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Released: 09/23/2022
Valid until: 09/23/2023
Time needed to complete: 30 minutes

ReachMD
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info@reachmd.com
(866) 423-7849

Management of ADPKD

Announcer:
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Dr. Dahl:
Hello, and welcome to this webcast entitled management of ADPKD. I'm Neera Dahl. I'm a Professor of Medicine in the Section of Nephrology at Yale University. I'm joined today by my very good friend and colleague, Dr. Craig Gordon.

Dr. Gordon:
Thank you. My name is Dr. Craig Gordon, I'm a Associate Professor of Medicine in the Division of Nephrology at Tufts University School of Medicine, and I'm very fortunate to be speaking here today.

Dr. Dahl:
Before we get started, let's review our learning objectives. Upon conclusion of this educational activity, participants should be able to describe updated best practices for initiation and management of pharmacotherapy in rapid progressors for loss of renal function in ADPKD, identify risk factors for rapid disease progression, review the general management of ADPKD regarding blood pressure, summarize the most recent clinical research in dietary modifications that have been shown to benefit patients with ADPKD.

Craig, let's look at the more straightforward approaches to managing a patient with ADPKD. First is pharmacology. There's only one approved treatment for ADPKD. That's tolvaptan, which was approved for patients with rapid disease progression. How would you define a rapid progressor?

Dr. Gordon:
Thank you. So, as you can see here, patients can be determined to be rapid progressors. And this study was defined as reaching ESKD, or kidney failure, by the age of 62. And this can be assessed in a number of different ways. The first would be through measuring height and age adjusted total kidney volume to determine someone's Mayo imaging classification. And those were Mayo imaging class 1C, 1D, and 1E disease. This requires bilateral renal cystic disease to be class 1.

Those individuals who have classes 1C through E are likely to be rapid progressors and candidates for treatment. One can also monitor the change in total kidney volume, or what's done more likely in clinical practice is monitor change in GFR n patients with PKD and no other major comorbidities to explain the decline in GFR. So in individuals where there's a GFR decline of greater than 2.5 mL's per minute per year, averaged over a 5-year period, including those with classes 1C, 1D and 1E disease would be candidates for treatment. Individuals with TKV growth if you have multiple measurements of greater than 5% per year. This is three measurements at least 6 months apart in time. It would be another way to determine individuals at risk of rapid progression.

There are some clues and factors that are suggestive but not definitive as far as to finding rapid progression. This would include a family history of earlier onset kidney failure under the age of 55, individuals with PKD-1 mutations, and individuals where there's data from the

PROPKD score of evidence of early onset renal cyst bleeding or infection, early onset defined as before the age of 35, onset of hypertension before the age of 35, and as we will review a little bit later, individuals with kidney length on ultrasonography of 16.5 centimeters or higher in patients with bilateral typical cysts and individuals under the age of 50 - 45.

Dr. Dahl:
And looking at this slide, I think we're just breaking up the data in a slightly different way. So talking about genetics, either a PKD-1 which is more severe than a PKD-2 mutation, and looking at environmental factors which we'll talk more about, low fluid intake or high salt intake, or obesity, which is - we're learning more about and these things can then lead to an increase in cell pro - I can never say this word. These things can then lead to an increase in cell proliferation, inflammation, and fibrosis. And we can note then from these things happening that there's early onset hypertension and urologic events that's part of the PKD score. And there can also be other findings. So more protein in the urine albuminuria can be associated with an increased risk of progression. And we'll talk about some novel biomarkers.

Dr. Gordon:
Yeah, one of these biomarkers that has become a recent interest is measuring a morning urine specimen assessing the urine to plasma urea, which was studied in the Netherlands. And basically, in this study where they had data from the DIPAK cohort of 538 patients, they were able to show, for each decrease in urine to plasma urea ratio, there was an increased risk of kidney function progression. And this was thought to be representing individuals who have difficulty concentrating the urine. And this seemed to be a parameter that functioned reasonably well statistically compared with other conventional measures of disease progression. It is something that we should use more often in our clinical practice to assess our patients.

Neera, I'm curious, in your clinical practice, how often do you use the urine to plasma urea ratio?

