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

Optimizing the Care and Quality of Life for Patients with ADPKD – Part 3: Management

Announcer:
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Dr. Rahbari-Oskoui:
Hello and welcome to this webcast titled Optimizing the Care with Patients with ADPKD. This is part 3 of 4 in CME series on improving the care and quality of life of patients suffering from autosomal dominant polycystic kidney disease, or ADPKD. In this webcast, we will talk about disease state management. I am Dr. Frederic Rahbari-Oskoui. I am a Professor of Medicine at Emery University and I am joined today by my colleague, Dr. Michel Chonchol from the University of Colorado. Dr. Chonchol, would you please introduce yourself?

Dr. Chonchol:
Thank you Fred. It is an honor to be doing this webcast with you and as you, I am a Professor of Medicine at the University of Colorado and we have expertise in PKD research and clinical care of PKD patients.

Dr. Rahbari-Oskoui:
Thank you very much. The objectives of this webcast are to review the general management of ADPKD regarding, particularly blood pressure, cholesterol control and dietary intervention, apply current guidelines for initiation and management for tolvaptan and rapid progressors and also summarize the dietary modifications that have shown benefit in ADPKD.

As the research over the last forty years, pretty much, has shown, there is a number of interventions that we can work on and strategies that we can actually optimize the care of the PKD patients. The number one and most important point is hypertension. We know that the prevalence of hypertension is very high in PKD. At the time of diagnosis of PKD, for whatever reason, you know, either a routine screening or a problem, about 40 to 60% of PKD patients already have hypertension. If you look at the pediatric population up to 20% based on this series actually report that even kids with PKD already have abnormal blood pressure readings. If you look at the end of life of PKD patients, the lifetime risk is almost about 90%. The 10% of people with PKD do not develop hypertension typically do very well and their kidney progression is not that bad.

So, this is clearly the most preventable and treatable risk factor for progression. We have several strategies and medications to choose from and we always recommend the renin angiotensin system blockers because there is an interveinal activation of this system that occurs very early in PKD. Therefore, agents such as ACE inhibitors and ARBs should be considered as first line drugs. Because the salt intake is typically high in our diet in the United States, diuretics are second line recommended for the management of blood pressure and third line is beta blockers. And the fourth line, calcium channel blockers should be kept to the last line and the reason for that is a defective calcium trafficking issue that is caused by polycystic defect and mutation in PKD mimics the effet of the calcium channel blockers. So, obviously if we can manage blood pressure with something else, we should choose the other agents first and if they still have a high blood pressure and that is not controlled, then we should come down to using calcium channel blockers.

I would ask you Michel, as far as the blood pressure goals based on the HALT-PKD trial, what is your guidelines in management strategies that you have as far as what is a good blood pressure goal in PKD patients?

Dr. Chonchol:
Yeah, thank you, Fred. First of all, I really enjoyed your initial slide where you talked on all the key clinical aspects that the clinicians should be aware of in the management of patients with polycystic kidney disease. And as you mentioned, hypertension is, honestly, a key clinical parameter that needs to be in control in this patient population. As you mentioned, both of our centers were part of the HALT-PKD trials and we have a lot of expertise with the management of blood pressure in this patient population and you are very well aware that there were two studies where they look at blood pressure control in those patients with a GFR greater than 60, as well as patients with true CKD, defined as a GFR less than or equal to 60. And in that patient population with normal or near normal kidney function, I do agree that blood pressure should be less than 110/75. As the late Dr. Bob Schrier used to say, who actually was the principal investigator from the HALT study, 'The lower the better'. And for patients with a GFR less than 60 and with more progressive renal disease, I also agree with you on the basis of the HALT study and actually the SPRINT study, even though it did not include patients with polycystic kidney disease, that the systolic blood pressure should be, you know, 130 or closer to 120, as much as possible.

Dr. Rahbari-Oskoui:
Thank you very much, Michel. Now we are moving to the V2 receptor antagonist, and tolvaptan is the only agent of the class that has a label for polycystic kidney disease. So, a series of clinical trials actually led to the science that is behind the effectiveness and safety of tolvaptan and finally the United States, it was improved in April of 2018. The two trials, TEMPO and REPRISE basically showed very similar effects and they have a radical protective effect on the kidney function in about, by a 31% lower annual rate of declining GFR. If you compare that to the gold standard that we have had prior to that, which is basically using ARBs or ACE inhibitors, if you take a comparison point that ARBs in diabetic nephropathy, that benefit was only about 15.2% in annual rate of decline of GFR. And this is really clearly superior to that protection.

I would like to ask Michel just to very quickly go over the two seminal trials, the TEMPO 3:4 and the REPRISE trial to see what was different between the two trials and how did we conduct these trials and what did we see for that, as far as results?

