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In this issue of *Kidney International Reports*, Perrone and co-workers[1,2] describe the results of 2 phase 2 studies comparing 2 formulations of tolvaptan; the immediate-release form (IR) and a new, modified-release form (MR).

Tolvaptan is a vasopressin V2 receptor antagonist. This medicine was granted market authorization by the European Medicines Agency in 2015 and by the U.S. Food and Drug Administration in 2018 for use in patients with autosomal dominant polycystic kidney disease (ADPKD) with normal to moderately reduced kidney function and whose disease is progressing rapidly. Tolvaptan blocks the vasopressin V2 receptor, and, via inhibition of adenylyl cyclase, the generation of cyclic AMP in collecting duct cells, resulting in decreased cyst growth and attenuation of renal function decline in ADPKD.[3] Scientific evidence for the beneficial effects of this drug in patients with ADPKD has been provided by the TEMPO 3:4 trial[4] and the REPRISE study,[5] which showed a decrease in growth rate of total kidney volume of 49% and a decrease in estimated glomerular filtration rate on treatment by 26% to 35% in patients with ADPKD early and later in the disease.

The obvious downside of treatment with a vasopressin V2 receptor antagonist (V2RA) is the resultant impairment of urinary concentrating capacity and consequently aquaresis. Subjects treated with the V2RA have an average urine volume of 6 to 8 l/d, nocturia, and thirst. In the TEMPO 3:4 trial, 8.3% of patients treated with tolvaptan discontinued treatment because of aquaresis-related symptoms. For some patients (and also for some nephrologists), this is a reason not to initiate treatment at all. In others, it was a reason to down-titrate to lower dosages, which may have less efficacy as we reason in the following paragraphs. To accommodate patients, Perrone *et al.*,[1,2] investigated, in 2 different studies published in this issue of *Kidney International Reports*, whether 1 daily dose of a new MR tablet of tolvaptan has similar efficacy but a better tolerability profile than the IR formulation that must be taken twice daily and that was used in the clinical trials.

The first study is a multicenter, parallel-arm, randomized placebo-controlled dose-ranging study.[1] In 2 study arms, 12 patients with ADPKD had 3 cross-over periods, using 7-day split-dose treatments (IR) versus MR formulation combined with placebo. Doses used were MR 20 mg, MR 40 mg (given as MR 20 + MR 20 mg), MR 60 mg, MR 120 mg, and IR 90+30. There were dose-dependent increases in pharmacokinetics and pharmacodynamics that were comparable for MR and IR formulations. Urinary burden was dependent on the dose of tolvaptan, not on the formulation.

The second study, the NOCTURNE randomized trial, investigated short-term efficacy and tolerability for 2 MR doses and 1 IR dose.[2] In this trial, 177 patients with ADPKD early in the disease (mean estimated glomerular filtration rate 81) were randomized in a 1:1:1:1 ratio to tolvaptan MR 80 mg/placebo, tolvaptan MR 50 mg/placebo, tolvaptan IR 60/30 mg, or placebo/placebo during 8 weeks. After 3 weeks of treatment, in all MR groups, total kidney volume decreased with 2.0% to 2.5% compared with baseline; in the IR group this was lower, with −1.17%. Mean urinary osmolarity was 408 in placebo, 207 for MR 50 mg, 159 for MR 80 mg, and 157 for IR 60/30. Remarkably, the IR 90/30-mg dose was not tested. Frequencies of thirst, nocturia, polyuria, and pollakiuria increased with dose, but were not different between the 2 formulations. Also, quality of life was not different for the different formulations of tolvaptan.

The main conclusion of these 2 studies was that pharmacodynamic effects and also aquaretic side effects increase with increasing dose.

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No differences in these parameters or in quality of life were observed, when comparing MR and IR formulations. This is disappointing, because it indicates that the new MR preparation is not the answer to the clinically relevant question of how to improve tolerability to V2RAs. Notwithstanding, these 2 studies are of interest also, because they touch on some issues that are worth discussing, to improve rational prescription of this drug in daily practice.