Dr. Dahl:
So I haven't started using that yet. But I agree with you, it's a very simple measurement to make. And it gives us something about inherent disease state. So I think it's definitely something to consider.

The other thing I liked about this paper is that they started using a composite risk score. So looking at things like the TKV, in addition to the mutation type or genotype. And then also, I think, for patients what's important, as they noted this important effect of increasing salt intake in terms of increasing progression, or TKV. And also, the importance of blood pressure and affecting these variables.

Dr. Gordon:
And I think that is a very important point is when we rely on just a simple single measure, we often find, I think, that we're not doing a great job of predicting with great accuracy when an individual patient will progress. But adding these other factors give us a little bit more precision.

Dr. Dahl:
Here's what we were talking about in terms of thinking about ultrasound and helping define risk. So in general, someone with an average kidney length, meaning the right and left kidney lengths added together and divided by 2, and average length greater than 16.5 in a patient who's less than 45 years old, with typical imaging, meaning bilaterally symmetrically enlarged kidneys, predicts high risk.

And although we say that volumetric measurements by MRI or CT are preferred, what this paper showed is that if volumetric ultrasound is used, a finding of C, D, or E kidneys predicts the risk of progression. However, if you get a volumetric MRI - volumetric ultrasound measurement that's between 1B and 1C, you may then want to consider some additional imaging, either MRIs or CT, to really confirm whether that patient is high risk or low risk. And this is helpful in determining which patients to treat and in finding those high-risk patients to treat to have normal renal function.

Craig, let's talk a little bit about how tolvaptan, the drug that's been approved for treatment of ADPKD, compares to other medications that we know impact the progression of kidney disease.

Dr. Gordon:
Absolutely. So tolvaptan, as many in our audience know, was studied in the TEMPO 3:4 and REPRISE studies. And in these studies, essentially, there was about a difference of 1 mL per minute per year difference in GFR decline when you compared tolvaptan treated patients to individuals receiving placebo. When you look at this, compared to other things we use in nephrology, it's actually a reasonably favorable comparison. And this would range from early studies looking at ACE inhibitors and ARB's to more recent studies looking at SGLT-2 inhibitors. I think the key point here is that a 1-mL per minute per year difference actually translates to a quite significant benefit, especially when we start early in a patient's course.

Dr. Dahl:

And here I think this is now data looking longer term. So the TEMPO 3:4 study was for 3 yours, this is now looking at 5 years' worth of data. And what's really reassuring here is that finding of that 1 mL per minute change continued over the 5 and a half years that this was followed. And this was happening, even though after the first year, there was no difference in the change in terms of rate of growth of total kidney volume.

Dr. Gordon:
So this gets to an important issue, which sometimes comes up of people asking, should we have repeat imaging done to assess are we making a difference? I don't think I do that very often in practice. I don't know how often you do that.

Dr. Dahl:
And the same for me, I don't repeat imaging unless there's a clinical need, flank pain or some other need.

Craig, another question that comes up is when we should consider stopping tolvaptan therapy. I know in general that we start tolvaptan therapy for anyone with a GFR of 25 or higher. Do you think there's a cut off where we should stop?

Dr. Gordon:
Yeah, so this study that came out about a year ago argues for an ongoing benefit of continuing tolvaptan. So this study took individuals in the REPRISE trial, and compared those who received placebo during REPRISE, but ultimately - or subsequently were treated with tolvaptan in the open label extension, and compared those individuals to individuals who received tolvaptan during REPRISE, and continue tolvaptan afterwards.

And in a relatively complicated analysis, basically the take-home message here is the group who started tolvaptan after receiving placebo early on, had a benefit, even though their GFRs were relatively low, you can see towards the right-hand side of the slide, this included individuals with a baseline GFR between 15 and 29, where with tolvaptan, the rate of decline of GFR was -3.4 mL per minute per year, compared with -5.2 for the same individuals when they received in REPRISE. And this finding was true, whether we were looking at people with a GFR between 25 and 29, and 15 and 24.

Essentially, I'll be curious to hear your thoughts about this. My interpretation of this is having relative comfort starting people with relatively low GFRs in the 20s, at least considering doing so in the teens. And, more importantly, continuing it through disease progression into the teens.

