Prescribing Tolvaptan for PKD in Scotland

Analysis, proposals, and service design

Summary

Tolvaptan is the first drug shown to slow loss of kidney function in patients with Polycystic Kidney Disease (PKD). It was licensed in Europe in 2015 and approved by NICE and SMC in Oct 2015 and Jan 2016. This document considers how to introduce its prescribing to capture those currently in the community at greatest risk of renal failure. Thereafter, at steady state we would expect to add up to 10 patients per million per year to those receiving treatment.

Background

In Autosomal Dominant Polycystic Kidney Disease, progressive cyst growth leads to enlargement of the kidneys, sometimes massive, and in many cases eventually to progressive loss of kidney function. The disease is the cause of end stage renal failure (ESRF) for 8-10% of patients on dialysis or living with a kidney transplant. The average age of patients reaching ESRF is substantially below the average for all diagnoses, at 55 years (Shaw 2014), so the majority need dialysis and transplantation during working/ child-rearing adult life.

The clinical severity in individuals is variable, risk factors for ESRF including (in approximate order of reliability)

- Loss of GFR, or rate of loss of GFR
- Kidney volume adjusted for height (ideally assessed by MRI; alternatively by CT)
- Genotype – PKD1 truncating mutations > other PKD1 mutations > PKD2 mutations
- Family history of early onset disease (ESRF before 55)
- Early symptoms or early hypertension

Loss of GFR is a relatively late change in PKD, as illustrated in Fig 1. However it typically occurs over many years; the 10 year profile shown in Fig 1 would not be unusual.

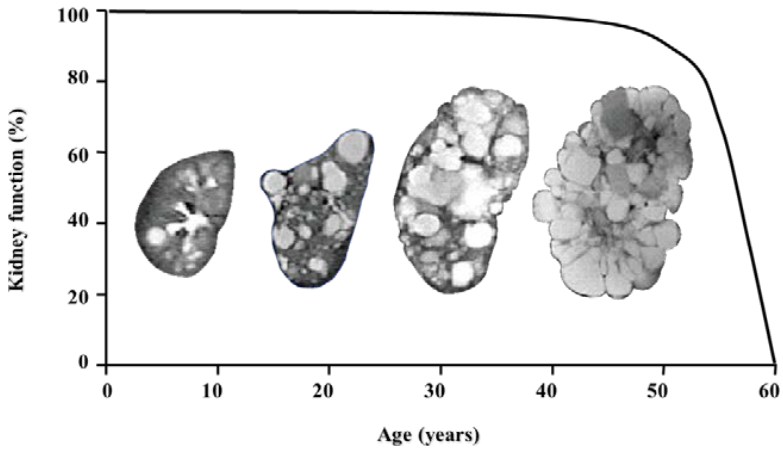

Fig 1. Indicative change in kidney size (photos of MRI scans) and GFR (line graph) with age in PKD. From EMA submission on use of TKV as a biomarker.

In addition to loss of kidney function, some patients experience significant symptoms from pain or infection in cysts, or simply from their size. PKD may cause other serious manifestations, notably subarachnoid haemorrhages, and severe involvement of the liver.

There are other, less common types of cystic kidney disease, but in these, progressive increase in kidney size is not usually a feature, and Tolvaptan is not effective in experimental models of these conditions.

Effective treatment

Until now management has been limited to general measures for care of CKD. None of these have a substantial impact on the rate of progression of CKD, as illustrated by the lack of change in the age at ESRF over the last two decades. By contrast, later ESRF has been seen in the genetic condition Alport Syndrome, progression of which is slowed by ACE inhibitors.

A number of drugs have been investigated in vitro and in vivo for ability to slow cyst enlargement, but the most promising, and the only one licensed so far, has been the ADH (AVP) receptor antagonist Tolvaptan. This drug was originally developed and investigated for management of severe hyponatraemia (for which it is in short-term occasional use), and heart failure.

