

Drug management of autosomal dominant polycystic kidney disease

SUMMARY

Autosomal dominant polycystic kidney disease is the most common genetic kidney disease affecting adults. Approximately 60% of patients develop kidney failure by 60 years of age due to slowly expanding kidney cysts.

A healthy lifestyle and rigorous control of blood pressure slow kidney cyst growth. These interventions can be effective in reducing progression to kidney failure and cardiovascular disease, especially if started in early adulthood.

Tolvaptan, a vasopressin receptor antagonist, slows kidney cyst growth and the decline in the estimated glomerular filtration rate by 1 mL/minute/1.73 m² per year. It is indicated in patients with chronic kidney disease who are at high risk of progression to kidney failure.

Chronic kidney pain is common and can be managed with analgesics, and input from pain specialists if refractory.

Introduction


Autosomal dominant polycystic kidney disease (ADPKD) is the most common genetic cause of Stage 5 chronic kidney disease (kidney failure) in adults, accounting for 6.4% of Australians receiving chronic dialysis or undergoing transplantation. It is a single-gene disorder due to germline variants in either the PKD1 or PKD2 gene, estimated to be carried by 25,000 Australians. The main clinical manifestation is the formation of hundreds of microscopic fluid-filled kidney cysts during childhood that grow slowly. Sixty per cent of patients develop massive kidney enlargement, chronic pain, hypertension, cardiovascular disease and kidney failure, as well as other extrarenal manifestations, by the sixth decade of life (see Box). The diagnosis of ADPKD is typically made in young adults with a positive family history who have multiple kidney cysts detected on a kidney ultrasound performed for screening (see Box). Genetic testing is only required to assist with family planning or if there is diagnostic uncertainty.

Stage 5 chronic kidney disease is the main cause of disability and death in patients with ADPKD and is usually preceded by a progressive decline in the estimated glomerular filtration rate (eGFR) by approximately 2.5 mL/minute/1.73 m² per year between the second and fourth decades of life. Encouraging young adults with ADPKD to engage in their health during the early asymptomatic period provides the best opportunity to significantly delay the onset of kidney failure and prevent cardiovascular

disease. In particular, there is good evidence that lifestyle modifications (smoking cessation, weight reduction, aiming for a body mass index less than 25 kg/m², reduction in dietary sodium intake to 80–100 mmol/day and regular physical activity) slow kidney cyst growth and the decline in kidney function. Providing education via PKD Australia fact sheets and genetic counselling are also recommended.

Blood pressure control to slow disease progression

Hypertension is a key complication that should be identified during early adulthood. It develops in most adults and up to 20% of children.¹ Hypertension occurs due to intrarenal activation of the renin–angiotensin–aldosterone system secondary to the

Thiveya Theivendran 
Resident medical officer,
Department of Renal
Medicine¹

Alister Ramachandran
Staff specialist, Anaesthesia
and Pain Medicine, and
Director of Pain Medicine¹

Gopi Rangan 
Senior staff specialist,
Department of Renal
Medicine¹

Professor in Genetic Kidney
Disease²

¹ Westmead Hospital,
Western Sydney Local
Health District

² Michael Stern Laboratory
for Polycystic Kidney
Disease, Westmead
Institute for Medical
Research, The University of
Sydney

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Box Typical hallmarks of autosomal dominant polycystic kidney disease

- Young asymptomatic adult with a family history of autosomal dominant polycystic kidney disease
- Multiple, bilateral kidney cysts on ultrasound – meeting the Pei–Ravine unified ultrasound criteria²
- Progressive symptomatic complications in approximately 60% with ageing (kidney pain, chronic kidney disease, hypertension or kidney failure)
- Variable extrarenal complications: aneurysms (intracranial 6–20%; aortic 5%), extrarenal cysts (hepatic >90%, 5% symptomatic), diverticular disease (40%), abdominal hernias (inguinal, incisional or para-umbilical 45%) and depression (up to 60%)
- Elevated risk of premature cardiovascular disease (50%) due to hypertension, chronic kidney disease or cardiac valvular abnormalities

growth of multiple kidney cysts and endothelial dysfunction. In young adults, biannual screening of blood pressure by a healthcare provider or at home using a validated monitor is one possible approach to screening for hypertension. Early detection and treatment of hypertension have significant benefits, as they prevent left ventricular hypertrophy, reduce albuminuria and slow kidney cyst growth.

