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Key considerations for the clinical management of rapidly progressing ADPKD

Practice aid for ADPKD education

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What is ADPKD?

- Estimated prevalence of 4:10,000; most common hereditary kidney disease and **one of the most common causes of ESRD**[1]
- Characterized by **progressive cyst formation**, leading to **kidney enlargement** and **progressive loss of function**[1]
- **Mutated *PKD1*** or ***PKD2***, encoding PC1 and PC2, respectively, is the **most common genetic cause**[1,2]

Symptoms of ADPKD[2,3]

Heterogenous disease with phenotypic variability.[4] Some patients remain asymptomatic, while others have some of the following symptoms[2,3]:

- **Early onset hypertension**
- **Abdominal fullness/ pain**
- **Haematuria**
- **Cyst infection**
- **Kidney stones**
- **UTI**
- **Renal insufficiency**

Rapidly progressing ADPKD[4]

No international consensus on the definition of rapid progression.[1,4] Varying definitions include:

- ESRD before 75% of ADPKD population who would eventually reach ESRD (~62 years)
- Stage 3 CKD at <40 years
- Hypertension at <18 years
- TKV greater than expected for given age
- Multiple complications

Risk factors associated with rapid progression:[4]

- Overweight/obese (BMI ≥25 kg/m^2)[5]
- Family history of ESRD ≤55 years in multiple members with typical ADPKD
- Truncating *PKD1* mutation
- Recurrent bleeding/infection of renal cysts ≤35 years
- Hypertension ≤35 years

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Predicting rapid progression in ADPKD[4]

Tools and prognostic biomarkers	Description	Indicator of rapid progression	Region used
Mayo imaging classification	Calculates age-adjusted htTKV in patients with typical bilateral diffuse cystic kidney disease (class 1)	Class 1C–1E	
PROPKD score	Predicts likelihood of kidney failure by 60 years	Score >6	
Genetic testing	Identifies patients with mutations associated with more severe disease	Truncating *PKD1* mutation plus early symptoms	
Ultrasound	Used to measure kidney length	>16.5 cm in patients by 45 years of age	
TKV growth rate/year	Measurements by planimetry or stereology at ≥3 time points at least 6 months apart	>5% per year	
htTKV	Baseline measurement predicts GFR decrease	>600 mL/m predicts stage 3 CKD in 8 years	
eGFR slope mL/min/1.73 m^2 per year	Measures progression instead of predicting risk	• >5 mL/min in 1 year • >2.5 mL/min per year over 5 years	

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Treatments for ADPKD

Approved disease-modifying drug[6–8]	Administration[6–8]	US FDA indication[9]	European indication[10]

Tolvaptan (V2RA)	Oral, Q2D	• Adults at risk of rapidly progressing ADPKD
		  • 18–55 years: GFR ≥25 mL/min[4]
		  • >55 years and evidence of rapid progression[4]
		• **Only available through a REMS programme**
			• Adults with stage 1 to 4 CKD with evidence of rapidly progressing ADPKD
			  • 18–30 years: GFR >45 mL/min[4]
			  • 30–40 years: GFR 45–90 mL/min[4]
			  • 40–50 years: GFR 45–60 mL/min[4]
			  • 50–55 years: GFR 30–45 mL/min[4]
			• **Must be initiated/monitored under supervision of physicians with ADPKD expertise**

Emerging disease-modifying drug[1,11]	Administration[11]	Phase[11]
Bardoxolone methyl (NRF2 activator)	Oral, QD	III
GLPG2737 (CFTR modulator)	Oral, QD	II
Lanreotide (Somatostatin analogue)	SC, Q4W	III
Metformin XR (Biguanide analogue)	Oral, daily	III

Emerging disease-modifying drug[1,11]	Administration[11]	Phase[11]
Octreotide-LAR (Somatostatin analogue)	IM*, Q4W	III
Octreotide-LAR + tolvaptan (Somatostatin analogue + V2RA)	Tolvaptan: Oral, Q2D Octreotide-LAR: IM, 1 dose†	II
RGLS8429 (miR-17 inhibitor)	SC, Q2W (x7 doses)	Ib

Supportive measures: Manage hypertension first-line with ACE inhibitors or ARB[2]

*Two intragluteal injections; †dose consists of two injections.