TEMPO (Torres et al 2012) was a randomized, placebo-controlled study of Tolvaptan in addition to usual care that enrolled 1445 patients internationally. Two Scottish centres, Edinburgh and Inverness, participated. Patients were treated for 3 years. Results demonstrated a 50% reduction in rate of cyst growth on the drug, and a 33% reduction in rate of GFR loss in this high-risk group. Side effects were mostly predictable consequences of taking an ADH receptor antagonist (polyuria). Rare patients developed abnormalities of liver function tests. There was biochemical evidence of variable dehydration and an acute reduction in GFR in those taking the drug. Acute GFR changes were reversible and comparable to those encountered with ACE inhibition.

Some patients have now been on treatment for over 7 years. Additional observations and analysis of earlier study data have so far suggested that the suppressive effects on kidney volume continue, and that there is no limitation of effect to particular disease stages. There were minor and uncertain increases in skin cancer and glaucoma in patients on Tolvaptan. No other serious safety signals have been seen, but LFT monitoring has been intensified.

Significant symptomatic benefits were also seen for patients on active treatment, mainly in reduced kidney pain. There did not seem to be benefits for liver cysts, and there is no reason to expect benefit for other manifestations.

Tolvaptan (Jinarc™) has been approved by EMA for treatment of patients with PKD who are over the age of 18 and at CKD stages 1-3, for whom there is 'evidence of rapidly progressing disease'. SMC have echoed this recommendation. In England, NICE have restricted its availability to CKD stages 2-3. Approaches to identifying patients at high risk are suggested below.

How many patients could benefit?

Modelling for an example population of ~1 million

At steady state

The incidence of ESRF in Scotland is 100-110 patients per million. A unit covering a population of about 1 million for dialysis commences about 100+ patients per year on renal replacement therapies. An average of 9-10 of these are due to PKD. Therefore at steady state, if we were targeting patients at risk accurately, we would be starting about 10 patients per million population per year on disease-slowing treatment.

In practice, our targeting will not be so accurate. On the other hand, a significant proportion of patients will have contraindications to the drug, or prove unable to tolerate it (around 20% in research studies); and we may not be able to identify all who might benefit. Around 10 per million per year commencing the drug is therefore a reasonable estimate at steady state, but there will be a large number of patients heading for ESRF in the community who could also benefit.

Backlog

PKD progresses lifelong (Fig 1). How many might benefit is sensitive to assumptions about duration of treatment, and our ability to identify them.

We suggest that the initial focus should be on patients who are predicted to reach ESRF in less than 25 years. The treatment effect seen in TEMPO suggests that patients likely to develop ESRF in an *average of 15* years would have this extended by 5 years (to 20 years). For many this could extend their RRT-free life beyond rearing a young family; for some into retirement. Patients progressing more rapidly will have shorter extensions of ESRF-free life.

Exclusions

Some patients will have comorbid conditions, or other drugs or circumstances leading to excess risk from dehydration, that will preclude prescription of tolvaptan.

In line with EMA, NICE and SMC, we do not seek to initiate treatment in patients with low eGFR (<30 ml/min/1.73m^2) who have little to gain because ESRF is close.

There is minimal experience so far in treating children and the European licence is for adults only. However advanced PKD in childhood is rare.

Early discussions of possible protocols included an age cut-off at 50 years. A European recommendation suggests complex rules for considering age together with eGFR bands. Studies have not extended much above age 50 years but older patients are included in some now under way. However there is no reason to suspect a step change in effectiveness at 50 or any other age. We do not propose to implement fixed upper age limits, although we expect a minority of patients commencing the drug to be over 55 years.

Total number likely to be treated

We have optimistically assumed that we might identify 200 (80%) of the 250 patients pmp most likely to reach ESRF in 25 years, and that 75% of these will accept and tolerate the drug so that 150 patients will remain on treatment. We propose moving towards this total over 3 years.

Depending on experience, and the possible development of alternative or additional agents, there may be scope for later applications to extend treatment to a wider group of patients treated earlier. This would raise the possibility that some patients may be prevented from ever developing ESRF.

Total number of patients by these estimates

The upper estimate in this guidance is relatively high. The reasons for this are (1) exclusion of stage 1 CKD in England; (2) proposed upper age limits in some guidance; (3) use of a different model for identifying eligible patients – surveys of progressive PKD in populations rather than the 'hard' data for ESRF; (4) optimism about our ability to discover relatives in the community who are not currently attending renal services.

