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NDT Perspectives

Recommendations for the use of tolvaptan in autosomal dominant polycystic kidney disease: a position statement on behalf of the ERA-EDTA Working Groups on Inherited Kidney Disorders and European Renal Best Practice

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ABSTRACT

Recently, the European Medicines Agency approved the use of the vasopressin V2 receptor antagonist tolvaptan to slow the progression of cyst development and renal insufficiency of autosomal dominant polycystic kidney disease (ADPKD) in adult patients with chronic kidney disease stages 1–3 at initiation of treatment with evidence of rapidly progressing disease. In this paper, on behalf of the ERA-EDTA Working Groups of Inherited Kidney Disorders and European Renal Best Practice, we aim to provide guidance for making the decision as to which ADPKD patients to treat with tolvaptan. The present position statement includes

a series of recommendations resulting in a hierarchical decision algorithm that encompasses a sequence of risk-factor assessments in a descending order of reliability. By examining the best-validated markers first, we aim to identify ADPKD patients who have documented rapid disease progression or are likely to have rapid disease progression. We believe that this procedure offers the best opportunity to select patients who are most likely to benefit from tolvaptan, thus improving the benefit-to-risk ratio and cost-effectiveness of this treatment. It is important to emphasize that the decision to initiate treatment requires the consideration of many factors besides eligibility, such as contraindications, potential adverse events, as well as patient motivation and lifestyle factors, and requires shared decision-making with the patient.

Keywords: ADPKD, tolvaptan, vasopressin V2 receptor antagonist

INTRODUCTION

Autosomal dominant polycystic kidney disease (ADPKD) is the most common hereditary kidney disorder [1, 2], accounting for ∼10% of European patients on dialysis or living with a renal transplant [3]. Approximately 70% of patients with ADPKD progress to end-stage renal disease (ESRD) at a median age of 58 years [4]. ADPKD is genetically heterogeneous and is associated with a high degree of inter- and intra-familial variability in disease course. The 85% of patients with *PKD1* mutations typically display a more severe disease course, especially when they have truncating mutations, with ESRD occurring 20 years earlier than in the 15% of patients with *PKD2* mutations [5].

ADPKD is characterized by the progressive development and growth of numerous bilateral renal cysts, resulting in urine concentration defects, hypertension, acute and chronic pain, kidney stones, haematuria, cyst and urinary tract infections, and, most importantly, renal function loss [6, 7]. Cyst development and growth usually start *in utero* and are continuous, but kidney function is typically conserved until the age of 30–40 years. Compensatory hyperfiltration by glomeruli serving non-cystic tubules maintains the glomerular filtration rate (GFR) of affected patients within a normal range for prolonged periods of time [7, 8].

Until recently, no interventions were shown to slow the rate of disease progression in ADPKD [9]. The treatment of ADPKD has therefore been symptomatic, with the aim of reducing morbidity and mortality associated with disease manifestations [9]. This changed with the publication of the TEMPO 3:4 trial, which tested the efficacy of the vasopressin V2 receptor antagonist tolvaptan [10]. In this trial, 1445 patients with ADPKD were randomized to receive either placebo or tolvaptan in a split-dose regimen of 45 mg in the morning and 15 mg in the afternoon, uptitrated to 90/30 mg when tolerated. The trial duration was 3 years, which is typical for trials investigating renoprotective effects of medical interventions [11–14]. Per protocol, all patients were advised to increase fluid intake. Inclusion criteria were age 18–50 years, an estimated creatinine clearance (eCrCl) (Cockroft-Gault) ≥60 mL/min and a total kidney volume (TKV) ≥750 mL. Study medication was discontinued in 23% of tolvaptan- and 14% of placebo-treated patients. The intention-to-treat analysis of this study showed that tolvaptan slowed the rate of TKV growth (primary endpoint) by 49% from 5.5 to 2.8% per year, and the rate of estimated GFR (eGFR) loss on treatment (secondary endpoint) by 26% from 3.70 to 2.72 mL/min/1.73 m^2 per year during the median observation period of 3 years [10]. Provided that this effect was maintained, it would translate into every 4 years of treatment delaying the incidence of ESRD by approximately one additional year. The renoprotective efficacy of tolvaptan in ADPKD compares well with the 15% reduction in eGFR decline (5.2 versus 4.4 mL/min/1.73 m^2 per year) and 15% reduction in creatinine clearance decline (6.5 versus 5.5 mL/min/1.73 m^2 per year) in the RENAAL and IDNT trials, respectively, which tested angiotensin-2 receptor antagonists in patients with type 2 diabetes and kidney disease [13, 14], and with the 35% reduction in decline in creatinine clearance in the study that tested angiotensin-converting enzyme inhibition in patients with type 1 diabetes and kidney disease [11]. Withdrawal from active treatment in these trials was 47, 24 and 19%, respectively [11, 13, 14].

Traditionally, the primary endpoint in trials testing renoprotective effects of interventions has been the incidence of ESRD or doubling of serum creatinine, which correlates to a 57% reduction in eGFR. Of note, ADPKD is a relatively slowly progressive disease. In a population such as that of the TEMPO 3:4 trial, which was selected to have early-stage ADPKD (eCrCl >60 mL/min), it cannot be expected that this endpoint will occur within the typical duration of a renal trial. Adopting this endpoint would therefore only pick up cases of acute kidney injury and not be of help for studying the effect of interventions on progression of the disease itself. To stimulate progress in developing renoprotective agents, especially for studies in early-stage chronic kidney disease (CKD) and diseases that are relatively slow in progression, the nephrological community has pleaded for the use of alternative endpoints for renal trials, namely lesser declines in eGFR [15, 16]. Regulatory authorities have accepted this proposal [17]. When studying the incidence of a 25% reduction in eGFR [*a priori* defined in the TEMPO 3:4 trial and accepted by the European Medicines Agency (EMA)], there was a significant 61% relative risk reduction with tolvaptan (number needed to treat to prevent one event was ∼11) [10].

Based on the results of the TEMPO 3:4 trial, the EMA approved in May 2015 the use of tolvaptan (JINARC®) for ADPKD [18]. The regulatory authorities in Japan, Canada, Korea and Switzerland recently also granted marketing authorization, whereas in the USA the Food and Drug Administration asked in 2014 for additional efficacy and safety data [19].

NEED FOR GUIDANCE ON IDENTIFYING PATIENTS FOR TREATMENT

According to the EMA label, tolvaptan 'is indicated to slow the progression of cyst development and renal insufficiency of ADPKD in adults with CKD stages 1–3 at initiation of treatment with evidence of rapidly progressing disease'. This indication incorporates two issues that need clarification: first, the CKD stage and age that qualify patients for treatment, and second, how to define 'evidence of rapidly progressing disease'.

