m²; 95%CI: -0.09 to 0.63; p=0.06). The frequency of ALT elevations >3-times ULN was 5.6% in the tolvaptan group versus 1.2% in the placebo group (difference = 4.40% (95%CI: 0.50 to 8.30); p=0.04). ALT elevations >3-times ULN was 5.6% in the tolvaptan group versus 1.2% in the placebo group (difference = 1.27 mL/min per 1.73m²; p<0.001). The frequency of ALT elevations >3-times ULN was 5.6% in the tolvaptan versus 1.2% in the placebo group, with the elevations in ALT reversing after stopping tolvaptan. The rates of new or worsening adverse events did not differ substantially between the tolvaptan and placebo groups (85.3% vs 82.3%) during the double-blind period, with tolvaptan-treated patients experiencing more aquaretic adverse events.

Comment: 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 per 1.73m². 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 per 1.73m² per year in this population with more significant renal dysfunction, similar to that observed in patients with relatively preserved renal function enrolled in TEMPO 3:4. Subgroup analyses demonstrated patients over the age of 55 years 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 or greater than or less than 45 mL/min per 1.73m². 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 inafferent 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 change. 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 to be 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 in autosomal dominant polycystic kidney disease

Authors: Edwards ME et al.

Methods: This retrospective study determined whether the reduction in the rate of eGFR decline observed with tolvaptan is sustained and cumulative. It considered all ADPKD patients who had participated in clinical trials of tolvaptan and had the opportunity to enrol into open-label extension studies. Three strategies were used to analyse the effects of tolvaptan on disease progression: (i) comparison of eGFR slopes and outcome (33% reduction from baseline eGFR) with controls matched by sex, age, and baseline eGFR, (ii) stability of eGFR slopes with duration of follow-up; and (iii) comparison of observed and predicted eGFR values at last follow-up.

Results: A total of 128 patients had participated in ≥1 study of tolvaptan. Of these, 20 patients participated in short-term studies or received placebo only. The remaining 108 patients were analysed for safety. Of these, 11 patients had received tolvaptan for <1 year. The remaining 97 patients were included in the efficacy analysis. They had been treated with tolvaptan for periods of time ranging from 1.1 to 11.2 years (mean±SD: 4.6±2.8). Tolvaptan-treated patients had significantly (p<0.001) slower rates of eGFR decline calculated from baseline (mean±SD: -2.20±2.18 mL/min per 1.73m² per year) and from month 1 after starting tolvaptan (mean±SD: -1.97±2.44 mL/min per 1.73m² per year) compared with controls (mean±SD: -3.50±2.09 mL/min per 1.73m² per year). Kaplan-Meier analysis showed that the risk of a 33% reduction in eGFR from baseline (RR: 0.63; 95%CI: 0.38 to 0.98) or from month 1 (RR: 0.53; 95%CI: 0.31 to 0.85) was significantly lower in tolvaptan-treated patients than in the control patients. Annualized eGFR slopes for tolvaptan-treated patients did not change during follow-up and differences between observed and predicted eGFRs at last follow-up increased with the duration of treatment.

Comment: 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.
Tolvaptan is associated with idiosyncratic hepatic toxicity for which tolvaptan is an orally-active vasopressin V2-receptor antagonist. Tolvaptan is generally well tolerated, with the most common adverse events being consistent with its aquaretic mechanism of action. Tolvaptan is associated with idiosyncratic hepatic toxicity for which tolvaptan provides preliminary evidence that its efficacy is sustained and 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.

Take-home messages

- ADPKD is an inherited kidney disorder characterised by the development of renal cysts that cause progressive renal function deterioration and eventually ESKD.
- ADPKD is associated with loss of HRQOL and substantial medical costs, which are higher in advanced versus earlier-stage disease.
- Tolvaptan is an orally-active vasopressin V2-receptor antagonist.
- Clinical trials show that tolvaptan can slow the rate of decline of ADPKD-related kidney function in patients with moderate to advanced ADPKD.
- A retrospective analysis of all ADPKD patients included in clinical trials of tolvaptan provides preliminary evidence that its efficacy is sustained and reducing cardiovascular morbidity and mortality.
- Tolvaptan is generally well tolerated, with the most common adverse events being consistent with its aquaretic mechanism of action.
- Tolvaptan is associated with idiosyncratic hepatic toxicity for which pre-testing and ongoing monitoring is required.

References


Company Commissioned Article

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