Identifying patients for treatment

Tolvaptan is approved for patients with rapidly progressing disease. Defining criteria for this has been the subject of a number of recommendations.

1. Declining eGFR

This is the most strongly predictive risk factor for ESRF, but it is a late change (see Fig. 1). Kidneys grow progressively for decades, probably usually consistently from birth, before a decline in GFR manifests. This criterion will identify a proportion of patients, but it is desirable to reduce rate of cyst growth before GFR falls.

Suggested treatment criteria (Renal Assoc draft guidance; Gansevoort et al 2016) include a documented GFR loss of ≥5ml/min/1.73m^2 in 1 year in a patient with large kidneys; or a trend of ≥2.5 ml/min/1.73m^2 per year over a period of 5 years or more. This latter would suggest a drop of eGFR from 60 to 15 over 18 years, or 90 to 15 over 30 years. This category is therefore similar to the 25 year scope proposed above.

2. Height-normalised kidney volume

Research studies aimed at identifying patients at highest risk for drug trials showed that patients with highest total kidney volumes (TKV; cysts plus renal tissue) are at greatest risk of loss of eGFR within 10 years. While the TKV at which GFR begins to decline shows substantial inter-patient variation, this variation is reduced by normalising for patient height (HtTKV) (Fig. 2).

3. Genetic testing

Mutations in *PKD1* or *PKD2* may cause PKD. *PKD2* mutations are associated with lower lifetime risk of ESRF. Truncating *PKD1* mutations are more likely to be associated with early ESRF than

other PKD1 mutations. However genetic testing for PKD is not yet routine: it is rarely required for diagnosis, and even in families with a given mutation there is considerable variation in age of ESRF. While genetic testing is used in some scoring systems for PKD risk, generally knowledge of mutation should be followed by a search for other evidence of high risk.

It is likely that increased availability and utility of testing will have a greater impact on risk assessment in the future.

4. Other symptoms and signs

Most of the symptoms and signs mentioned on page 1 as associated with early ESRF amount to soft evidence alone, but should lead to ascertainment of other risk factors.

Criteria and methodology for total kidney volume (TKV)

Ultrasound measurements have shown poor reproducibility, but the CRISP investigators found that kidney length ≥16.5 cm in patients aged under 45 predicted CKD stage 3 development within 7 years; so not a very early sign (Bhutani 2015, Cornec Le Gall 2015, Ong 2016, Gansevoort 2016). A lesser length might possibly be used to identify patients with increased kidney size for TKV measurement by MRI.

Serial measurement of kidney volumes to show rate of expansion requires multiple episodes of imaging and staff analysis, and at this stage has not been shown be more predictive than a single measurement. However risk bands are close together at young ages, so except in patients with larger kidneys, TKV should ideally be measured not before the age of 25, and may need to be repeated in 5-10 years (Fig 2) to be more confident of prognosis.

TKV can be measured by CT or MRI. MRI is preferred as kidney outlines can be clearly seen without contrast medium, and ionising radiation is avoided. For patients unsuitable for, or unable to tolerate MRI, CT without contrast is usually adequate.

The Mayo Clinic group have shown that for kidneys with typical PKD morphology (multiple evenly distributed cysts), volume can be estimated simply by measuring kidney length, width and depth, and this data can be used to put patients into risk categories (Irazabal 2015). An online calculator permits entry of these data to calculate risk for individuals: bit.ly/pkdedren or mayocl.in/1mFSfgh