To date, there have been no widely accepted clinical guidelines for the treatment of ADPKD. With tolvaptan having now been granted marketing authorization in the EU, there is a need for treatment guidance that is applicable to clinical practice. In this paper, on behalf of the ERA-EDTA Working Groups of Inherited Kidney Disorders (WGIKD) and European Renal Best Practice (ERBP), we aim to provide guidance for making the decision as to which ADPKD patients to treat with tolvaptan. The present position statement includes a series of recommendations, which result in a hierarchical decision algorithm encompassing a sequence of risk-factor assessments in a descending order of reliability. By examining the best-validated markers first, we aim to identify ADPKD patients with demonstrated rapid disease progression or likely rapid disease progression, who may be considered for treatment with tolvaptan. Patients who are identified as having possible rapid disease progression should not be started on treatment, but can be followed to reassess the indication for start of treatment after 3–5 years. In addition, this algorithm will help to screen out those who are ineligible. It is important to emphasize that the decision to initiate treatment requires the consideration of many factors besides eligibility, such as contraindications, potential adverse events, as well as patient motivation and lifestyle factors, and requires shared decision-making with the patient.

CKD STAGE AND AGE AT THE INITIATION OF TREATMENT

The EMA label for tolvaptan allows the treatment of patients with CKD stages 1–3, i.e. with an eGFR of >30 mL/min/1.73 m^2. One of the inclusion criteria for the pivotal TEMPO 3:4 trial was a creatinine clearance as estimated with the Cockroft-Gault equation ≥60 mL/min/1.73 m^2 [10]. Due to tubular creatinine secretion, creatinine clearance overestimates GFR by ∼20% [20]. Consequently, the TEMPO 3:4 trial included a considerable number of ADPKD patients ($n = 247$; 17%) with an eGFR, as determined by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation, of <60 mL/min/1.73 m^2. A *post hoc* analysis indicated that in these patients, treatment efficacy was similar or even slightly better than in those with higher eGFR [10]. However, the number of patients with CKD stage 3b, i.e. an eGFR of 30–45 mL/min/1.73 m^2, was small ($n = 42$; 3%). The REPRISE study investigating the value of tolvaptan in 1300 patients with lower levels of eGFR (25–65 mL/min/1.73 m^2) is ongoing [21]. It is our opinion that until the results of this study become available, information on the benefit-to-risk ratio of tolvaptan in patients with 30–45 mL/min/1.73 m^2 (CKD stage 3b) is too limited to warrant treatment.

The UK National Institute for Health and Care Excellence (NICE) recommends excluding patients with CKD stage 1 from treatment [22]. The exclusion of this subgroup is based on a cost-effectiveness analysis that was performed using data on the change in eGFR of patients participating in the TEMPO 3:4 trial. These data were used to model lifetime risk for ESRD in placebo- and tolvaptan-treated patients per CKD stage. The effect of tolvaptan in decreasing the rate of change in eGFR was 16, 29 and 31% in CKD stages 1, 2 and 3, respectively [23]. These data seem to suggest that tolvaptan has less renoprotective efficacy in CKD stage 1. However, change in eGFR is a less valid outcome measure to assess treatment effect in early-stage ADPKD. As expected, patients with CKD stage 1 in the TEMPO 3:4 trial were younger. Because of the fact that in ADPKD patients, eGFR can remain stable for a relatively long time before progressing towards ESRD, it is difficult to assess the efficacy of treatment on disease progression when using change in eGFR as the outcome. When using change in TKV instead, no lesser effect was observed in patients with CKD stage 1. The decreases in the rate of TKV growth on tolvaptan versus placebo were 40, 60 and 40% in CKD stages 1, 2 and 3, respectively [23]. Given these data, we believe that, at present, there are no indications suggesting that tolvaptan is less effective in delaying disease progression in young ADPKD patients with CKD stage 1. However, it should be emphasized that the use of tolvaptan in this patient category should be limited to those who are likely to have rapidly progressing disease (see below).

According to the label of tolvaptan, all ADPKD patients older than 18 years are eligible for treatment. However, we believe that an age >50 years argues against initiation of this drug, for two main reasons. First, the age inclusion range in the TEMPO 3:4 trial was 18–50 years [10]. Consequently, information on the benefit-to-risk ratio of starting tolvaptan in individuals older than 50 years is lacking. Second, ADPKD progresses steadily over time and thus markers of disease severity and prognosis must be interpreted in conjunction with age. In our opinion, ADPKD patients with a relatively high eGFR for their age group are unlikely to show rapid disease progression. This would argue against treating patients aged >50 years who still have an eGFR >45 mL/min/1.73 m^2 (CKD stages 1–3a), which is the minimum eGFR level for start of treatment, because these patients have a high probability of slowly progressive disease. Likewise, we also recommend not to treat patients aged 40–50 years who have an eGFR >60 mL/min/1.73 m^2 (CKD stages 1 and 2), or patients 30–40 years who have an eGFR >90 mL/min/1.73 m^2 (CKD stage 1). Of course, this advice should be interpreted with caution. The concept that biological rather than chronological age is important is gaining increased attention in medicine, and should also be considered in the context of these recommendations. Thus, in individual cases, it may therefore be prudent to base the assessment of whether or not to start treatment also on a global risk profile and to allow some flexibility, also taking into account patient motivation.

Recommendation 1.1: *We suggest that tolvaptan can be prescribed to adult ADPKD patients aged <50 years with CKD stages 1–3a (eGFR >45 mL/min/1.73 m^2) who have demonstrated or who are likely to have rapidly progressing disease, but that CKD stage must be interpreted in conjunction with age.*

Recommendation 1.2: *We recommend not starting tolvaptan in patients aged 30–40 years with CKD stage 1 (eGFR >90 mL/min/1.73 m^2).*

Recommendation 1.3: *We recommend not starting tolvaptan in patients aged 40–50 years with CKD stages 1 or 2 (eGFR >60 mL/min/1.73 m^2).*

EVIDENCE OF RAPID DISEASE PROGRESSION

General considerations

While the EMA does not state why the indication for tolvaptan use focuses on patients with rapidly progressing disease, it is plausible that the benefit-to-risk ratio is highest in such patients. In contrast, patients who are slowly progressive would receive long drug exposure for little or no benefit. However, no official recommendations are provided as to who qualifies as having 'rapid disease progression'.