The first issue to discuss is the efficacy outcome that was used. Because it was a short-term study, no firm conclusions can be drawn on the most important efficacy outcome, that is, the rate of kidney function decline. In the NOCTURNE study, change in kidney volume after 3 weeks was chosen as the surrogate efficacy parameter. Such a short-term change in volume may reflect only a temporary effect on fluid secretion into cysts, and cannot be indicative for a structural benefit of tolvaptan to preserve kidney architecture and functioning kidney tissue. Moreover, in the NOCTURNE trial, change in kidney volume for the MR formulations was different from baseline, but for the IR formulation this was not the case, although this formulation is proven to be renoprotective on longer term, again an indication that it is difficult to translate this short-term effect on total kidney volume into a sustained decrease in rate of renal function decline over time.

The second issue is tolerability. Because these studies used in the treatment arms with the MR preparation an additional placebo to match for the evening dose of the IR form, the intake of medication once versus twice daily cannot be investigated. It seems more patient-friendly to take only 1 instead of 2 pills. On the other

hand, the aquaretic effects are immediately absent after skipping 1 dose. This means that patients who take tolvaptan IR twice daily have the possibility to skip the afternoon dose and, for instance, can go to a theater without having to miss scenes because of toilet visits caused by aquaresis-driven polyuria. Patients who take the slow-release formulation of tolvaptan in the morning will not have this possibility.

The third issue is the dose of the IR formulation of tolvaptan that was used in NOCTURNE. The authors state that this 60/30-mg dose was chosen because it was used in most clinical trials. This is, however, not the case. In the previously described landmark trials of tolvaptan in ADPKD,[4,5] subjects were uptitrated to 120 mg (90/30 split-dose). Those who did not tolerate this dose, could be downtitrated to the highest tolerable dose. In the TEMPO trial, 55% tolerated this 120-mg dose, whereas 21% tolerated only 90 (60/30) mg and 24% only 60 (45/15) mg. In REPRISE, 61% used 120 (90/30) mg. Thus, renoprotective efficacy has been proven for a treatment strategy in which patients are uptitrated to 120 mg or the highest tolerated dose. There is no evidence that administration of lower dosages will be as effective. We therefore advocate to use in clinical practice the same dosing strategy, that is, target for 120 (90/30) mg/d.

To improve tolerability, alternative dosing strategies have been proposed that do not primarily aim for prescribing 120 mg/d, but at inducing a urine osmolarity <300 mOsmol/l. The latter strategy would generally result in less 24-hour urine volume. The 2 trials in this issue[1,2] also use this osmolarity cutoff. The rationale for this strategy is based on the results of a post hoc study of the TEMPO 3:4 trial.[6]

In this study, it was found that when tolvaptan-treated subjects are divided into quartiles of urinary osmolarity at the end of treatment phase, subjects with a value <251 mOsmol/l (i.e., quartiles 1, 2, and 3) have approximately the same annual rate of estimated glomerular filtration rate decline. The authors therefore suggest that inducing an additional decrease in urinary osmolarity with tolvaptan will not further improve treatment efficacy. However, both baseline kidney function and tolvaptan have an effect on urine osmolarity and both are associated with disease outcome. This makes it difficult to dissect treatment effect on rate of kidney function decline. For instance, in this post hoc study, subjects in the quartile with highest urinary osmolarity on tolvaptan treatment (i.e., a urinary osmolarity >250 mOsmol/l) actually had the highest baseline estimated glomerular filtration rate and the lowest rate of kidney function decline thereafter. This reflects probably their intrinsic better disease prognosis, that would have been more favorable even without treatment. These latter data should not be used to decide that lowering tolvaptan dose to achieve a higher urinary osmolarity on treatment would be beneficial. We therefore believe that no firm conclusions can be drawn based on these non-randomized, observational post hoc analyses of urine osmolarity data. It makes sense that if urinary osmolarity can decrease further from for instance 251 to 140 mOsmol/l by increasing tolvaptan dose, apparently there was residual vasopressin activity that can be inhibited, and perhaps this additional vasopressin inhibition results in more treatment effect. The dose-dependent decrease in urinary osmolarity is also shown in
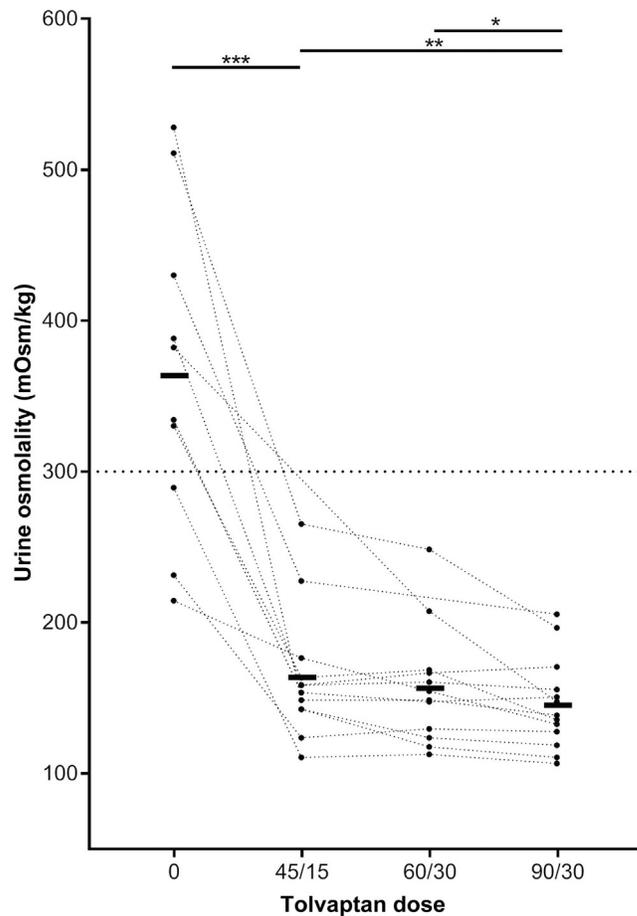
Figure 1. The V2 receptor antagonist tolvaptan induces a decrease in urine osmolarity that is dose dependent until the highest dose used in trials and in clinical practice. $*P < 0.05$; $** P < 0.01$; $***P < 0.001$.

