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Optimizing the Care and Quality of Life for Patients with ADPKD – Part 4: Emerging Therapies

Announcer:
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Dr. Chapman:
Good afternoon, and welcome. Today we are going to be talking about optimizing care and quality of life in patients with polycystic kidney disease: Part 4 – Emerging Therapies. I’m most fortunate today to be joined by my colleague, Michel Chonchol, who is the Chief of the Division of Renal Disease and Hypertension at the University of Colorado. I’m Dr. Arlene Chapman. I’m Professor of Medicine at the University of Chicago, and I’d like Dr. Chonchol to introduce himself as well. Michel?

Dr. Chonchol:
Thank you so much, Arlene. The honor is mine, and I’m a Professor of Medicine and the current Section Chief of Renal Diseases and Hypertension, here at the University of Colorado in Denver.

Dr. Chapman:
Terrific. And so, I’m just going to briefly go over our learning objectives for this webcast, and by the end of our presentation, hopefully all of you who are participating should be able to recognize novel pathways targeted for interventions in autosomal dominant polycystic kidney disease, and be able to summarize clinical studies using targeted pathways for treatments in this disorder. So, just as a brief reminder, ADPKD pathophysiology is related to the development and expansion of cysts within the kidney. These cysts develop due to mutations in the PKD1 and PKD2 genes in over 93% of cases. In ADPKD, even though it is diagnosed in adulthood, renal cysts develop in utero and continue to develop and enlarge throughout life. In the majority of patients, clinical symptoms begin before renal insufficiency and are observed in the first two to three decades of life. And these include hypertension, nephrolithiasis, abdominal pain, hematuria and urinary tract infections – the Big Five. So the typical renal presentations are related to cyst burden and kidney size, and occur long before loss of kidney function occurs. These cysts form due to physiological mechanisms related to reduced availability of polycystin-1 and polycystin-2. Polycystin-1 and polycystin-2 are the protein products of the PKD1 and the PKD2 genes.

They are pleomorphic in their function, and they are located in multiple areas of epithelial cells. PC-1 and PC-2, i.e., polycystin-1 and polycystin-2, are located together on primary cilia of tubular epithelial kidney cells. Their exact function is not completely understood, but it appears that the primary cilia need the polycystins to sense their environment and to be able to transduct signals into the cell, that relate to the levels of intracellular calcium that are needed for proper function. In addition to alterations in ciliary function, there are mitotic orientation defects. These defects occur simultaneously with alterations with cyst fluid secretion, primarily chloride and water, into the lumen of these cysts. When there is not enough polycystin-1 or 2 around, or present, it is believed that then there is a decrease in intracellular calcium levels. There is an increase in adenylate cyclase 5-6 activity, with reduced phosphodiesterase-1 activity, and there is also increased intracellular cyclic AMP levels, and this results in activation, a proliferation, and secretory pathways on the apical surface of the cell, as well as increases in proliferation.

The current state of management in ADPKD has been already discussed in this module. It involves using renin angiotensin aldosterone system inhibitors for blood pressure control and reduction of proteinuria. And they have been shown to reduce the rate of increase in total kidney volume, a marker of cyst burden, and delay the rate of loss of kidney function in ADPKD. In addition, tolvaptan, which I think

you've heard about, is a vasopressin V(2) receptor antagonist, and is a newly approved therapy for ADPKD, particularly for those who are at high risk for progression to end-stage kidney disease. Tolvaptan therapy reduces the rate of increase in total kidney volume approximately 40% per year, and also reduces the loss of estimated GFR approximately 1 ml per minute per year. Despite these available therapies, however, total kidney volume can still increase, and kidney function can still decline, leading to CKD progression and end-stage kidney disease in ADPKD. So there are a number of emerging therapies in ADPKD that are currently under study and review. There are several novel approaches, many of which involve dietary interventions, such as the ketogenic diet and time-restricted feeding. Both of these result in decreased mTOR activity and STAT3 signaling, precursors for cell proliferation. There are antioxidants, anti-inflammatory agents such as bardoxolone which promotes activation of the Nrf2 or nuclear factor erythroid 2 derivative, and suppresses inflammation. And there are drugs that rely on AMP phase stimulation, such as metformin which has been shown to inhibit cystic fibrosis transmembrane conductance, which results in chloride secretion and fluid accumulation, and also the mTOR pathways that are involved in dietary interventions. So with that, I am going to hand over the podium to Dr. Chonchol, who's going to share with us the results of some of these very exciting studies.

