

Understanding PKU and New Treatment Options

Webcast

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Introduction

Andrew Schorr:

Hello and thank you for joining us for the first in our series of special-edition live webcasts on PKU. I don't know if there has ever been a series like this, and we're grateful to BioMarin for providing an unrestricted educational grant so we can do these programs and connect you with leading experts, inspiring caregivers, people touched by PKU to give you their perspectives and for you to ask them questions. Now Carlene, our announcer, just mentioned the phone number, and many of you will want to ask questions to you can do it in two ways; we got many e-mails already, and you can call in. We'll try to get to your questions as we go on. Obviously you want to keep your questions brief and to the point.

Today we're talking about the new landscape in understanding PKU treatments and now that there's a new, the first FDA approved medication, how does that come in with the diet, how do we manage PKU, and we have leading experts to help answer your questions. Also remember that you can send us an e-mail as well, and many people have. Here's that e-mail address again: PKU@patientpower.info.

Two other points I want to make right off the bat. We're doing two other webcasts and maybe more, but certainly two more are already scheduled. On May 27, 2008, we're going to talk about access to care, insurance and reimbursement support programs for new PKU treatments. So I'll reserve our questions related to that to that time. I know many of you have sent some in now, lots of questions. We're going to tackle them then and talk about understanding the new treatment options today.

Then on June 19, 2008, we'll be doing a program helping people understand patient approaches to the management of PKU, and you'll get a little bit of that today with our first guest.

Now admittedly, my family has not been touched by PKU. My daughter does have a chronic GI condition, and she took for a little while the elemental diet. We know how difficult a restricted diet can be and being compliant with that and with a teenager for

sure and I know that's going to come up tonight. Also, I was in a clinical trial, and as a cancer patient, I had to consider a lot, and certainly with new or even experimental medications saying, well what's the benefit to me short term? Are there concerns long term?

Corinna's Story

Andrew Schorr:

We're going to discuss all that tonight, so thank you for your questions in advance. Let's start by meeting someone who thinks about PKU every day because she has not one but two children with PKU, and that's Corinna Vonderwell who joins us from southern Indiana, Vincennes, Indiana. Corinna, you have three kids, and in our bio that we've done, they have letters after their names; Kaleb who's 13 with PKU, Kameron your middle child, and he likes to have letters behind his name, "REG," and I understand that stands for "regular." He wants to have letters too, and then Karlye who is just nine.

So you think about this every day. How do you view right now where we are with the management of PKU?

Corinna:

You know, I'm really excited that we live in a time where we're not having to reinvent the wheel. My children were born in an age where treatment was already established. Consequently, they are beautiful, happy, healthy children, and what we consider normal, and we use that word carefully, but we consider our kids perfectly happy and healthy, and we're blessed to have these new treatment options that have come along in their lifetime. You always hope for a cure in your children's lifetime, but when something like this happens and this sort of door opens it's really exciting.

Andrew Schorr:

Now, you have two children who have been taking the new medication, KUVAN, and trying to tweak that for them. They have to take pills and figure out how that fits into their diet, and also still staying on a pretty restricted diet. How is it going because certainly with kids they change every day, and they have their own view of the world, and you've got a teenager; so it requires vigilance and helping them take responsibility too doesn't it?

Corinna:

It really does, and every child is different. Every personality is different, the way they respond and the way that they react to just life in general is different, and that's the case certainly with my two PKU children. Both of my children were participants in the clinical trial. My oldest son was always compliant with his low-protein diet and was drinking his formula. My daughter as well, who is nine. We really never had any problems, and their levels always were maintained between two and six, which is considered normal, and when Caleb turned 13 in the middle of this clinical trial, all of

a sudden his levels began to spike, and we didn't know why, and when I say a spike, with him, it was maybe a 14 or 15 that might have been his highest level, but understand that his normal was two to six, so for them that was incredibly high. His grades began to drop in school. He began to have some conduct disorders. We were really concerned about this such that we had him tested in the school. Come to find out, we had an admission on the way to a clinic visit, 'Oh by the way mom, I've been dumping my formula in the morning when I walk the dog.'