Dr. Dahl:
Yeah.

Dr. Gordon:
And I'm curious to hear if that's how you approach things.

Dr. Dahl:
I do the same. I - for patients who are losing kidney function and have stage 5 CKD, I often keep them on tolvaptan therapy, until the time of transplant or initiation of dialysis. And really have only stopped tolvaptan if there was another need, so they needed high doses of diuretics because they were developing edema.

So, Craig, a good question that often comes up is what to do about those patients who are over 55, but clearly progressing. I know in REPRISE, there was not a clear benefit for these older patients. What do you think of this new poster?

Dr. Gordon:
Yeah, this is a really interesting poster that basically looks at tolvaptan versus non-tolvaptan care in individuals over the age of 55, with CKD stages 3 and 4. So these are people who are progressing, maybe not rapidly. If you remember earlier, we talked about rapid progression being approaching ESRD in the early 60s. So this is a group who sort of progressing but maybe not quite as rapidly. It's a relatively small study of 95 individuals between 56 and 65 years of age, and the majority of whom are CKD 3, and lesser group of CKD 4. And here's the key point, which is even in this older group, those treated with tolvaptan here in green experienced about a -2.3 decline in GFR annually. And those not treated with tolvaptan labeled SOC, or standard of care here, continue to progress at the usual rate of -4 mL's per minute per year. So the take-home point is over the course of 4 to 5 years here, there was a continued benefit of tolvaptan, even in this older group, as you can see, by about an absolute risk difference of 1.66 mL per minute per year.

Dr. Dahl:
Terrific. And I think in my practice, I often have this conversation with older patients who are clearly progressing. And I've seen some nice slowing of progression in these patients.

I think we'll change gears a little bit and now talk about non-pharmacologic interventions in terms of management of ADPKD patients.

And the first one is blood pressure control. So after the HALT PKD study, especially for those patients who are at high risk of progression, we've all adopted a goal blood pressure of about 110/75. This is particularly a good target for those patients who still have preserved renal function, a GFR greater than 60 mL per minute, and are relatively younger.

And then looking at how we define progression, these are the Mayo class 1C to 1E patients, or perhaps patients who have an intracranial aneurysm, or some other evidence of risk, such as valvular heart disease. And for patients who start to lose GFR, or for older patients, most of us are still using the older blood pressure target, which is 130/85.

Craig, do you have a preference of which medications you use for treatment of high blood pressure?

Dr. Gordon:
Yeah, I tend to take an approach that is fairly nephro-centric, I suppose, which is a focus on ACE inhibition and ARB's as my first line choice of agents. The agents that were studied in the HALT study would be one reason for it. Our patients, as we alluded to earlier, occasionally will have albuminuria, which would be another reason to prefer this choice of agent. And obviously, as nephrologists, we're very familiar with these.

Following this, probably beta blocker would be my next choice of agent, followed by calcium channel blockers and diuretics. With the potential issue of diuretics being a concern, sometimes when we're also thinking about tolvaptan use.

On top of that, as we'll talk about in a little bit, dietary approaches. So Dietary Approaches to Stop Hypertension, the DASH diet, is something that I frequently urge my patients to follow.

Dr. Dahl:
And I think we were all waiting to see what the results of this study were. This is a study where they looked at water as a outcome in changing TKV and changing progression of PKD. And I think this study was done nicely in that they tried to target osmolarity and tried to keep the osmolarity fixed, and then target specific water prescriptions based on that. And here are the results of that trial.

And what they found, I think somewhat surprisingly, was that there was really no difference for those patients who got the prescribed water intake, versus those patients who were told to just simply drink water in a liberal way.

And here, I think is another critical finding. This is one of those papers that when it came out, it went straight into the clinic. And it looks at the difference between salt intake and protein intake on change in GFR. And really what I thought was so interesting here is that there's clear association of salt and decline in GFR in ADPKD. And that similar change was not seen with protein intake. And if you look to the right, it looks like really that mediation is not because salt increases blood pressure, but because salt increases vasopressin release and copeptin levels. So here, and we saw in the prior slide to that salt increases cyst growth. So I think it's a clear message for our PKD patients to really limit the amount of salt that they're ingesting.