The main renal outcome of ADPKD is ESRD. The underlying premise to define rapidly progressing disease should therefore, in our opinion, be progression to ESRD at an early age. Unfortunately, there is no generally accepted definition of early-onset ESRD in ADPKD. However, it seems logical to define it as occurring before the average age for initiation of renal replacement therapy (RRT) in ADPKD, which in Europe is around 58 years of age [4].

A number of studies have tried to identify markers that can predict rapid progression to ESRD in ADPKD [24, 25]. Figure 1 shows that a wide variety of markers has been considered, but in the present article we will concentrate on those that are better validated (highlighted in Figure 1), bearing in mind that not all factors are independent. The most important ones are kidney function (as assessed by eGFR) and TKV.

As discussed above, measurement of change in eGFR during early-stage ADPKD is of limited value for predicting disease progression, because kidney function remains relatively stable in the near-normal range for prolonged periods of time. In contrast, TKV typically increases from the very early stages of the disease, usually long before renal function declines. Importantly, it was shown that change in TKV predicts a subsequent change in eGFR [26], and that both the change in TKV over time and baseline TKV predict a future rate of eGFR loss [26–30].

Despite the clear association of TKV with renal function decline in patient groups, there is significant interindividual variability, and renal function remains the more relevant parameter for assessing disease severity and prognosis. For instance, when a young ADPKD patient already has impaired kidney function, without a possible cause other than ADPKD, this indicates severe disease, independent of the TKV. Likewise, when an older ADPKD patient has excellent kidney function, this indicates mild disease, irrespective of TKV. For this reason, the working groups have given more weight to kidney function than to TKV in the design of the treatment decision algorithm. It should be noted, however, that specifically in young patients with CKD stage 1, kidney function may be less sensitive for assessment of disease severity, progression and prognosis (see below).

Documented change in GFR to define rapid disease progression

GFR can be measured by calculating the clearance of exogenous filtration markers, such as iothalamate or iohexol (mGFR), or estimated using equations that incorporate serum concentrations of endogenous filtration markers and demographic variables (eGFR). In the TEMPO 3:4 trial, serum creatinine level was used to estimate GFR, applying the CKD-EPI equation [31]. This is in accordance with clinical practice. One study concluded that, in ADPKD, equations used to estimate GFR may be less reliable and may fail to detect changes in GFR over time [32]. Two other reports, however, showed that equations to estimate GFR perform as well in ADPKD as in non-ADPKD CKD, suggesting that these equations can be used in clinical care of ADPKD patients [33, 34]. Although potentially valuable, measurement of GFR using exogenous markers such as iothalamate or iohexol will probably be limited to research settings and individual patients in whom muscle mass is obviously abnormal for age and/or stature, because of the costs and limited availability of such measurement methods.

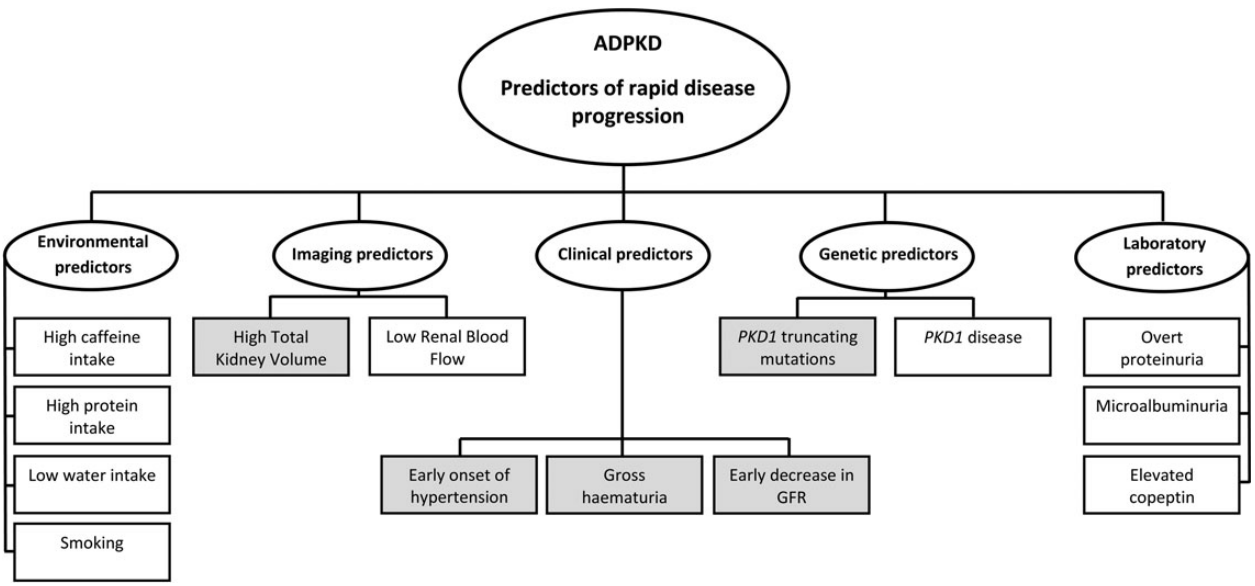

FIGURE 1: Markers used to assess prognosis in ADPKD. Shaded rectangles represent the best-validated markers (adapted from ref. [24]).

Taking the natural variation in kidney function and measurement error in creatinine determination into consideration, small changes in eGFR may not reflect a true decline in renal function, especially in early CKD stages when a relatively small change in creatinine may result in a relatively large change in eGFR. To confidently identify 'rapid disease progression', the rate of eGFR decline should therefore be supported by multiple measurements. For this reason, this criterion should also be defined more strictly when historical data are available for only a short period instead of a longer period. Consequently, rapid disease progression may be identified by a confirmed eGFR decline ≥5 mL/min/1.73 m^2 within 1 year, as suggested by the KDIGO CKD Guideline [35], or by an average annual eGFR decline of ≥2.5 mL/min/1.73 m^2 over a period of 5 years, which is comparable to the decline in eGFR in class 1C patients of the Mayo classification of ADPKD (see below) [30].

It should be emphasized that, in ADPKD patients aged <30 years with CKD stage 1, the observation of 'no change in eGFR' in general is not considered a reliable predictor of slow disease progression, because eGFR can remain fairly stable during a prolonged period of time, whereas TKV increases steadily. In such patients, changes in TKV and/or prediction models should be used to assess or predict disease progression.

Importantly, when 'evidence of rapid disease progression' is based on historical eGFR data, the decline in renal function should be due to ADPKD and not related to other diseases, medications or factors that may contribute reversibly or irreversibly to the loss of renal function [e.g. diabetes mellitus, non-steroidal anti-inflammatory drugs (NSAIDs), calcineurin inhibitors, dehydration or contrast agents].