Dr. Chonchol:
Thank you so much, Arlene. So to start, we will start with the dietary interventions and just as an introductory slide, I wanted to present to the audience a very simple observation, that it was the association between higher body mass index, or BMI, with PKD progression. So this is data from the HALT-PKD Study A, one of the largest PKD studies ever done, looking at the effects of blood pressure on progression, and as a post hoc analysis, these patients were evaluated to look and examine their BMI and its association with progression. The population was stratified by normal weight, overweight, and obese, and pretty much the five-year longitudinal association between changes in total kidney volume that was examined by MRI was examined. As we can see on the slide on the right, you can see that those patients – the overweight patients as well as the obese patients – had a significantly higher annual percent change in total kidney volume, when compared to patients that were in the normal weight. Again, this was a very simple association, but very telling that there was a link between metabolism and PKD progression. In fact, there is well-documented data regarding the cell metabolism and energy production in PKD cells. It is known that polycystic kidney disease cells referentially use aerobic glycolysis, rather than oxidative phosphorylation for energy. This is what has been called the Warburg effect, which is also present in cancer cells. It's a less efficient means of energy production, and pretty much really the goal is to overregulate glucose importation, as well as systolic degradation. Therefore, glucose starvation, as a hypothesis, could nicely reduce proliferation of PKD cells, and this has been shown, and there is also a lot of interest that cellular metabolic sensors may play a critical role in cyst formation as well as progression. So, what happens if we alter diet in patients with polycystic kidney disease? And a lot of the data that I am going to show you in this area is really based on animals. There is some human data will be coming out soon, but at this point, most of the provost data is in animal models of PKD. So glucose starvation will reduce proliferation of PKD cells. If we inhibit anaerobic-like, it will decrease kidney weight as well as cyst formation in animal models. Now, we'll establish that caloric restriction without malnutrition, so a 10-40% decrease in caloric intake will slow the disease progression in animal models. These are well-accepted animal models of PKD, in which it has been shown to have a reduce in cyst area, kidney fibrosis, inflammation, as well as injury in a dose-dependent fashion. And a lot of the pathways, the mTOR pathway and MT pathway are some of the pathways that Dr. Chapman spoke in previous slides, and I will show you another slide, showing these different pathways, as they're also involved in potential benefits that metformin may have in PKD patients.

The ketogenic diet and the time-restricted feeding appears to increase renal cystic burden among rat, mouse, as well as feline models of PKD. As we know, cats – this is well-established in the literature – tend to have a significant instance of kidney failure and, in some fashion, also polycystic kidney disease.

These are studies that were done in animal models. Pretty much, they were exposed at ketogenic diets, as well as time-restricted feeding in these animal models. All these diets consisted of similar caloric value. The normal diet – ad lib – had normal chow that consisted of 13% fat, 62% carbohydrates, as well as 25% protein. The ketogenic diet had pretty much a very high content of fat – around 91%, with a low content of carbohydrates as well as protein. The time-restricted feeding was done pretty much in a very similar way as is done in humans, where the animals had access to normal chow eight or twelve hours in the dark cycle. You can see in the lower panel that rats that were exposed to ketogenic diets – males and females – you can see the PKD rats, compared to the wild type, and you can see a pretty nice reduction in both males and females regarding the overall total kidney volume of the kidneys of this rat. In the same slide, or in the same diagram, you can see, kind of, the date of the time-restricted feeding in rats where, again, in males and females, you can see that the rats with PKD that were exposed to the time-restricted feeding have a decrease in total kidney size in these rats, when compared to the ad lib diets. I can suggest that this intervention – dietary interventions – may have a profound effect on PKD progression, and there are ongoing studies in humans, with a lot these diets, including weight loss, time-restricted feeding, ketogenic diet, to see if a lot of those findings translate into human disease.

Switching gears a little bit, we'll be speaking about metformin. Metformin as we know it, is a very well-established drug that has been

approved by the FDA for the management of diabetes, as well as metabolic syndrome. As we have spoken in this module, in ADPKD there is an elevation of vasopressin. Vasopressin tends to operate like intracellular toxic AMP, and we know that the inter polycystin-1 and polycystin-2 is unable to negatively regulate this true calcium signaling. This cyclic AMP, to make PKA and the map kinase mTOR signalling pathway, causing changes in transcription. If you see – on the diagram on the right, you can see that everything that is in blue is a normally increasing PKD, and that includes cyclic AMP. This results in elevated growth factors and cytokines that tend to obviously promote fluid secretion as well as cyst formation and cyst growth.