So really, we consider KUVAN a blessing, but we are still PKU diet for life. Those levels are really important, and we monitor them regularly.

A New Treatment Option for PKU

Andrew Schorr:

I think that's a point we're going to make a lot is this new drug KUVAN has been approved, but it's to work with a diet, and we're going to learn more about the appropriate use of medication and who it applies to.

Let's meet an M.D. who deals with this all the time and has these discussions. He's in the Bay area in San Francisco, Gregory Enns, M.D. Dr. Enns is Associate Professor of Pediatrics, and he's Director of Biochemical Genetics at Stanford University School of Medicine and the Lucile Packard Children's Hospital. Welcome, Dr. Enns. So how would you characterize the situation now? I mean for a number of years, decades now, all the kids in America when they're born they are screened for PKU, and that's helped identify and let people have a strict diet and manage their Phe levels by following that diet as best they can. Now we add a medication to it. How would you describe the situation now?

Dr. Enns:

Well, first, thanks very much for allowing me to speak tonight. It's a pleasure to be here. I think that it's an exciting time. This is a treatment that has been a long time coming. I'm happy to be able to discuss a novel treatment with patients who come to my clinic, and everybody has a little bit of optimism I would say that perhaps things may be improved by taking KUVAN, and as has already been stressed, this in no way means that you can stop taking the diet low in phenylalanine. Dietary therapy is clearly an important part of the care of PKU patients. In fact, the special diet is a groundbreaking treatment, and PKU newborn screening and institution of diet therapy is a true success story in the treatment of metabolic disorders. Perhaps it would make some sense to discuss what PKU is a little bit. I am sure there are plenty of people who understand and are very well versed in PKU, but maybe we should talk a little bit to those who might not have such a clear understanding.

Andrew Schorr:

Yes sir, please do.

Dr. Enns:

So PKU or phenylketonuria is an inherited disorder of metabolism that can affect children, and because of a buildup of phenylalanine in the brain these children can become retarded and severely brain damaged unless therapy is instituted very early in life. So this is a metabolism problem. Phenylalanine is a component of protein, and as such if you have a deficiency or you're not able to metabolize certain components of protein, in this case phenylalanine, normally, the phenylalanine level tends to get high in the body and especially in the blood and in the brain. Phenylalanine at high levels is toxic to the brain, and, especially during the critical period of brain development in the first several years of life, it is absolutely critical to have as well-controlled phenylalanine levels as possible, in order to protect yourself from any developmental difficulties that could ensue.

So before the 1960s there was not newborn screening. Robert Guthrie with his Guthrie test made newborn screening for PKU possible, and I've seen the effects. Believe it or not, I've seen patients who were born before the time of newborn screening who have severe neurological symptoms, are wheelchair bound, have psychiatric manifestations and are just severely impaired, and I compare those individuals to the healthy well-adjusted, normal children that I see in clinic, and it is really truly a remarkable story.

So that has always been the case since newborn screening and the diet therapy. There have been improvements that have been incremental. The diet has improved. There have been better ways to treat this disorder with special medical foods, etc., but this is truly a new treatment and it's a new approach, at least in North America. Biopterin, which is what KUVAN essentially is, has been used as a screening tool in Europe for a number of years, but having this available for PKU patients is a real difference.

Andrew Schorr:

Thank you for those remarks. Now let's meet our other clinical expert, and that's Dr. Susan Waisbren, and she's across the country in Boston, Massachusetts, where she's a psychologist at Children's Hospital in Boston, one of our leading Children's Hospitals as is the Lucile Packard Children's Hospital at Stanford, and Dr. Waisbren has devoted 30 years of her life to studying PKU.

So Dr. Waisbren, there are some really smart and accomplished people who are diagnosed with PKU who are doing pretty well, and you know they tried the diet as best they can, and some people say I've done pretty well. There's a medication, should I be taking it as an adult? We'll discuss all that along the way, but it seems like, and I know from your study, PKU can be very variable, can't it?