Recommendation 2: *A confirmed annual eGFR decline ≥5 mL/min/1.73 m^2 in 1 year, and/or ≥2.5 mL/min/1.73 m^2 per year over a period of 5 years, defines rapid progression.*

Documented change in TKV to define disease progression

The increase in TKV corresponds to an increase in total cyst volume, with exponential cyst enlargement being predictable within individual patients [27, 28]. Methods that reliably and accurately measure TKV have been developed using magnetic resonance imaging (MRI) and computed tomography (CT). Non-contrast MRI is preferable over CT on safety grounds, because it avoids radiation exposure [36]. It has been shown that, when using MRI, a change in TKV can reliably be detected after a period of 6 months [37]. However, because of intra-individual and intra-observer variability in TKV measured by MRI, we advise assessing changes in TKV by repeated measurements, especially when measurements are performed within a shorter period of time (three or more times, preferably 6–12 months apart). Although MRI measurement of TKV is accurate, and also fast and easy to calculate when using the ellipsoid equation to derive volume [36, 38], reimbursement policies and healthcare organizations may limit access to repeated MRI scans that would allow TKV change to be measured. Measuring TKV sequentially using ultrasound may be more feasible, but this technique is expected to be associated with too much variability to reliably assess change in TKV, although this has not been formally studied.

The working groups recommend adopting an established TKV growth rate ≥5% per year, preferably measured by MRI, for defining rapid progression, which is likely to be a conservative threshold. This recommendation is supported by the 4.5% growth rate threshold defining Mayo class 1D patients (see below) [30], and the average TKV growth in studies of ADPKD patients with preserved renal function has been measured as ∼5.0–5.5% per year [10, 27, 28, 37]. This criterion of ≥5% TKV growth per year has also been advocated by the Japanese regulatory authorities to define patients eligible for treatment [39]. It is expected that only a few patients will qualify for tolvaptan treatment based on this criterion of historical change in TKV, because in clinical practice serial MRI data will at present be available in only a limited number of patients.

Recommendation 3: *A TKV increase of >5% per year by repeated measurements (preferably three or more, each at least 6 months apart and by MRI), defines rapid progression.*

Risk prediction using a single TKV value

Historical patient data on eGFR and/or TKV changes to assist decision-making are not always available. In such cases, prospective testing or risk prediction using data available at the moment of assessment may be required.

The implications of large kidneys relate not only to disease progression, but also to patient stature and age. A certain TKV obviously has different meaning in patients with large versus small stature, and similarly, different meaning in a young versus an old subject. TKV should therefore be adjusted for height and age. This concept was recently used by Irazabal *et al.* [30] to develop a risk prediction tool. This risk prediction tool is based on data from 590 ADPKD patients from the Mayo Clinic Translational PKD Center with CT/MRI scans available and three or more eGFR measurements over ≥6 months of follow-up. Patients were classified radiologically as typical (class 1 patients, $n = 538$) or atypical (class 2 patients, $n = 52$), where 'typical' means those with bilateral and diffuse cyst distribution in both kidneys, with mild to severe replacement of kidney tissue by cysts, and all cysts contributing similarly to TKV. Patients with 'atypical' disease are those who do not fulfil the criteria for 'typical' disease, and represent ∼5–10% of ADPKD patients [30]. The 'typical' patients were randomly partitioned into a development and an internal validation set, and subclassified according to height-adjusted TKV (htTKV) ranges for age (labelled 1A–1E). Thus, a model was developed to classify ADPKD patients according to prognosis (Figure 2). The proposed classification was able to predict eGFR decline and progression to ESRD in patients with typical ADPKD over a broad range of CKD stages, even in patients at early stages of the disease with preserved renal function. eGFR slopes over time were significantly different between subclasses and, except for class 1A patients, different from those in healthy kidney

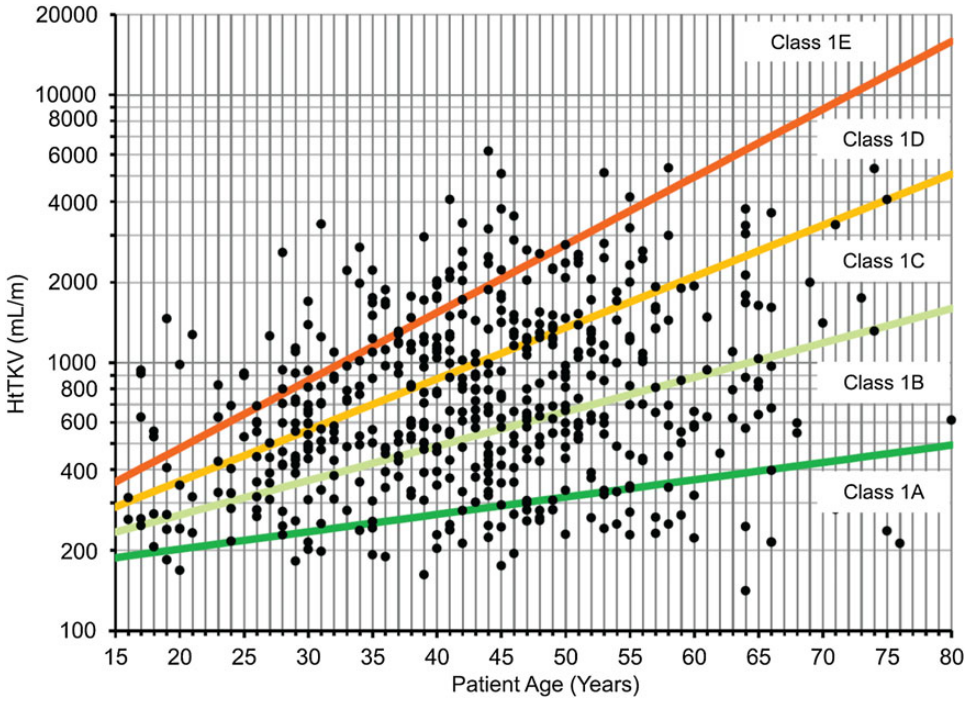

FIGURE 2: The Mayo classification for prediction of disease progression in ADPKD by htTKV and age. In general, class 1C, 1D and 1E patients will have rapid disease progression and qualify for treatment (derived from ref. [27]). Limits are defined based on estimated TKV growth rates of 1.5, 3.0, 4.5 and 6.0% per year. Estimated slopes of eGFR loss by subclass (1A–1E) are −0.1, −1.2, −2.5, −3.4 and −4.6 mL/min/1.73 m^2 per year, respectively, with no significant differences between men and women. The incidence of ESRD at 10 years increased by subclass (1A–1E), being 2.4, 11.0, 37.8, 47.1 and 66.9%, respectively [30].

donors. The frequency of ESRD at 10 years increased from subclass 1A (2.4%) to 1E (66.9%) [30]. These findings were confirmed using data of another, independent cohort (CRISP) [30]. Patients with Mayo classes 1C, 1D and 1E are thus predicted to have rapid disease progression and, accordingly, would qualify for treatment in cases where historical data on the rate of disease progression are lacking or not reliable, and if patient age and eGFR are within the appropriate strata. A calculator to estimate htTKV and classify patients with typical ADPKD according to this classification scheme is available online [40]. Patients with atypical disease, in general, show slowly progressive disease, which does not warrant treatment.