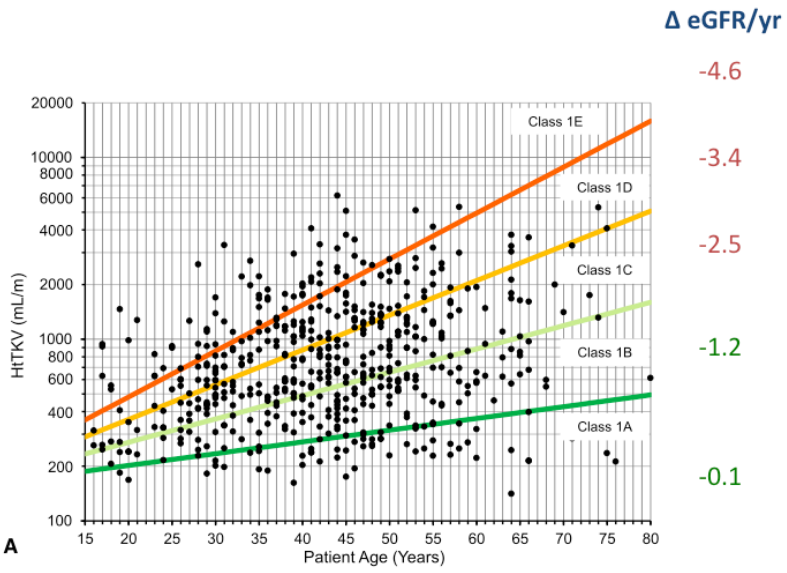

Fig 2. GFR loss in ml/min/yr/1.73m^2 over 10y predicted by a single estimation of height-normalised kidney volume (Irazabal 2015; http://1.usa.gov/1Q9sRg9)

10 year risk of ESRF in the Irazabal study was 2.4% for class 1A patients; 67% for class 1E; for younger patients 2.2% to 22.3%.

Tolvaptan for PKD

Proposed guidance for implementing treatment in Scotland

These proposals are based on current evidence for patients at high risk of progressing to ESRD, which we have interpreted as meaning at high risk of developing ESRD within 25 years. They differ from draft guidance for England (Renal Assoc 2016) in including Stage 1 CKD (excluded by NICE). They are similar to expert recommendations produced by a group of European specialists (Gansevoort 2016) (see footnote *).

Diagnosis

Patients must have a definite diagnosis of ADPKD. Other types of cystic kidney disease can generally be excluded on clinical grounds, by the classic imaging features of PKD and absence of features of other conditions. Other etiologies only occasionally cause diagnostic confusion.

Possible treatments to slow PKD should be discussed with all patients who have or may have PKD. This may influence decisions about seeking a definite diagnosis.

For patients with reduced eGFR, or a downward trend in eGFR

Consider treatment with Tolvaptan for patients over the age of 18 in whom:

- A fall in eGFR of ≥5 ml/min/1.73m^2 in one year is likely to be due to PKD, judging by grossly enlarged kidneys (will not usually need TKV), and absence of other explanations
- OR a fall in eGFR of ≥2.5 ml/min/1.73m^2 over a period of several years of observation
- AND there is no other explanation for the decline
- AND they are likely to reach ESRF in their lifetime. *

Kidney size in patients with stable GFR

For those who might accept treatment, or who are seeking prognostic information, kidney size should first be assessed by ultrasound examination. If ultrasound confirms substantial kidney enlargement (e.g. ≥15 cm in patients under 45), MRI should be requested, and TKV calculated using the calculator linked from bit.ly/pkdedren (the Mayo calculator mayocl.in/1mFSfgh is equivalent). Automated volume measurements may become a future option (Kline 2015).

In young patients, kidney length should be estimated by ultrasound around age 20-25, but earlier if kidneys are easily palpable or family/ genetic risk high. Those with normal kidney size and few cysts should be reassessed in 10 years. If there is significant increase in size, or many visible cysts, the re-scan interval should be shorter, eg 5 years.

Consider for treatment patients whose HtTKV falls into Mayo category 1C or higher (Fig 2).

For all patients

Possible risks versus benefits of treatment should be carefully considered and discussed with patients, especially if there are comorbid conditions or other risk factors for dehydration. Safety and monitoring requirements must be understood.

Management

For reasons of licensing, dose adjustment and monitoring, it will be usually be necessary to restrict prescription and management of Tolvaptan to new specialist services, probably initially located in each major renal unit.

* A European recommendation (Gansevoort 2016) has proposed complex age-GFR limits to treatment, for example excluding older patients with relatively preserved GFR. These are attempts to exclude patients unlikely to reach ESRF until their later decades. We prefer not to use specific age limits, but to base treatment on predictions of GFR trajectory combined with individually assessed and discussed risk/benefit.