Dr. Waisbren:

Yes, not only intolerance of phenylalanine but also in outcome, and I think it's important to remember that who you are depends a lot on where you came from, who

your parents were. For example, 42% of the variability in IQ can be explained by the genetic contribution from your own parents. So before you even start there are some influences on how you'll turn out. There are also influences stemming from the mother-infant bond. Some recent studies are showing that if the bonding doesn't take place well, then the child doesn't develop as well and has a lower IQ. If you think about that very early period of a parent getting a diagnosis of PKU in her child, you can imagine how that may disrupt the mother/infant relationship. And then beyond that, of course, is how well the child maintains metabolic control, especially during those first five or six years in life.

And then there are different kinds of PKU. There are the more classical forms where there is very little tolerance and it's much harder to keep blood phenylalanine levels within the recommended range, and there are the more mild forms, but even within those there is variability. We haven't been able to show that with certain types of PKU the outcome will definitely be better or worse, so there are a lot of factors that go into this.

Andrew Schorr:

Corinna mentioned numbers, Phe level numbers a little while ago, but how does someone know what's the optimal Phe level number for them? It would seem like with all these genetic factors in the background that could be different for different people.

Dr. Waisbren:

The recommendation from the NIH Consensus Conference that took place in 2000 was to maintain blood phenylalanine levels between two and six mg/dL and that's pretty much what most clinics recommend in the United States now. As the children get older in the teenage years, that can be raised a little bit and then for adults maybe a little more.

Andrew Schorr:

Now I know you look at the developmental challenges. So we're asking kids as they get older, and Corinna faced it, to follow a really strict diet to try to grow up and be around other kids and your school and your neighborhood, etc, and follow that strict diet. I know as I mentioned with my daughter with a different condition it was really tough. So if you now have KUVAN, and we'll understand who it may be right for, how does that help in meeting these challenges as kids develop and yet try to keep those Phe levels down and avoid the toxic effects of the condition?

Dr. Waisbren:

I think it's all about choice and options. I tell parents that the first rough spot usually occurs around age three. Age six is another challenging time, when children enter first grade. All kids have troubles at age 13, and the college kids are also having a really hard time. By the time they're 24 or 25 they come around again. So those are the rough spots, but throughout you don't want the diet and maintaining blood phenylalanine levels to be the battlefield. So the more choices that you can give

families and children, say well maybe you're having trouble with the diet, let's try liberalizing it through using a medication like KUVAN. That gives hope. That gives some sense of control to the kids, and even little kids need that kind of choice in order to maintain their identity as they get older.

PKU Classifications

Andrew Schorr:

Dr. Enns, we've received many questions, and a number of them fall into this category in saying, and we mentioned classic PKU, and maybe you can help us understand the sort of different classifications, if you will, but who is this new drug right for? What version, if you will, of PKU?

Dr. Enns:

That's a terrific question, and I think it's probably best to take a minute again to step back, and as you say maybe define the different classifications of PKU. If you talk to three or four different geneticists you'll probably get three or four different classification schemes, but for the sake of simplicity, I try to keep things as simple as possible. Classical PKU, the most severe form of PKU, is associated with the most severe form of enzyme deficiency.

PKU is caused by a deficiency in an enzyme that's called phenylalanine hydroxylase. If you have an enzyme that is absent or not working at all, your blood phenylalanine levels if you don't use a special diet at all will be very, very high. They'll be over, I'll use the mg/dL, over about 20 mg/dL in classic PKU. On the other hand, if you have some enzymatic activity or a more moderate form of PKU, some people call it variant PKU, but I'll just use the term moderate, levels between 10 mg/dL and 20 will be reached if you don't restrict the diet at all. And then the most mild forms of PKU tend to have phenylalanine levels less than 10 mg/dL, which is still above the normal range. Normal blood phenylalanine levels are in the range of maybe 2 mg/dL and below, so even the mild form of PKU has phenylalanine levels quite higher than normal, but still quite a bit less than the most severe forms.