The treatment of hypertension follows standard guidelines and should be integrated with routine screening for other cardiovascular disease risk factors (such as hyperlipidaemia and impaired glucose tolerance).² The first-line drug classes for treating hypertension are blockers of the renin-angiotensin-aldosterone system (either ACE inhibitors or angiotensin receptor antagonists).² The choice of second-line drugs is tailored to specific patient circumstances. Contrary to historical opinion, the addition of thiazide diuretics or calcium channel blockers is not contraindicated as second-line drugs and they can be used in combination with angiotensin blockers.^{2,3}

In patients with early-stage disease (eGFR >60 mL/min/1.73 m²), the recommended blood pressure target is between 120/70 mmHg and 130/80 mmHg. In patients who can tolerate lower blood pressures without significant lightheadedness, a target of 110/75 mmHg can be specified.² For such lower targets, home monitoring using a validated instrument is a good method for monitoring blood pressure. In patients with advanced disease (eGFR 25–60 mL/min/1.73 m²), a blood pressure target of 120/70 mmHg to 130/80 mmHg is appropriate.²

Disease-modifying drugs to slow disease progression

Arginine vasopressin augments the postnatal growth of kidney cysts. Tolvaptan is a specific oral vasopressin type 2 receptor antagonist and is indicated in patients with ADPKD at high risk of developing kidney failure (see Pharmaceutical

Benefits Scheme reimbursement criteria, Tables 1–2). The regulatory approval was based on the results of two large phase III multicentre randomised controlled trials (TEMPO 3:4 and REPRISE), which showed that tolvaptan reduced the annual decline in the eGFR by approximately 1 mL/minute/1.73 m² compared to placebo (Table 3).⁴⁻⁶

The main adverse effect of tolvaptan is massive aquaresis (mean urine volume of 5–7 L/day) due to the off-target suppression of vasopressin-mediated water reabsorption in the collecting duct. This occurs in all patients and requires behavioural adaptation to increase daily fluid intake. At least 23% of patients eventually discontinue tolvaptan due to the impact on daily life. About 5% of patients develop reversible idiosyncratic hepatic toxicity, so monitoring of liver function is essential. It should be performed before starting treatment, monthly for the first 18 months and then three-monthly lifelong while continuing to receive tolvaptan. Maintaining adequate hydration also reduces vasopressin, but high-quality evidence indicates that drinking more than 2–2.5 L of water a day does not slow disease progression in patients with ADPKD.⁶

Pharmacological management of flank, abdominal or back pain

Flank, abdominal or back pain is experienced by 60% of patients with ADPKD before the age of 40 years. Acute and severe nociceptive flank, abdominal or back pain usually signifies an acute kidney event:

- the rupture of a kidney cyst, which is often associated with macroscopic haematuria
- a bacterial urinary tract or kidney cyst infection
- renal colic due to a kidney stone.

Appropriate investigations (imaging, midstream specimen of urine for microscopy and culture) can be used to easily diagnose these problems. In contrast, chronic flank, abdominal or back pain is complex (consisting of nociceptive, neuropathic and nociplastic

Table 1 Pharmaceutical Benefits Scheme (PBS) reimbursement criteria and indications for tolvaptan in patients with autosomal dominant polycystic kidney disease

Criteria	Specified requirements as per the PBS
Practitioner	Must be treated by a nephrologist
Kidney function	Must have an eGFR 30–89 mL/min/1.73 m ² at the time of starting drug treatment
Historical evidence of rapidly progressing kidney disease	Must have an eGFR decline of either >5 mL/min/1.73 m ² in 1 year OR >2.5 mL/min/1.73 m ² /year over 5 years

eGFR estimated glomerular filtration rate

Table 2 Prescribing considerations for tolvaptan for autosomal dominant polycystic kidney disease

Category	Prescribing considerations
Indication	To slow the progression of cyst development and renal insufficiency in adults with ADPKD and CKD Stages 1–3 with rapidly progressing disease
Targets and mechanism of action	Selective vasopressin V ₂ receptor antagonist, which reduces the reabsorption of water in the collecting duct and promotes free water diuresis. Metabolised by the CYP3A4 system
Contraindications	Elevated liver enzymes, liver injury, volume depletion, anuria, hypernatraemia, poor thirst regulation, hypersensitivity to constituents, pregnancy and breastfeeding
Limiting factors and precautions	Severe liver injury, potent aquaresis, hypernatraemia, hyperkalaemia, dehydration and hyperglycaemia
Drug interactions	CYP3A inhibitors and inducers (e.g. grapefruit juice, clarithromycin, ketoconazole, rifampicin, phenytoin, carbamazepine), P-glycoprotein inhibitors (e.g. ciclosporin and quinidine), digoxin, vasopressin analogues (desmopressin), diuretics
Adverse effects	Aquaretic symptoms (thirst, polyuria, nocturia, polydipsia), drug-induced liver injury, palpitations, constipation, dyspepsia, reduced appetite, gout, hypernatraemia, hyperuricaemia, dry skin, eczema, rash, diarrhoea
Dosage and administration	Oral route. Split-dose regimen. Initiating dose of 60 mg daily (45 mg every morning and 15 mg at night). Uptitrate dose gradually (over weeks to months) to 90 mg daily (60 mg and 30 mg split dose) and then to 120 mg daily (90 mg and 30 mg split dose), based on the patient's tolerance of aquaretic symptoms