Tolvaptan for PKD

Resource and management requirements

Implementing the policy described will incur additional needs for advice, clinic visits (mainly during the first 18 months of treatment) and for monitoring; and will create a need for some additional investigations.

Specialist PKD Clinic

Requirements for staff training, patient counselling and advice, hospital-based prescribing and ongoing monitoring make it desirable to manage patients in a specialist, multi-professional clinic.

- This clinic may also review occasional patients with possible PKD, or difficult questions around PKD. More of this work is likely to arise by correspondence, email and telephone.
- Patients not falling into the high-risk bracket will usually remain at their regional or usual general nephrology clinic.
- Patients unable to tolerate the drug will usually return to their regular clinic.
- The need for continuing to attend the clinic after the period of required intensive monitoring will be reviewed.

The tasks for the specialist clinic will include

- Confirm eligibility for treatment
- Discuss issues around taking the drug, including
    - Discuss side effects and possible risks
    - Ensure patients understand management, notably including
    - Need to drink plenty, plus extra when thirsty
    - When to omit the drug to prevent dehydration
    - Need for monthly liver function tests during the first 18 months of therapy
    - For pre-menopausal women, importance of contraception during treatment
- Prescribe the drug
- Monthly check on LFTs before issuing next prescription
- Genetic testing and advice as indicated, in conjunction with Clinical Genetics
- Investigation and management of PKD renal and other complications
- Attention to CKD issues (blood pressure, cardiovascular risk, bone disease prophylaxis, anaemia if relevant).
- Referral to appropriate services in preparation for dialysis and transplantation

Resourcing

Staff and clinic needs (modelled for Edinburgh, population ~1M)

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Pharmacist (FTE)	0.1	0.2	0.2	0.1	0.1	0.1
Specialist nurse (FTE)	0.3	0.4	0.5	0.3	0.3	0.3
Consultant (FTE)	0.4	0.4	0.3	0.2	0.2	0.2
Number on therapy *	50	100	150	160	170	180
Treatment starts *	55	60	60	20	10	10
Visits per month to start	7	8	8	3	2	2
Monthly monitoring visits/ mo *	50	90	90	50	20	15
Long term ~3/yr / mo	0	8	16	34	40	43
Other clinic appts / mo	4	4	4	4	4	4
Total clinic visits/ mo *	**60**	**110**	**120**	**90**	**66**	**64**
Clinics/ month	1 -> 4	6	6	4	4	4

* by end of each year

Assumptions:

- continuing prescribing via hospital
- nurse management of monitoring
- nurse and pharmacist counselling
- dose titration managed remotely by nurse practitioner
- monthly monitoring visits months 0-18, reducing to 3-6 monthly (average 4) thereafter (cf average approx 6 monthly now).
- Team members are available working in other areas during most of each week.

Additional investigations

In order to identify the approximately 150 patients falling into the risk category for treatment we estimate that

- 30 may be eligible on the basis of declining eGFR alone
- 20 of the remainder may have adequate imaging already to determine that they are eligible
- 100 patients may be identified by MRI scans to determine TKV
- These patients will be identified over 3 years @ up to 100 scans per year – assumes a ratio of 1:2 eligible:ineligible for treatment on size criteria.
- We propose to use ultrasound pre-screening to keep this ratio high. Many of these investigations are already requested but kidney length is not consistently reported: it is difficult to estimate the increase in ultrasound requests until we look further, but there will again be 2-3y of catch-up.

We are commencing an audit project to test these assumptions and figures

Further info

edren.org/gotpkd is a landing page for patients, GPs and others seeking information about PKD, getting a diagnosis, and ascertaining risk and whether treatment may be indicated. It points to detailed information for patients (at edren.org/info – Polycystic Kidney Disease), and to the algorithm and protocol at bit.ly/pkdedren

bit.ly/pkdedren describes the Edinburgh algorithm and principles for assessing patients. The latest version of this document can be downloaded from the foot of that page, as can the detailed guidance for implementation in Edinburgh. This is part of the Edren Handbook, edren.org/handbook

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