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Aquaresis: Monitoring and management

Symptoms[9,10,12]

- Nocturia
- Thirst
- Polyuria
- Increased urinary frequency

Potential consequences[9,10]

- Hypernatraemia
- Dehydration
- Hypovolaemia

Monitor for[9,10,12]

- Weight loss (daily)
- Electrolyte imbalance (Q3M for LT treatment)
- Fluids
- Tachycardia
- Hypotension

Prevention[12]

- Start tolvaptan on **non-working day** to help adjustment
- **Increase fluid intake** throughout day and night[9,10]
- **Low sodium and protein** diet (optimal serum sodium: 135–143 mEq/L)
- Maintain **optimal blood pressure**[3]

Hold tolvaptan if:[9,10,12]

- Signs of **sodium imbalance/dehydration** (e.g. dizziness, fainting, weight loss, palpitations, confusion, weakness, gait instability)
- **Restricted access to water or** increased **water loss** (e.g. in hot weather)
- FDA: Undergoing **elective surgery** (hold treatment 24–48 hours before; restart once adequate hydration is maintained)[9]

For contraindications to the use of tolvaptan, please consult the tolvaptan PI or SmPC

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Hepatotoxicity: Monitoring and management

Symptoms[9,10]

- Abnormal liver enzymes
- Anorexia
- Dark urine
- Fatigue
- Fever
- Jaundice
- Nausea
- Pruritus
- Rash
- Right upper abdominal discomfort
- Vomiting

Potential consequences[9,10]

- Acute liver failure
- Serious hepatocellular injury

Monitoring[9,10]

LFT (ALT, AST and bilirubin levels):

- Prior to treatment
- FDA: At 2 weeks and 4 weeks after initiation
- 1–18 months: Monthly
- >18 months: Every 3 months

For liver injury symptoms (as above)

Hold tolvaptan if:[9,10]

- Symptoms of **hepatic injury**
- Clinically significant **increases in ALT/AST levels** (FDA: >2 x ULN)

Monitoring LFTs:

- Repeat **within 48–72 hours**
- Test more **frequently**
- **Reinitiate tolvaptan** with increased frequency of monitoring **once symptoms/LFTs stabilize or resolve**
  - (FDA: LFTs <3 x ULN)

Permanently discontinue tolvaptan if ALT/AST levels:[9,10]

- >8 x ULN
- >5 x ULN for >2 weeks
- >3 x ULN with persistent hepatic injury symptoms
- >3 x ULN and bilirubin >2 x ULN or INR >1.5
- FDA: >3 x ULN

For contraindications to the use of tolvaptan, please consult the tolvaptan PI or SmPC

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Abbreviations and references

Abbreviations

ACE, angiotensin-converting-enzyme; ADPKD, autosomal dominant PKD; ALT, alanine aminotransferase; ARB, angiotensin receptor blocker; AST, aspartate aminotransferase; BMI, body mass index; CKD, chronic kidney disease; CTFR, cystic fibrosis transmembrane conductance regulator; eGFR, estimated GFR; ESRD, end-stage renal disease; FDA, Food and Drug Administration; GFR, glomerular filtration rate; htTKV, height-adjusted TKV; IM, intramuscular; INR, international normalized ratio; LAR, long-acting release; LFT, liver function test; LT, long-term; NFR2, nuclear factor erythroid-2-related factor 2; PC, polycystin; PI, prescribing information; PKD, polycystic kidney disease; PROPKD, predicting renal outcome in PKD; Q2D, twice daily; Q2W, every 2 weeks; Q3M, every 3 months; Q4W, every 4 weeks; QD, once daily; REMS, risk evaluation and mitigation strategies; SC, subcutaneous; SmPC, summary of product characteristics; TKV, total kidney volume; ULN, upper limit of normal; UTI, urinary tract infection; V2RA, vasopressin V2 receptor antagonist; XR, extended release.

References

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Clinical trial numbers for emerging disease modifying drugs

Bardoxolone methyl	NCT03918447	Metformin XR	NCT04939935	Octreotide-LAR + tolvaptan	NCT03541447
GLPG2737	NCT04578548	Octreotide-LAR	NCT01377246 NCT00309283	RGLS8429	NCT05521191
Lanreotide	NCT01616927 NCT02127437				