Con: Tolvaptan for autosomal dominant polycystic kidney disease—do we know all the answers?

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ABSTRACT
According to recent literature, tolvaptan ameliorates the natural decline of renal function in autosomal dominant polycystic kidney disease. Tolvaptan is an orally available vasopressin V2 receptor antagonist. We describe herein the remaining questions and problems: it is unclear from the published work what influence tolvaptan has on total kidney volume. The consequences of hepatotoxicity for the subsequent dosing of tolvaptan have not been reported. A vasopressin V2 antagonist will cause polyuria and polydipsia and tolvaptan may influence quality of life (QOL), however, there are no QOL data. The cost-effectiveness of tolvaptan is borderline. It is unknown at which stage of renal failure tolvaptan therapy may have to be stopped. There are no established criteria to determine the ineffectiveness of tolvaptan. It is presently undecided whether a steady high water intake is able to imitate the renal effects of tolvaptan. Finally, the cause of worsening glomerular filtration rate after the start of tolvaptan is unknown.

Keywords: autosomal dominant polycystic kidney disease, cost-effectiveness, hepatotoxicity, tolvaptan

VARIABLE EFFECTS OF TOLVAPTAN ON TKV
In trials [6–8], the mitigating effects of tolvaptan on TKV were described in three different ways: (i) in the initial Phase 2 trial in Japan [6], the annual increase of TKV was 70% lower in treated patients than in historical controls and the effect was steady and linear over the 3 years of the trial; (ii) in the Phase 3 Tempo 3:4 trial [7], the annual increase of TKV was 49% lower in treated patients than in controls and the improvement was again seen as a steady and linear function over the 3 years of the trial; (iii) in the Tempo 4:4 continuation trial [8], there was no longer a linear relation between the increase in TKV and years on treatment. Instead, in the first year, the increase in TKV actually turned negative, that is, in response to tolvaptan, kidneys became smaller than at baseline. Over the next 4 years, the growth rate of TKV was at control levels. The discrepancies raise several questions: which rate of growth will eventually be reproducible, does the initial effect of tolvaptan on TKV diminish progressively over years on treatment and will it become negligible eventually? This is not trivial. In the Tempo 3:4 trial, TKV and its changes were important enough to be used as the primary endpoint [7]. Landmark work has indicated a close relation between renal function and TKV [10]. Patients prepared to take tolvaptan over a long period may want to know its status, therefore reliable information on TKV should be obtained.

DOES TOLVAPTAN AFFECT QUALITY OF LIFE?
The tolvaptan publications [6–9] do not address quality of life (QOL) issues, yet significant QOL changes could have occurred. In a study on the effects of tolvaptan in hyponatraemia [11], a 30-mg dose was associated with a daily urinary volume of 3.1 L. In the ADPKD studies [6–9], up to 120 mg of tolvaptan per day was given. This should have resulted in larger daily urinary volumes than 3.1 L. Would this have an impact on patients’ QOL? Indications suggest that this was the case. Polyuria, nocturia, thirst and pollakiuria were reported in up to 30% of tolvaptan-treated patients [7]. These were the most commonly reported adverse events in tolvaptan studies of ADPKD [6–9]. In the Tempo 3:4 trial [7], 8.3% discontinued tolvaptan because of
these adverse events and 45% of participants were unable to tolerate the high dose of tolvaptan because of polyuria and polydipsia. QOL is a fundamental aspect in patients’ cooperation and long-term adherence to treatment. Prescribing physicians would be helped in their decisions by QOL data and by actual measurements of aquarexis and fluid intake volumes. No such information has been made available.

HEPATOTOXICITY AND DOSING OF TOLVAPTAN

The clinical impact of hepatotoxicity remains unclear. Torres et al. [9] report an incidence of drug-induced liver toxicity [i.e. an increase in the liver function test alanine aminotransferase (ALAT) to pathologic levels] of 3.7%. This seems to suggest a low impact of hepatotoxicity. However, in the trial [9], hepatotoxicity was defined as an increase in ALAT to at least 2.5 times the upper limit of normal. In this way, only the more advanced cases of ALAT elevation were reported. Although this may be justified scientifically in a tightly controlled study, clinicians delivering care have to consider any elevation of ALAT as hepatotoxicity, even if it is only by 10 or 20%. It is likely that such lesser though significant ALAT elevations occurred more frequently than the increase to 2.5 times normal. Such details were not reported by the REPRISE trial. Likewise, it would have been instructive to learn about any consequences of hepatotoxicity (How long was tolvaptan interrupted until recovery of ALAT occurred? How often and how much was the dose of tolvaptan reduced after hepatotoxicity?). In the absence of such data, physicians can only guess at the real clinical impact of hepatotoxicity and it is possible that the reported 3.7% underestimates the impact.