Dr. Chonchol:
Thanks, Fred. I agree that tolvaptan has really added to our armamentarium of how to deal and treat patients with polycystic kidney disease. As you mentioned, there were two key trials in the tolvaptan program. The TEMPO 3:4, as well as the REPRISE. Both of them, a very large population, over 1,000 patients with polycystic kidney disease and the time frame of the TEMPO was an earlier study between 2010 and 2013. And the REPRISE came out later between 2015 to 2017. And the REPRISE included patients on the way to 64 and

TEMPO was mainly 18 to 50. But the big difference, to your point, is that TEMPO included patients with GFR greater than 60 and the REPRISE have patients with GFRs between 45 to 65 and 25 to 44. So, in other words, patients with more advanced chronic kidney disease. There is no question that another big difference between these two studies is that in TEMPO, they look at total kidney volume requiring them to be in the study and actually changes in total kidney volume was an endpoint and that was not the case in REPRISE. REPRISE really, the main premier outcome was change in EGFR in contrary to total kidney volume.

So, those I think, I think that focusing on the inclusion criteria, as well as the outcomes were, kind of, the main key differences between TEMPO 3:4 and REPRISE.

Dr. Rahbari-Oskoui:
Thank you very much. These are basically the graphs from the New England Journal of Medicine, the TEMPO 3:4 results on the left side basically showed a net almost 1.2 mL/min of kidney protection per year of usage and exposure to tolvaptan in TEMPO. And as far as the total kidney volume patients who were on placebo, they had about 5.5% increase in the total kidney volume per year versus 2.8 for the patients who were on tolvaptan. Obviously, in REPRISE, we did not have a TKD endpoint, we only had a GFR endpoint. And the GFR endpoint was extremely close to what we were seeing in TEMPO and it was basically paralleling and mimicking exactly those results. So, the two trials were complimentary but very consistent with each other and that is basically what gave birth to the science behind the regulatory approvals in all the countries that actually tolvaptan became available in. There are models to extrapolate the effect of tolvaptan on kidney function and the onset of end-stage renal disease or dialysis or transplantation. We assume that the earlier that you start and the higher the GFR is, the more you are going to get the benefit of postponing dialysis. Based on TEMPO, we think that if you start tolvaptan around a GFR of 90, you could actually postpone dialysis by 7.5 years, almost, versus if you start at 30 of GFR, you would only have about 1.5 years of difference in the onset of ESRD. So, the sooner the better. REPRISE had very similar projections and extrapolations. If you started around 60, you were gaining about 6.8 years, time of onset of dialysis. Or if you started at 30, you were only reaching about 2.3 years. So, again, the sooner the better and the higher the GFR the better, as far as the protection that you are getting from tolvaptan.

And I am going to ask Michel now, as far as for any drug, you know, you have risks and benefits, and I would like him to basically

summarize what are the benefits and what are the risks of considering tolvaptan?

Dr. Chonchol:
Yes. No, thanks Fred. I wanted to make a comment on your previous slide that although when we see the data from the clinical trials, maybe the differences do not appear tremendously clinically significant, it is important to remind a clinician that this is an additive and these extrapolations are really bringing the point that this benefits add to the years and potentially, we can significantly delay progression to end-stage kidney disease in patients with polycystic kidney disease.

Regarding the risk/benefit ratio, you are absolutely right, I mean, like any drug, I mean, what tolvaptan has been proven to show is that it slows kidney growth, it slows EGFR in kidney function decline, it will delay the need for kidney replacement therapy and very important for us to keep in mind, it reduces pain, hematuria, kidney stone, as well as urinary tract infections events, and it even has an effect on blood pressure reduction.

Nonetheless, it does have some side effects, like polyuria and nocturia. It does increase thirst and fatigue. It has been shown to elevate uric acid and it may be, at times, associated with gout. It, one of the harms that people are most concerned is about this elevation of transaminase and the risk of severe hepatocytotoxicity or liver failure. Nonetheless, this is the reason why these patients need very frequent monitoring of liver function. It may have some possible drug interactions and there is no question that the drug is expensive and it may create some financial burden. However, it has been the coverage of the tolvaptan, at least here in Colorado has improved significantly since it was launched out into the community.

Dr. Rahbari-Oskoui:
The next topic is really kidney stones that could happen in about 20% of PKD patients over their lifespan. What is atypical with ADPKD is that most people with PKD actually would make uric acid stones, which is, kind of, contrary to the garden variety calcium oxylate stones that non-PKD patients will have. There is clearly an issue with hypocitraturia, so the citric level in the urine are lower in PKD patients and the stones formed are typically hypocitraturia, therefore, the treatment includes, you know, what we recommend typically to all stone formers drinking plenty of fluids, at least three liters of water a day, low salt diet, alkalinizing the urine if uric acid stones are present, and also supplementing the diet with citrate and citric tablets and if we have a kidney stone that is stuck in the kidney, you know, we can consider lithotripsy and take them out to avoid obstruction issues an pain issues.