Using ultrasound to measure kidney volume is less expensive and more accessible than MRI, but is hampered by operator-dependency and low resolution [41]. Notwithstanding, the CRISP studies suggested that a kidney length of 16.5 cm as measured by ultrasound qualifies patients younger than 45 years as having rapidly progressing disease [41]. A comparison of ultrasound and MRI suggested that using either modality, kidney length was able to predict disease progression. The optimal cutoff for predicting the development of CKD stage 3a over a period of 8 years using ultrasound was a kidney length of >16.5 cm (sensitivity 85% and specificity 92%) [41]. Importantly, in this study, ultrasound-derived kidney length was not normalized for height or age of the patient, which, as reasoned above, is likely to be important. Given these considerations, it is our opinion that ultrasound-measured kidney length may be useful to identify young ADPKD patients with clearly enlarged or small kidneys for their height and age, in whom MRI may not be required. In other cases, we suggest the use of MRI to accurately measure TKV and predict the rate of disease progression.

Recommendation 4.1: *We recommend the use of the Mayo classification of ADPKD that makes a distinction between 'typical' and 'atypical' morphology and adjusts TKV in patients with 'typical' morphology for age and height to define five classes of patients according to prognosis (1A–1E).*

Recommendation 4.2: *We suggest that in ADPKD patients with Mayo classes 1C–1E disease (corresponding to a predicted eGFR decrease ≥2.5 mL/min/1.73 m^2 per year), rapid disease progression is likely.*

Recommendation 4.3: *We suggest that in patients with atypical morphology of ADPKD, as described in the Mayo classification, rapid disease progression is unlikely.*

Recommendation 4.4: *We suggest that in a patient with age <45 years and a kidney length of >16.5 cm as assessed by ultrasound, rapid disease progression is likely.*

Risk prediction using genetic and clinical factors

As previously described, in ADPKD the genotype provides prognostic information. On average, patients with *PKD1* mutations, especially truncating *PKD1* mutations, show a significantly faster progression to ESRD than those with *PKD2* mutations [5]. A cross-sectional study of 1341 patients from the Genkyst cohort has been used to establish the

Table 1. The PRO-PKD score to assess prognosis in ADPKD (derived from ref. [42])

Being male: 1 point
Hypertension before 35 years of age: 2 points
First urological event (macroscopic haematuria, flank pain or cyst infection) before 35 years of age: 2 points
PKD2 mutation: 0 points
Non-truncating *PKD1* mutation: 2 points
Truncating *PKD1* mutation: 4 points
A score of ≤3 excludes progression to ESRD before the age of 60 years with a negative predictive value of 81.4%.
A score of >6 predicts rapid disease progression with ESRD onset before the age of 60 years with a positive predictive value of 90.9%.
For those with an intermediate score (4–6 points), the prognosis is unclear.

'PRO-PKD' risk-scoring system on the basis of PKD mutation as well as clinical parameters [42]. Using multivariate survival analysis to identify variables significantly associated with age at ESRD onset, a scoring system was developed that gives a value ranging from 0 to 9. This scoring system is shown in detail in Table 1. A score of ≤3 excludes progression to ESRD before the age of 60 years with a negative predictive value of 81.4%, and a score of >6 predicts ESRD onset before the age of 60 years with a positive predictive value of 90.9%. For those with an intermediate score (4–6 points), the prognosis is unclear [42]. The limited availability and the significant costs of genetic analysis in ADPKD still represent barriers to the incorporation of this analysis into standard clinical practice. While genetic testing is at present advised in only a limited number of situations and is certainly not mandatory for defining a treatment indication, it may gain importance in the future, because of the potential therapeutic consequences. In those cases in which information on specific PKD mutations is available from routine care, this information, in conjunction with clinical findings and symptoms, may help to predict prognosis using the PRO-PKD score.

Recommendation 5: *We suggest that in patients with a truncating PKD1 mutation in conjunction with early onset of clinical symptoms, consistent with a PRO-PKD score of >6, rapid disease progression is likely.*

Risk prediction using family history

Although intra-familial variability occurs with respect to the age at start of RRT [43], a detailed family history can provide important information for risk prediction. It has been shown that an ADPKD patient with two first-degree family members reaching ESRD before the age of 58 years has a high sensitivity (75%) and specificity (100%) for being affected by a *PKD1* mutation [44]. This suggests that a patient, who does not qualify for the initiation of treatment by the recommendations above, but has a family history of most affected members reaching ESRD before the age of 58 years, may be at risk for rapid disease progression. In such patients, the markers that may indicate treatment initiation should be reassessed every 3–5 years.

Recommendation 6: *We suggest patients with a family history of ESRD before age 58 years be reassessed for rapid disease progression on a 3–5 yearly basis.*

AN ALGORITHM TO ASSESS ELIGIBILITY FOR TOLVAPTAN TREATMENT IN ADPKD

A hierarchical algorithm may be of help to assess whether ADPKD in patients is rapidly progressing or likely to be rapidly progressing, taking into account documented kidney function (eGFR) decline, documented (ht)TKV growth and other clinical factors as discussed above (Figure 3). This algorithm starts with the most reliable markers of progression, moving on to less definitive indicators in cases where historical data on eGFR decline or TKV growth are not available or not reliable. Given the constraints on patient testing, we believe that this procedure offers the best opportunity of identifying patients with rapidly progressing disease who are most likely to benefit from therapy, thus improving the benefit-to-risk ratio and cost-effectiveness of treatment.

Initiating treatment with tolvaptan should be considered for patients having demonstrated rapid progression, or who are likely to have rapid progression. For patients with possible rapid progression, additional information should be sought before treatment is initiated, for example by *ad hoc* assessment of htTKV or genotype, or subsequent monitoring for changes in eGFR and/or TKV. Patients with possible rapid progression should be re-evaluated for treatment every 3–5 years, or earlier if new, relevant patient data or better prediction models become available.