Metformin is known to activate AMP kinase, with a potential of decreasing both cell proliferation and fluid secretion. Therefore, I will be presenting the results of two studies that have been recently published, looking at the feasibility of using metformin in a human polycystic kidney disease. Until these two studies, there were only animal data about the effects of metformin on animal models of PKD, which have revealed that metformin may have a role in kind of reducing cyst size in animal models of polycystic kidney disease. I will present two studies in tandem. One is the TAME study that is in press in Kidney International, and the other one is the Colorado study, which is press in the American Journal of Kidney Diseases. Both studies have similar age group of patients, around 42 for the TAME study, 48 for the Colorado study.

The GFR in the TAME study was around 86, a little bit lower for the Colorado study, and overall the feasibility of using metformin in this population showed that this drug was safe, and the main concern about cases of lactic acidosis really was not reported in either study. What was interesting is that both studies, none of – all of – 100% of patients were able to tolerate the metformin full dose. In this TAME study that, again, I – it was a multicenter study versus the Colorado study that was a single-center study – only 67% in the TAME study of the participants were able to tolerate the metformin at the full dose, that I'll show you that is 1,000 milligrams, twice a day – versus 50% of participants in the Colorado study, which was a single study.

So the follow-up slide will show you a little bit of the difference between the two studies. The TAME study had almost double the population of the Colorado study. Both of them were a one-to-one randomization of metformin, that was titrated up to 1,000 milligrams, twice a day. You can see, pretty much, the time frame for each of the studies, and age range for the TAME study was 18 to 60, versus 30 to 60 for the Colorado study. The GFR ranges were quite similar, and there was no total kidney volume requirement, both for the TAME or the Colorado study. One advantage of the TAME study was a much larger follow-up – longer follow-up of two years, 24 months, versus 12 month follow-up for the Colorado study. But again, the primary outcome was mainly the same for both and it was safety and tolerance. And there were some secondary and exploratory endpoints for the TAME and Colorado, that really focused on kidney function and total kidney volume.

So, as I'm showing you here, kind of the mean results of the exploratory endpoints or secondary endpoints for the TAME study and the Colorado study, we can see that both in the TAME and the Colorado study, the changes really in total kidney volume were quite similar in the metformin versus the placebo study. And actually, the p-value was a non-significant p-value. The Colorado study does present in their publication some data stratified according to size of kidney volume, and they do mention that in those patients in which the total kidney volume is greater than 800, they were able to observe a difference in total kidney volume. Again, this was mainly exploratory, and not a predefined, secondary or endpoint in this study. What was interesting was the data in EGFR. Although the p-value was nonsignificant for either study, it was quite clear that metformin reduced the progression of renal disease, defined as a yearly decline of EGFR, when compared to the placebo. The changes in EGFR in the TAME study was 1.71, versus 3.07, and in the Colorado study, was 0.41 versus 3.35, all obviously inclined in kidney function.

Again, this therapy may show some promise. However, it will need a follow-up, phase 3 study, which I understand is happening in Australia, with a much larger population, looking at the effects of metformin as a primary endpoint for kidney function decline and total kidney volume.

I will pass the podium back to Dr. Chapman, who will give you, pretty much a synopsis on a very exciting therapy that is bardoxolone, and its effects on kidney function decline in patients with polycystic kidney disease.

Dr. Chapman:
I'm going to share with you very briefly, some new developments and a new pathway of interest for patients with autosomal dominant polycystic kidney disease. So, it's been shown that when kidney cysts develop in the kidney, there is significant renal inflammation, particularly surrounding cysts, as well as renal fibrosis. And so, there has been renewed interest in targeting anti-inflammatory therapies in ADPKD. Nrf2, which is also called nuclear factor-erythroid 2 related factor 2, is a canonical, critical transcription factor that regulates the expression of hundreds of genes that are involved in multiple pathways, including the antioxidant response, metabolism and lipid regulation, and mitochondrial function. Nrf2 activation can reduce the inflammatory cascade. It can prevent fibrosis, and it's been shown in a number of kidney disorders to restore kidney function. Therefore, therapeutic agents that favorably modify the Nrf2 pathway is really an attractive candidate for novel therapies in adults with ADPKD.