The other topic is the urinary tract infections. Urinary trat infections are basically a big topic. They are very common in PKD. Most PKD patients during their lifetime will get at least one episode, whether it is going to be a bladder infection a tube kidney infection with pyelonephritis or sometimes just an individual cyst infection that basically behaves like an abscess. We can see all these problems in PKD patients. We typically recommend doing a urine culture in all PKD patients who have symptoms of a UTI. There is going to be burning, frequency, fever, chills, and if they have a kidney function, the difference with non-PKD patients that the length of treatment for kidney infections should be much longer. So, a typically kidney infection in PKD patients means about four weeks minimum of antibiotics and in non-PKD patients you typically two weeks is enough. And the other difference is that for non-PKD patients, we just want the antibiotic to get to the urine. Whereas here, we have to think about cysts and we have to choose agents that actually penetrate into the cell, into the cyst. And typically, the ones that are, that have very good penetration are quinolones such as cipro or Levaquin and Bactrim and vancomycin. The group that is actually poorer in penetrating the cysts is the class of penicillin and ciclosporins that have good urinary penetration but they do not get into the cysts, as well. And we should think about that, particularly when you are thinking about kidney infection or cyst infection. For bladder infection, it does not matter that much, unless, you know, the bladder is the infection has been ascending to the kidneys.

Chronic pain is also a very, very common problem in polycystic kidney disease. There is a correlation between kidney size and pain. But the correlation is not perfect. We all have those patients who would have relatively smaller kidneys and they are hurting a lot and I have had patients who have massively, massively enlarged kidneys and they do not have that much of pain. They may have some discomfort, as far as the size, but not really painful. Obviously, if the pain is very severe and chronic and daily, you know, it can affect your social, job performance, your mood, your, you know, mental health, and pain management a lot of times comes to the picture. So, you can go from simple giving some

Tylenol to, you know, narcotic prescription now with the narcotic issues that we have, we have to be careful about the risk of dependence and tolerance and try to use everything before that.

And then the cyst drainage, you know, by just based by needle drainage could be used. My colleague at Harvard, Ted Steinman has actually developed a very predictive model that it works really well. If the area of the pain corresponds to a major or two major or three major cysts that are much larger than the other ones, and that is where the patient is hurting, and the size is at least three to four centimeters, going after those individual cysts has actually a pretty high yield in relieving the pain. And you would know that because as soon as you put the needle in there, patients say, ‘Wow, my pain is almost 80% or 60% or 90% gone’. But if the cysts are all over

the place and there are too many of them and the size is, kind of, all over the place usually it does not help, you know, going after those individual cysts and it actually may hurt them to have more pain and have you know complications of infections and things like that.

The more radical treatment is a cystorrhaphy, which is a surgical procedure. It was very commonly performed in the 80s and 90s and we, kind of, backed away from those because we realized that it actually does not help protecting the kidney function. If anything, when you do cystorrhaphy, you are also removing some good tissue and the kidney function may go down. But the major, major problem with those is that if we end up in a situation of non-healing and oozing intraabdominal wounds, then you get ascites and that becomes a really complicated situation and a lot of time, you know, you basically have to go and take the kidney out.

So, there are some other more invasive treatments such as renal sympathetic denervation, that is invasive, it should be done by a group that is really familiar with that and it should be only considered in patients who have really excruciating pain that is refractory to the typical treatment plans that we have.

Another associated feature of polycystic kidney disease is actually liver cysts. Liver cysts are extremely common. If you wanted just to go by a presence of one cyst, and look at all PKD patients, at least 75% of them would have at least one cyst at some point in their life. Most people have more than one. And if you look at the end of life, pretty much 90% of them have at least one cyst. The interesting thing about these cysts is that they do not cause liver failure. They do not cause liver cirrhosis, but they can cause, you know, mechanical compression issues with rupture, infections, and also, you know, if the liver is extremely big, then it can actually cause malnutrition because you do not have room to eat food and you basically chronically become malnourished. There are some strategies as far as either medications, somatostatin analogs and octreotide have shown actually a reduction of the cysts, which is moderate but they also come with the risk of inducing diabetes and also, you know, you have to see whether the insurance companies will cover that drug. One of my patients just recently, the insurance said, 'We are not covering that indication'. And as far as surgical options, if the left the liver, which is th much, much smaller part of the liver, is actually involved and is very big and it is pushing against the stomach, it can actually very easily resect that and that gives people more room to eat and I have used that trick in many of my patients with these situations. But then the larger cystorrhaphy surgery is more complicated and again, you know, it has more post-operative issues as far as healing and infections and scarring. But it can be considered, as well.