Recommendation 7: *We suggest using a hierarchical decision algorithm to assess whether ADPKD patients are rapid progressors or likely to be rapid progressors, and accordingly may qualify for treatment.*

CONTRAINDICATIONS, SPECIAL WARNINGS AND PRECAUTIONS

Besides a careful assessment of which patients may benefit most from tolvaptan, other considerations should be taken into account when considering prescribing this drug, including the contraindications to its use in ADPKD. These are summarized in Table 2 [45].

A special warning relates to potential liver toxicity. During tolvaptan use, an increased incidence of liver function test abnormalities was observed. An alanine transaminase (ALT) and aspartate transaminase (AST) level at least three times the upper limit of normal (ULN) was observed in 4.4 and 3.1% of tolvaptan-treated patients, respectively, compared with 1.0 and 0.8% of placebo-treated patients [10]. In addition, three ADPKD patients showed a 2-fold rise in bilirubin alongside a 3-fold rise in transaminases (so-called Hy's Law cases) [45, 46]. The simultaneous increase in transaminases and bilirubin is considered as a high-risk signal, since the hepatic capacity to excrete bilirubin is high and any impairment of this capacity in conjunction with an increase in transaminases is considered to be associated with the risk for severe hepatic side effects [47]. Nearly all cases of liver function test abnormalities occurred during the first 18 months of treatment [46]. Based on the incidence of the Hy's Law cases, it has been estimated that per 10 000 treated patients potentially three cases of