the first randomized trial published in this issue (where 56% reached a urinary osmolarity <300 mOsmol/l when using MR 60 mg versus 92% when using MR 120 mg) and described in literature.[7] We also see this phenomenon in our patients, who we uptitrate to the highest tolerable dose. Urinary osmolarity decreases when uptitrating from 60/30 mg to 90/30 mg (Figure 1). Figure 1 also shows that some patients already have a urinary osmolarity <300 mOsmol/l before starting tolvaptan. These are especially patients with more severe disease, which has impaired their ability to concentrate urine. Such patients may have particular benefit of tolvaptan, again indicating that this urinary osmolarity threshold of <300 mOsmol/l cannot be used as a marker to

titrate tolvaptan dose to achieve maximal renoprotection.

Some nephrologists decrease the dose of tolvaptan when urinary osmolarity is <300 mOsmol/l to improve tolerability. As explained, we do not favor such a strategy. We often observe that when disease progresses, 24-hour urinary volume decreases again under treatment and consequently that urinary osmolarity increases. In such patients, we increase the dose of the V2RA based on an animal study that showed beneficial effects when tolvaptan was uptitrated to maintain a high urinary volume and low urine osmolarity.[8] Of course, we realize this will not help to improve tolerability of the drug, but in our opinion it is important that we first take care that treatment efficacy on rate of disease

progression is maintained. To improve tolerability, 2 alternative strategies come to mind. Because therapy with tolvaptan mimics nephrogenic diabetes insipidus (a blocked vs. a defective receptor), the same treatment strategies are likely to help. When concentrating capacity is impaired due to the V2RA, and consequently urine osmolarity is near the maximal urine dilution capacity value, the amount of osmoles ingested will dictate the level of aquaresis. The first strategy to lower urine volume is therefore to decrease salt and protein intake.[9] But also taking the last meal some hours earlier will likely help to decrease the level of nocturia. The second strategy is to add medication. In nephrogenic diabetes insipidus, hydrochlorothiazide effectively decreases polyuria by increasing absorption of sodium and water in the proximal tubule. Whether this treatment also works in patients with tolvaptan-induced diabetes insipidus is safe and does not influence the renoprotective efficacy of tolvaptan in ADPKD remains to be studied.

In conclusion, the 2 studies published in this issue found similar pharmacodynamics and tolerability for tolvaptan MR versus IR. An MR preparation is therefore not the answer to the question of how to improve tolerability of tolvaptan. To do so, without compromising the renoprotective efficacy of this drug, we suggest investigating other treatment strategies, that is, coprescribing a low osmolar diet and/or anti-aquaretic drugs such as hydrochlorothiazide.

DISCLOSURE

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