The next very important topic is actually screening and detection and treatment of intercranial aneurysms and I am going to ask Michel to go over that.

Dr. Chonchol:
Thanks, Fred. I agree with you. This is really a key clinical area that we need to pay attention in patients with polycystic kidney disease. And as we know, it presents in 10 to 12% of all screened PKD patients. Usually, it is in the 75% is these aneurysms are located in the arterial circulation. It is important to remember that these aneurysms are more important in families with histories of intracranial aneurysms. It is not only intracranial aneurysm, but also the dolichoectasias, which means an elongation, dilation without really the vessel without an aneurysm, and that can happen in approximately 5% of cases. We need usually to screen. Screening needs to be offered to those patients who are obviously symptomatic, like headaches. Headaches positive family history of stroke or cerebrovascular events, high-risk job. The job that always comes to mind is obviously an airline pilot or pretransplant or any other type of surgery. There is no question that an MRA of the brain without gadolinium is recommended as a first line treating tool. If this one is negative, there is no need to repeat it for another five to ten years.

Obviously we need to avoid uncontrolled hypertension, smoking, heavy alcohol consumption, all, kind of, logical things in the management of aneurysms, as well as stimulant medications, illicit drugs, and excessive straining on Valsalva maneuvers. The full embolization or surgical clipping I needed if the site is greater than 7 mm. However, some patients might really be very concerned if the size is smaller and request consultation with some of our neurosurgical colleagues.

Fred, do you want to maybe summarize, kind of, the nutritional recommendations for this population?

Dr. Rahbari-Oskoui:
Sure. The main things based on this studies that have been done, we recommended moderate protein restriction diet in ADPKD and that is based on the MDRD study that had a fair number of PKD patients in that and over long term that is an effective intervention. From the HALT-PKD study, we clearly linked urinary sodium excretion, which basically reflects your salt intake and we know that when you are eating more salt and you are excreting more salt in the urine, that is a risk factor for kidney growth and also to the drop in GFR and then in ESRD. And this is data from HALT-PKD trial. So, we are really adamant about that it could be actually a completely new way of not only treating hypertension but also prolonging the kidney life in polycystic kidney disease.

High water, the same way that tolvaptan blocks, you know, the vasopressin effect, you know, if you drink a lot of water, you can suppress vasopressin. We know that from this single study that was done it was a relatively small study in Japan, they did not actually

show a clear difference in either kidney size or kidney function. But again, there were caveats with that study, it was a small study. There is a much larger study now in Australia that is going on and we will have the results, hopefully by the end of the year. Caffeine in animal models of polycystic kidney disease clearly fuels food secretion in ADPKD and increased size of the kidneys. In human studies, when we looked at a healthy kidney in CRISP retrospective data after the studies were done and we knew whether patients were taking caffeine or not, we did not see much of a difference between caffeine consumers and versus non-consumers. Caffeine clearly can still worsen the blood pressure. We do not recommend smoking at all, both in animal models and in human studies, the risk of

progression of kidney disease is higher in smokers. And obesity, as Michel already talked about from the HALT-PKD trial, obesity and overweight, being overweight, is clearly associated with faster progression both in change of kidney volume and slope of the decline of the kidney function. So, those are the things that have been established. Now, the ketogenic diet and time-restricted fasting are very hot topics and there is some animal models that have shown that in the clinical trials that are pilot studies are ongoing, so we are waiting for the results and hopefully we will have larger trials to go over the final results of those interventions.

As a summary, take-home message, what would you recommend if I wanted to point out five strategies for PKD patients; what would be the take-home message to take care of these patients?

Dr. Chonchol:
Thank you, Fred. I, you know, I think I modeled the key treatment areas have had an impact in our PKD population as we know that the longevity of these patients is increasing steadily with more than ten years over the last forty years. If you would ask me, I think hypertension is probably the most common and treatable associated complication in PKD. We need to do our best to lower to a systolic blood pressure of 110 in those with a GFR of greater than 60 and at least a systolic blood pressure of 130, if not 120 in those who have more advanced polycystic kidney disease. We need to screen and treat for intracranial aneurysm. I cannot stress this more as this could be a devastating complication in patients with polycystic kidney disease especially in those who have a family history of aneurysm. We need to remember that the vasopressin receptor antagonist, tolvaptan should be considered in all patients who have high risk of progression because it is the only modifying drug that has been really approved by the FDA. And as you mentioned, we will talk about the dietary interventions, low salt, protein restriction, high water intake, as well as avoiding cigarette smoking in this population as other, kind of measures to improve the outcomes of PKD patients.

Dr. Rahbari-Oskoui:
Thank you very much Michel for all your help and input in this presentation. I hope that this webcast has been useful for the audience.

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