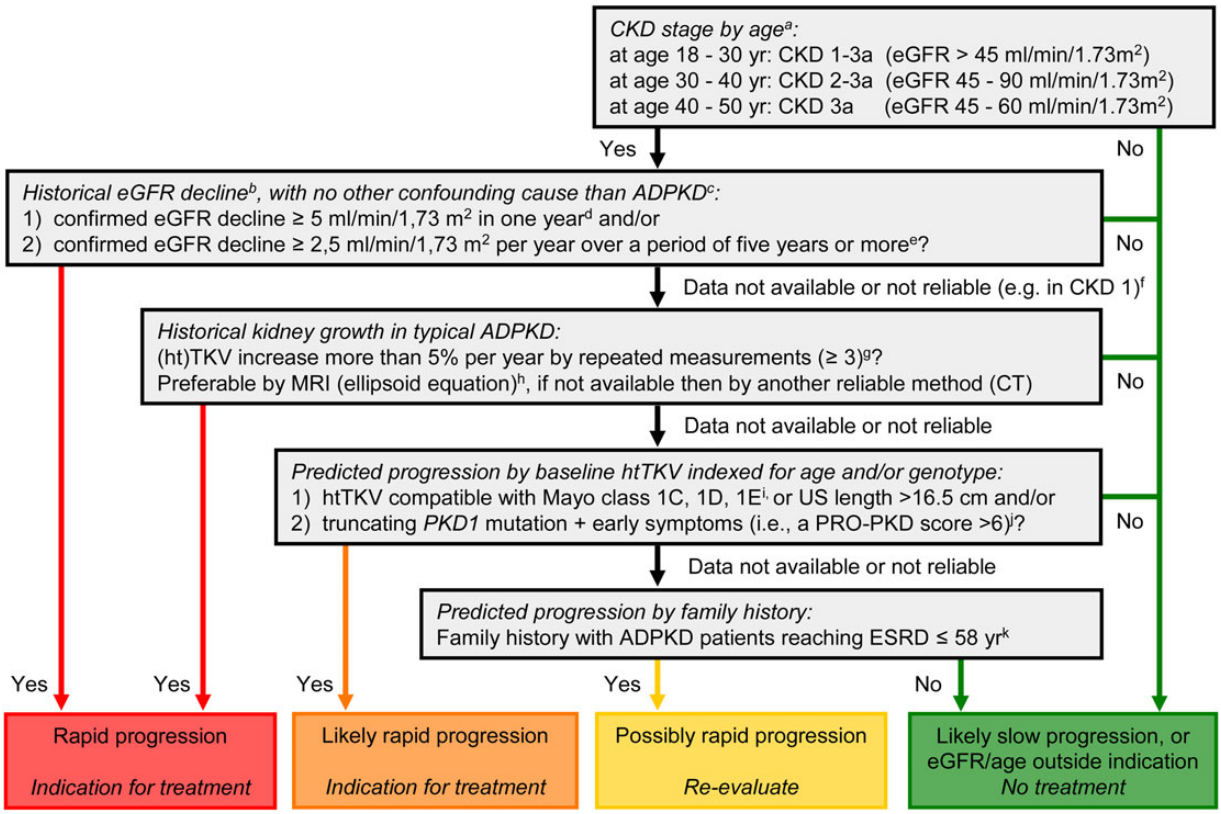

FIGURE 3: Algorithm to assess indications for initiation of treatment in ADPKD. The EMA label for tolvaptan states that this drug is indicated for 'ADPKD patients with CKD stages 1–3 and evidence of rapid disease progression at initiation of treatment'. A definition of 'evidence of rapid disease progression' is not provided. The diagram aims to define rapid progression, and thus allow the identification of patients eligible for treatment. It is based on the assumption that GFR for age, or historical changes in GFR, provides more information on disease progression than changes in TKV or risk prediction scores based on (ht)TKV or *PKD* gene mutation analysis in conjunction with clinical signs. Patients identified as showing 'rapid progression' or 'likely rapid progression' may be considered for treatment with tolvaptan. Patients with 'possible rapid progression' should be re-evaluated during follow-up visits. Besides assessing the indication for treatment, contraindications to and special warnings for tolvaptan use in ADPKD should be considered (see Table 2). Notes to the decision algorithm. (a) In our opinion, the indication 'CKD stages 1–3 at initiation of treatment' is not sufficiently specific as eGFR should be indexed for age. ADPKD patients with a high eGFR for age are unlikely to show rapid disease progression. There is currently no published evidence for the effect of tolvaptan in patients below the age of 18 or above the age of 50 years. (b) eGFR may vary over time in individual patients, especially when close to the normal range. To confidently define 'rapid disease progression', the rate of eGFR decline should be supported by multiple measurements that reliably indicate a rate of decline in eGFR. For this reason, this criterion should also be defined more strictly when historical data are available for only a short period compared with when available for a longer period. (c) When 'evidence of rapid disease progression' is based on historical eGFR data, the decline in renal function should be due to ADPKD and not related to other diseases, medications or factors that may contribute (reversibly or irreversibly) to a decline in renal function (e.g. diabetes mellitus, NSAIDs, calcineurin inhibitors, dehydration or contrast agents). (d) The criterion decline in eGFR ≥5 mL/min/1.73 m^2 in 1 year is adopted from the KDIGO CKD Guideline [35]. (e) The criterion decline in eGFR ≥2.5 mL/min/1.73 m^2 per year over a period of 5 years is comparable to class 1C patients in the Mayo classification of ADPKD [30]. (f) In young ADPKD patients with CKD stage 1, the observation of 'no change in eGFR' in general is not considered a sensitive marker of slow disease progression, as eGFR often remains fairly stable during a prolonged period of time, whereas TKV increases steadily, suggesting disease progression. In such patients, changes in TKV and/or prediction models should be applied to assess historical or predicted disease progression. (g) The criterion of increase in TKV ≥5% per year is likely to be conservative. It is based on the threshold defining the Mayo class 1C patients [30]. This criterion has also been advocated by the Japanese regulatory authorities [39]. The average rate of TKV growth in placebo-treated patients in the TEMPO 3:4 trial was 5.5% per year [10]. (h) The ellipsoid equation estimates TKV reliably when compared with classical volumetry [30, 34]. (i) The Mayo classification of ADPKD is based on height-adjusted TKV indexed for age. It predicts that patients with class 1C, 1D and 1E have more rapid disease progression [30]. A kidney length ≥16.5 cm, as assessed by ultrasound (or MRI), can be used in patients younger than 45 years to indicate a high likelihood of rapid disease progression [41]. (j) The PRO-PKD score suggests that patients with a truncating *PKD1* mutation and early onset of clinical signs (i.e. hypertension, macroscopic haematuria, cyst infection or flank pain before the age of 35 years) have rapid disease progression with start of RRT at a relatively young age [42]. (k) Although there is significant variability in the age of reaching ESRD within families that share the same mutation, clinical experience as well as observational studies have shown that a detailed family history can provide important information for risk prediction [44].

fatal liver toxicity could occur [48]. The EMA has therefore advised monitoring of liver function tests on a monthly basis during the first 18 months of treatment and 3 monthly thereafter [18]. The label of tolvaptan provides rules regarding when to stop tolvaptan treatment in case of *de novo* liver function test abnormalities, which are summarized in Table 2 [45]. In all

Table 2. Contraindications, special warnings and precautions for the use of tolvaptan in ADPKD as derived from the EMA-approved label [45]

Contraindications	
• Hypersensitivity to the active substance or to any of the excipients	
• Elevated liver enzymes and/or signs or symptoms of liver injury prior to initiation of treatment that meet the requirements for permanent discontinuation of tolvaptan	
• Volume depletion	
• Hypernatraemia	
• Patients who cannot perceive or respond to thirst	
• Pregnancy	
• Breast-feeding	
Special warnings and precautions	
Idiosyncratic hepatic toxicity	Tolvaptan has been associated with idiosyncratic elevations of blood alanine and aspartate aminotransferases (ALT and AST) with infrequent cases of concomitant elevations in bilirubin-total (BT). While these concomitant elevations were reversible with prompt discontinuation of tolvaptan, they represent a potential for significant liver injury. Guidelines to stop tolvaptan include: ALT or AST >8 times ULN ALT or AST >5 times ULN for >2 weeks ALT or AST >3 times ULN and BT >2 times ULN ALT or AST >3 times ULN with persistent symptoms of hepatic injury
Access to water	Tolvaptan induces aquaresis and may cause adverse reactions related to water loss, such as thirst, polyuria, nocturia and pollakiuria. Therefore, patients must have access to water (or other aqueous fluids) and be able to drink sufficient amounts of these fluids to avoid dehydration.
Dehydration	Special care must be taken in patients having diseases that impair appropriate fluid intake or who are at an increased risk of water loss, e.g. in case of vomiting or diarrhoea. Such patients should interrupt or reduce the dose of tolvaptan and increase fluid intake.
Urine outflow obstruction	Urinary output must be secured. Patients with partial obstruction of urinary outflow, for example patients with prostatic hypertrophy or impairment of micturition, have an increased risk of developing acute retention.
Fluid and electrolyte disturbances	The aquaretic effect of tolvaptan may cause dehydration and increases in serum sodium. Therefore, serum creatinine and electrolytes have to be assessed prior to and after starting tolvaptan to monitor for dehydration.
Anaphylaxis	Anaphylaxis has been reported very rarely following administration of tolvaptan. In case of anaphylaxis, administration of tolvaptan must be discontinued immediately and appropriate therapy initiated.
Diabetes mellitus	It has been suggested that tolvaptan may cause hyperglycaemia. Therefore, diabetic patients treated with tolvaptan must be managed cautiously.
Uric acid increases	Decreased uric acid clearance by the kidney is a known effect of tolvaptan. Adverse reactions of gout were reported more frequently in tolvaptan-treated patients (2.9%) than in patients receiving placebo (1.4%).
Effect on GFR	A reversible reduction in GFR has been observed at the initiation of tolvaptan treatment.

ADPKD patients, liver function test abnormalities were reversible after drug cessation and as yet no case of fatal liver toxicity has occurred [46].

There are special precautions for the use of tolvaptan in patients with gout, those using diuretics, patients with diabetes mellitus and patients with possible bladder dysfunction/voiding problems. In the TEMPO 3:4 trial, a higher incidence of gout was observed in patients treated with tolvaptan when compared with placebo [10]. In this trial, physicians were advised not to prescribe diuretics, out of fear that electrolyte disturbances might occur. Whether this is a real concern or not is difficult to assess at present because due to this advice the concomitant use of tolvaptan and diuretics has been low. Until more data become available, it seems prudent to restrict the concomitant use of diuretics. It has been suggested that tolvaptan may cause hyperglycaemia. V2 receptor blockade results in a slight compensatory increase in circulating arginine vasopressin [49], which in theory may stimulate hepatic glucose production via increased activation of V1a receptors [50]. In line with this, prior placebo-controlled trials in hyponatraemia suggested a higher incidence of hyperglycaemia in tolvaptan-treated subjects compared with placebo. In the TEMPO 3:4 trial, poorly controlled diabetes mellitus (i.e. fasting glucose >126 mg/dL or glycosuria by dipstick) was an exclusion criterion, but in this trial the incidence of hyperglycaemia as treatment-related adverse event was actually lower with

tolvaptan compared with placebo (0.6 versus 2.1%) [10]. Until further data become available, diabetic patients treated with tolvaptan should be managed cautiously. Because of the high 24-h urine outputs that result from using tolvaptan, care should be taken not to prescribe this drug to patients with possible bladder dysfunction or voiding problems in order to prevent post-renal obstruction and consequent renal damage. A careful urological history should therefore be taken in patients who are considered for treatment.