This cartoon shows you what happens to Nrf2 under both normal and oxidative stress conditions, which would be akin to having cysts growing within the kidney. And you can see that Nrf2 is kept in with Keap1, and plays a role in ubiquitination, which is a protein degradation process that provides protection in the extracellular space of multiple organs including the kidney. This degradation results in inactive transcription of multiple genes that could otherwise play a negative role in kidney disease and progression. On the right, you can see what happens under the stress conditions, and this doesn't have to be limited to cysts. It can be a number of different kidney disorders that are associated with inflammation, or basement membrane dysfunction, and you can see that Keap1 is now inactivated, and no longer holds on to Nrf2. So Nrf2 is no longer available for this protein ubiquitination process, and it starts to accumulate in the nucleus, and no longer works properly. Because it's not working properly, it can't inactivate transcription, and transcriptional activation begins. And there are a number of target genes that are critical for oxidative stress responses, as well as metabolism, as well as inflammation, which are shown on the bottom. So when Nrf2 is not available, there's a lack of an antioxidant response. There's a lack of NADPH synthesis. Glutathione metabolism is abnormal, and mitochondrial function is also changed. And all of these result in tissue destruction in the kidney. So this is a critical pathway that, although it's not specific to the polycystins, it has a significant role in response to the presence of cysts in kidneys.

So we have toxins, eschemia, trauma, structural defects – cysts would be considered such – and then activation of NF-kappaB is very, very important, as it orchestrates and produces pro-inflammatory cytokines, all of which Nrf2 is responsible for removing.

It can happen in multiple cell types, including the podocytes in the glomerulus, from the tubular epithelial cell, from the mesangial cell, and from all of the endothelial cells that are in the kidney. They all play a role in TNF, interleukin 6, interferon alpha, as well as permeability across the cell types. So this is a critical, canonical pathway that can have a significant role in ADPKD, with regard to tissue fibrosis and inflammation.

So, bardoxolone, which is a Nrf2 activator, which will help subdue the inflammatory and oxidative process, has been tested already in ADPKD patients, in the Phoenix Phase 2 clinical trial. And so, leading into this study, before randomization, there were 31 patients who had historical kidney function data that predated entry into the study by up to two years. And so, in 29 of 31 individuals, kidney function rate of decline could be measured prior to enrollment into the study, and it was found to be 4.8 ml per minute per year, prior to enrolling. This is probably in the days before tolvaptan was available, and that is a higher rate of decline than we typically see today in our tolvaptan, blood pressure controlled, high-risk, ADPKD patients. Nonetheless, after bardoxolone was administered in a randomized fashion, there wasn't a reduction in the loss of kidney function; there was actually an increase in EGFR of close to 10 ml per minute per year. Oh, sorry, this was at 12 weeks of therapy, and this was the duration of the study. So, safety data was collected during this time. There were no serious adverse events found. There were side effects related to bardoxolone therapy that had been observed before in humans, and included muscle cramps, constipation, and perhaps some additional leg moving, but not to the point where patients discontinued from the study. So these preliminary data have led to the development of a Phase 3 randomized clinical trial, which has been named FALCON – ADPKD. And this is a trial of 104 weeks of duration. The first year is a randomized study in a one-to-one fashion, with individuals grouped further based on their level of proteinuria. And in these individuals, they are randomized starting off with a bardoxolone dose of five milligrams, going to 10 milligrams, and then 20 or 30 milligrams, if they are in the high proteinuria group, meaning those with greater than 300 milligrams per gram of creatinine a day. And this is in comparison to placebo. The duration of this phase of the study lasts approximately 48 weeks. There is then a washout period, where the patients are stopped, both placebo and active therapy, and then all patients are randomized to receive bardoxolone for another year. And then there is an off-study drug period, again for four weeks duration, before the final measurement of kidney function using serum creatinine is performed. With this two-year study, and the number of subjects that they plan to enroll, they should be able to determine if there is a sustained effect on EGFR that is found throughout the two years of study. Remember, this is not a study where EGFR decline is lessened. It's a study where the drug performs and increases EGFR over a period of time.

So in closing, I think what Dr. Chonchol and I have covered today includes the rationale for drug development in how the polycystins work, the rationale for considering changes in dietary exposure with regard to keto analogs as well as duration of feeding in a 24-hour period, as well as the potential exciting role for metformin therapy from an efficacy standpoint for reductions in EGFR, as well as the potential for a non-PKD-specific pathway that relates to inflammation in the kidney that, if it is reduced with Nrf2 activation, may provide extended increases in kidney function. And on the horizon, the potential availability for drugs that block the V2 receptor – the vasopressin V2 receptor – that are no longer hepatotoxic. And with that, I would like to close and thank you very much for your time and attention.

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