ADPKD autosomal dominant polycystic kidney disease CKD chronic kidney disease CYP cytochrome P450

Table 3 Efficacy of tolvaptan and increased water intake on a decline in the estimated glomerular filtration rate in clinical trials⁴⁻⁶

Parameter	TEMPO 3:4 ⁴	REPRISE ⁵	PREVENT-ADPKD ⁶
Therapy investigated	Tolvaptan	Tolvaptan	Increased water intake*
Number of patients	1445	1370	184
Age (years)	18–50	18–65	18–67
Baseline eGFR (mL/min/1.73 m ²)	>60	25–65	>30
Efficacy on decline in renal function (therapy vs placebo or standard)	-2.61 vs -3.81 mL/min/1.73 m ² /year	-2.34 vs -3.61 mL/min/1.73 m ²	-2.31 vs -2.38 mL/min/1.73 m ²
Discontinuation (therapy vs placebo or standard treatment)	23% vs 14%	9.5% vs 2.2%	12% vs 16.3%
Adverse effects	Aquaresis (100%) Hepatic injury (4.9%)	Aquaresis (100%) Hepatic injury (5.6%)	Mild reversible hyponatraemia (8.7%)

* Water intake prescribed to reduce 24-hour urine osmolality below 270 mOsmol/kg
eGFR estimated glomerular filtration rate

elements). It fluctuates in intensity, duration and quality, with episodes occurring suddenly and inexplicably. This can be debilitating and cause mental and physical fatigue, reduced quality of life, and depression. The mechanisms of chronic pain are multifactorial:

- kidney capsular distension or intrarenal obstruction due to expanding cysts
- mechanical axial pain caused by an abnormal posture due to large kidneys (with some weighing up to 1–3 kg)

- pain unrelated to the kidneys (inguinal hernia, severe polycystic liver disease, gastro-oesophageal reflux or diverticulitis).

Chronic flank, abdominal or back pain in patients with ADPKD is often overlooked by healthcare providers and it should be screened for at every clinical visit. Management should begin with careful clinical assessment, including the identification of any obvious medical causes and biopsychosocial contributors, such as the presence of anxiety or depression, lack

of social support, and previous experiences of pain.⁷ Due to the lack of specific evidence, pharmacological management should follow therapeutic guidelines for managing chronic non-cancer pain (using a multidimensional approach with a sequential trial of analgesics – paracetamol, non-steroidal anti-inflammatory drugs (NSAIDs) and then adjuvants).⁷ However, there are some practice points specific for the management of ADPKD:

- the use of NSAIDs should be restricted to a maximum of five continuous treatment days per episode of pain in chronic kidney disease Stages 1–3 and on a per-case basis in Stages 4–5 to reduce the risk of precipitating acute-on-chronic kidney failure
- the analgesic dose should be modified according to the glomerular filtration rate
- in some patients, a large dominant kidney cyst (>5 cm in diameter) may be responsible for pain, and cyst aspiration by an interventional radiologist can be highly effective
- pain refractory to analgesics warrants prudent re-assessment and a consideration of referral to a pain specialist.

Conclusion

ADPKD is a common genetic kidney disease and the engagement of patients with their GP is imperative to improve long-term outcomes. In young asymptomatic patients, a focus on lifestyle modifications, the monitoring and treatment of blood pressure, and the selected use of disease-modifying drugs reduce the risk of kidney failure and cardiovascular disease. Chronic pain is a common and overlooked clinical problem in ADPKD. Recognising pain and providing effective pharmacological management can significantly improve the well-being of people with ADPKD. ◀

Conflicts of interest: Gopi Rangan was a principal investigator of grants from the National Health and Medical Research Council of Australia and conducted a clinical trial on prescribed water intake in ADPKD (GNT1138533, PREVENT-ADPKD study). He was also a principal investigator of a grant to conduct a clinical trial on prescribed water intake in ADPKD funded by Danone Research (France, manufacturer of bottled water). He is Chair, Scientific Advisory Board, PKD Australia (not-for-profit consumer group for patients with PKD). He is also a site investigator for clinical trials conducted with tolvaptan and a recipient of research grant funding from Otsuka Australia (manufacturer of tolvaptan).

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