Dr. Gordon:
The somewhat sobering news here is that despite there being at no lower limit of salt intake that was actually the more - the lower the salt intake, the better the patient did. When you look at data from various studies, and this is also coming out of the Netherlands, basically, over the course of a 6-year study, the dietary salt remained fixed at a level that's higher than what our goals should have been. So this was measured in a 24-hour urine. And basically, despite a desire to lower dietary salt in this population, there really wasn't a profound effect. So we really do have our work cut out for us on educating our patients, and maybe even working with the food industries, etc., to really address this goal.

Dr. Dahl:
I think this is another really important message and now with good treatment for obesity, something that I spend a lot of time talking about. So this is a study looking at the annual change in total kidney volume. And looking at patients who were either normal weight, overweight, or obese. And what you can see is as the weight - as the BMI goes up, there's an increase or an acceleration in the annual change in total kidney volume.

Dr. Gordon:
And this has led to a real interest in looking at dietary interventions as potentially disease-modifying treatments in PKD. You can see here several of the diets that are under investigation and of interest right now. So the first is caloric restriction, which is essentially just restricting the number of calories taken in daily. Intermittent fasting is alternating between days of eating and days or periods of fasting. The third of these is time restricted eating, where a window of restricted eating occurs. And in other periods, eating is allowed ad lib. And finally, is ketogenic diet, which has also been of great interest recently, which is a diet high in fat, moderate in protein, and very low in carbohydrate.

Dr. Dahl:

So one of the nice pieces of data presented at the ASN in 2021 was the work coming out of Colorado from Katharina Hopp and Kristen Nowak, about the role of obesity in ADPKD. And what they showed was that in treating those patients who were obese, who lost weight, had a decrease in growth of total kidney volume. Has that changed your management?

Dr. Gordon:
Yeah, I mean, I think from my perspective, I am not just focused on ADH antagonism and tolvaptan. I'm now really pushing my patients in a number of these areas, including dietary salt, as well as for those who are overweight and obese to consider, under the guidance of a dietitian, various of these dietary interventions. We're in early days here, there's not a lot of data. But these diets for the most part, are well studied in other conditions and are safe, especially under the auspices of a dietitian. So our focus has really changed to a more extensive discussion about weight loss, and these various diets.

Dr. Dahl:
And I think from a patient point of view that patients really appreciate that very holistic approach, talking about diet and fluid and lifestyle, in addition to therapy.

And in the final minutes, just to talk about other management in ADPKD. So we spoke a lot about managing kidney and blood pressure, but the patient has a full complexity of findings, including thinking about extra renal manifestations, liver cysts, intracranial aneurysms, sometimes cardiac abnormalities, and really we're treating that entire panel of problems, right, of kidney pain, kidney cysts, liver cysts, infections, things like that, and to really think about this in the broader context of treating the entire patient, and from very early stages through the ESRD process and either to transplant or to dialysis.

And that brings us to our summary and key takeaways. So the Mayo imaging classification of 1C to 1E predict a rapid risk of progression in patients with ADPKD. Tolvaptan, a vasopressin or v2 receptor antagonist, is at the time the only approved drug to slow the progression of disease in ADPKD. It's recommended for high-risk patients with relatively early disease. Tolvaptan should also be considered in patients with more advanced disease, i.e., in stage 3 to 4 CKD. And there's an interaction with genetic, epigenetic, and environmental factors which influences disease progression. Intensive blood pressure control less than 110/75 is preferred, particularly for those patients with preserved renal function with an ACE inhibitor or with an angiotensin receptor blocker as the first line of drug treatment. High water intake and low dietary salt should be recommended. Reduced caloric intake, intermittent fasting, and ketogenic diet are promising, but are unconfirmed dietary interventions to slow disease progression.

And with that, Craig, I would like to thank you for being part of this nice discussion. And we hope to all of you that you find this presentation useful in your clinical practice. Thank you for your time and attention.

Dr. Gordon:
Thank you.

Announcer:
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