THE COST-EFFECTIVENESS OF TOLVAPTAN IS BORDERLINE

Tolvaptan treatment of ADPKD is expensive. The cost of 1 year of tolvaptan is 30 700 euros in Germany at this time. Would this be cost-effective? According to the World Health Organization (WHO) Commission on Macroeconomics and Health [12], the cost-effectiveness of an intervention depends on the local gross domestic product (GDP). Interventions are classified as highly cost-effective (the cost of the intervention per disease-adjusted life year saved is less than the GDP per person), cost-effective (one to three times the GDP per person) or not cost-effective (more than three times the GDP per person). According to the REPRISE trial [9], 3.2 years of tolvaptan treatment (costing ~98 000 euros) may extend the time to CKD Stage 5 by 1 year. The GDP per person in Germany is ~34 000 euros at this time. Hence, comparing 98 000 euros with 102 000 euros, it may be concluded that tolvaptan treatment is borderline cost-effective by WHO standards.

SHOULD TOLVAPTAN BE STOPPED BEFORE END-STAGE RENAL DISEASE?

There are recommendations for the initiation of tolvaptan therapy [13]; however, it is not known whether and when tolvaptan might (have to) be stopped. In the Tempo 3:4 trial in patients with CKD Stages 1 and 2, the therapeutic effect of tolvaptan was a difference in the decline of renal function by 1.2 mL/min/year [7] when compared with controls. In the REPRISE trial of patients in CKD Stages 3 and 4, a therapeutic effect of 1.01 mL/min/year was found [9]. In a subgroup analysis, REPRISE patients in the most advanced stages of CKD 4 were evaluated; in these patients, the therapeutic effect was a difference of 0.81 mL/min/year [9]. These data suggest the possibility of a progressive diminution of tolvaptan effects on glomerular filtration rate (GFR) with advancing stages of chronic renal failure. Alternatively, the observations might be explained by some but not all ADPKD patients sustaining a reduction or a loss of tolvaptan effect in higher stages (CKD Stages 4 and 5) of chronic renal failure. This may become relevant if more patients in CKD Stages 4 and even 5 were to receive tolvaptan for ADPKD in the future. Conceivably, specific measurements or parameters could then protect patients from potentially ineffective tolvaptan treatment. However, no measures of this kind have been proposed [9].

WILL HIGH FLUID INTAKE IMITATE THE EFFECTS OF TOLVAPTAN?

In PCK rats, an animal model of ADPKD, an increase of water intake by a factor of 3.5 was sufficient to reduce the growth of renal cysts and improve kidney function [14]. The question has been raised whether increased ingestion of plain water in patients is a way to reduce the long-term impact of vasopressin in ADPKD, potentially imitating the effect(s) of tolvaptan [15]. It has been said that daily drinking volumes of up to 3 L are often recommended in renal stone – forming patients, that they are apparently adhered to and that such volumes might suffice in ADPKD [15]. A small clinical study tried this approach [16]. Eighteen patients had early stage ADPKD and consumed ~3 L of water/day for 1 year. Changes in TKV and estimated GFR in these polydipsic patients were not different from controls. However, the duration of the study was short and the number of participants was small. Furthermore, the urinary osmolality of 329 ±90 mOsm/kg in polydipsic patients suggests less suppression of vasopressin than was observed in the Tempo 3:4 trial [17]. In the latter, >80% of tolvaptan-treated patients reached urinary osmolalities of <300 mOsm/kg and patients with larger reductions of urinary osmolality showed less renal function decline [17]. Hence the issue of a high water intake instead of tolvaptan for ADPKD should be considered undecided at present.

WORSENING OF GFR DURING TOLVAPTAN THERAPY

Tolvaptan therapy is associated with a functional worsening of GFR by 3–5% lasting as long as the agent is taken [7–9]. One study of 20 ADPKD patients reported the effects of 1 week of tolvaptan treatment on GFR [18]. The agent reduced body weight by 1.6%, increased plasma sodium by 1.1% and diminished total body water by 1.1% [18]. Serum creatinine, cystatin C and uric acid increased by 8.9, 8.9 and 13%, respectively. Plasma renin activity, plasma aldosterone and renal blood flow
did not change measurably. It is possible to interpret these data as an indication of tolvaptan-induced dehydration. However, no intervention to keep total body water at baseline levels during tolvaptan were undertaken. Therefore dehydration may not yet be considered as a proven cause of the worsening of GFR, and further work is necessary. The presence of dehydration would be an important issue in long-term tolvaptan therapy since it would increase the risk of renal injury from incidental volume loss and nephrotoxins.

In summary, this communication outlines arguments against prescribing tolvaptan for ADPKD in some patients. The arguments relate to interference with QOL by polydipsia/polyuria, hepatotoxicity and functional worsening of GFR in response to tolvaptan. The question of high water intake to imitate the effects of tolvaptan is unclarified and will continue to be of great interest to patients. Still, other aspects are primarily for the therapist’s consideration, such as the eventual effect of tolvaptan on TKV, the potential point of discontinuation of tolvaptan therapy and cost-effectiveness. Progress in these areas would help to further improve the therapy of ADPKD.

CONFLICT OF INTEREST STATEMENT

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REFERENCES


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