Issues to be discussed with patients when considering prescribing tolvaptan include the mechanism of drug action, expected adverse events and need for lifestyle modifications. Blocking the vasopressin V2 receptor by tolvaptan induces a strong dose-dependent aquaretic response, leading to an average 24-h urine volume of 5–6 L on the 90/30 mg dose [49]. Consequently, patients can experience thirst, dry mouth, polyuria and nycturia with disturbed night rest. In general, ADPKD patients are highly motivated to start disease-modifying treatment, because of personal experience with family members encountering complications associated with RRT. In line with this, only 7.4% of tolvaptan-treated patients discontinued treatment in the TEMPO 3:4 trial due to an aquaresis-related adverse event. Most discontinuations because of aquaresis occurred in the first 3 months of treatment [10]. Patients should be advised to stop tolvaptan immediately in case of impending dehydration, for instance in case of vomiting, diarrhoea or excessive sweating. Patients should be counselled on recommendations for adequate fluid intake to maintain water homeostasis and avoid reflex vasopressin increases. They should be advised to drink sufficient water to prevent thirst throughout the daytime period and an additional 1–2 cups of water before bedtime. Patients may require considerable assistance in order to manage the aquaretic side effects of tolvaptan. Screening patients for the likelihood of successful adherence, educating them on the aquaretic side effects before initiating tolvaptan and providing guidance on necessary lifestyle adjustment is critical.

Given these considerations, tolvaptan treatment should be initiated and monitored under the supervision of physicians with expertise in managing ADPKD and a full understanding of the risks of tolvaptan therapy, including liver toxicity, and monitoring requirements. It should also be emphasized that treatment with tolvaptan should not replace or offset current medical management of ADPKD.

Recommendation 8.1: *We recommend discussing adverse effects and impact on lifestyle with patients when considering starting tolvaptan.*

Recommendation 8.2: *We recommend taking into account contraindications and adverse effects such as hepatic toxicity and other precautions as listed in Table 2 when considering starting tolvaptan.*

Recommendation 8.3: *We recommend that prescription and documentation of safety monitoring of tolvaptan is performed under supervision of physicians with expertise in managing ADPKD.*

INITIATION, TITRATION AND MAINTENANCE OF TREATMENT

Importantly, initiation of tolvaptan is associated with an acute decrease in eGFR [49, 51]. After 3 weeks of treatment with a total daily dose of 120 mg, a fall in GFR was noted ranging from −0.7 to −7.8 mL/min/1.73 m^2, depending on baseline GFR [49]. This acute fall in GFR was reversible after treatment withdrawal, similar to what is observed when using renin–angiotensin–aldosterone system (RAAS) inhibitors. Physicians should be aware of the initial acute and reversible GFR decrease upon treatment initiation. As patients approach ESRD, tolvaptan should be discontinued in order to allow GFR to improve, which may postpone the start of RRT.

In non-ADPKD CKD, the efficacy of renoprotective treatments can often be assessed in the short term by investigating the effect on surrogate markers of efficacy, such as blood pressure and proteinuria. For instance, in patients with IgA nephropathy, if proteinuria is not lowered sufficiently by agents inhibiting the RAAS, treatment is deemed to be suboptimal. These agents are then uptitrated, or other medication is added [52]. Unfortunately, as yet there are no established short-term markers of tolvaptan treatment efficacy in ADPKD. The dose of tolvaptan should therefore be prescribed as used in the clinical trial that demonstrated treatment efficacy, i.e. starting tolvaptan at 45 mg in the morning and 15 mg in the afternoon, to be uptitrated, when tolerated, to 60/30 and 90/30 mg, respectively. In the TEMPO 3:4 trial, 23% of patients withdrew from therapy during the 3 years of the trial. The remaining patients used an average total daily dose of 95 mg tolvaptan. Of the patients who completed the trial, 55% took the high dose (a total daily dose of 120 mg), whereas 21 and 24% took the middle dose (90 mg) and low dose (60 mg), respectively [10].

In the TEMPO 3:4 trial, the effect of tolvaptan treatment on the rate of TKV growth was larger during the first year than during the second and third years of treatment [20]. It has been shown that tolvaptan induces an acute effect on TKV that is observed after 1 week of treatment and that is reversible after treatment cessation [49, 51]. This acute effect is assumed to be related to a rapid decrease in cystic fluid secretion [51], while later effects on TKV growth rate appear to be more sustained [23]. The results of the TEMPO 3:4 trial do not indicate diminishing treatment efficacy with respect to the rate of change in eGFR during the 3 years of the trial. In line with the assessment report by the EMA, the working groups consider it rational to continue treatment beyond 3 years, unless long-term treatment data in the uncontrolled open-label extension study that followed the TEMPO 3:4 trial suggest otherwise [21]. This study is ongoing.

Recommendation 9.1: *We suggest tolvaptan treatment to be started with a dose of 45 mg in the morning and 15 mg in the evening.*

Recommendation 9.2: *We suggest uptitrating the dose of tolvaptan to 60/30 and 90/30 mg when tolerated.*

Recommendation 9.3: *We suggest tolvaptan treatment to be discontinued when patients approach ESRD.*

CONCLUSIONS

Tolvaptan is the first pharmaceutical treatment approved to slow disease progression in ADPKD. Given the side effect profile of this drug, and for cost reasons, it is necessary to identify those patients who are most likely to benefit from this drug. To achieve this, we have proposed a hierarchical decision algorithm to assess whether treatment is warranted, and defined recommendations for the safe use of tolvaptan in ADPKD.

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CONFLICT OF INTEREST STATEMENT

R.T.G. is a consultant for Otsuka, Ipsen and Sanofi-Genzyme (manufacturers of tolvaptan, lanreotide and Genz-682352, respectively, agents that are developed as disease-modifying agents in ADPKD) and a member of the Steering Committee of the TEMPO 3:4 and REPRISE trials, as is O.D. The units of W.V.B., H.B., G.C., A.C., K.U.E., R.T.G. and R.V. participated in the TEMPO 3:4 trial and/or REPRISE trial. H.B. is an investigator in the Burden of Illness of Polycystic Kidney Disease in the Nordic countries (sponsored by Otsuka). H.B., O.D., F.S., Y.L.M, A.C.M.O. and R.T. are consultants for Otsuka. A.O. received speaker fees from Otsuka. F.E. and R.T. were members of IDMC of PKD-Tolvaptan trials.

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