When we look at those different classification schemes, patients will respond differently depending upon the severity of their PKU with a broad-stroked view of this. Individual patients, however, might respond very well if they have classical PKU or very well if they have moderate and very well if they have mild. You have to test each patient, but when you look at the data that has been published on how well patients respond to KUVAN or to biopterin, the classical PKU patients respond less often than the most mild forms, so it's a little bit the reverse of what we would want of course. We would want a medication that would have the most classic forms responding the best because they certainly need the most help, but, be that as it may, ranges of between 10% and 25% have been reported overall of classical PKU patients who will show a response to KUVAN. When you get more into the moderate range, the percentage of responders goes up to maybe 55% to 60%, and when it's when you hit

the most mild patients that nearly everybody responds. About 90% or more will respond if you have the most mild form of PKU.

What do I mean by response? Maybe we should define that a little bit too. People use different criteria for this, but one criterion that has been used in clinical trials has been a decrease of blood phenylalanine levels without changing the diet of 30% or more, and that's a fairly high bar to jump over, but that's been used in trials. It depends upon what your starting level of phenylalanine is of course as to how significant that response is going to be. If you have an exceptionally high level, and your level is 30% better, but it still remains exceptionally high that's not so good. If on the other hand you have a moderately high level of phenylalanine and you're 30% lower, and that changes your life, and you feel better, I think that's a very good response.

So in a nutshell, anybody who has any form of PKU is a potential candidate for treating with KUVAN. You have to basically take it on a case-by-case basis. I think every classical patient should be screened for responsiveness because there is a portion who do respond, although the majority do not. The moderate patients who have levels greater than 10 mg/dL untreated, the majority of those or a good proportion of those respond, so I think that again those patients should at least be tried on KUVAN, again, in the context of what is the patient expectation, what is the family expectation.

As far as the most mild forms of the disorder, when I first heard about the KUVAN responses that patients were achieving, I was happy of course but also a little frustrated because it works best for the mild patients. I thought well, most of my mild patients are probably not really going to need this because their blood levels are pretty decent, they don't have too much restriction in the diet compared to the most severe cases. That being said the first patient I ever treated had a mild form of PKU. This was a teenager who came into my office who brought in boxes of unused medical foods because she couldn't stand the taste of the stuff. Her levels were still quite good, but she was malnourished. Her protein intake was below recommended levels, and our nutritionist was really quite concerned about the low level of protein that she was able to tolerate or get into herself because she couldn't tolerate the medical foods, so we put her on the KUVAN and liberalized the diet. She still maintains fantastic levels, but her health and her nutrition are so much improved.

So it really depends in a nutshell is what the situation is with the individual patient, but anybody could potentially be a candidate for KUVAN.

Andrew Schorr:

Thank you for that explanation. Now you, as you said, there are some people with families touched by this, people like Corinna who even lecture on it and have the graduate-level understanding, and for other people you know you just found out recently your little baby was diagnosed with PKU, this is all new to you, and believe

me there's a whole community of support there for you, and this is part of it, but you'll want to listen to this again. So remember that there will be a replay certainly by tomorrow on our website of this whole program, and then we'll be adding a transcript within a couple of weeks. You can discuss it with your pediatrician, with your nutritionists, with the folks that you consult with to try to understand this better, so lots of information.

How Does KUVAN Work and Who Can Use It?

Andrew Schorr:

So help us understand this then. Just one other clinical question for you Dr. Enns before we move on to other issues as well and that is how does KUVAN work? So is it a very foreign substance to the body, or does it work well with our own metabolism or the parts of metabolism or the substances that still can be intact naturally occurring in the body maybe to a lesser degree with somebody with PKU, but can it work synergistically? What's its mechanism of action if you will?

Dr. Enns:

Right, the mechanism of action is most like related to its ability to increase activity of the enzyme phenylalanine hydroxylase. Exactly how it increases that activity is still being investigated, but I think for most people it is maybe simple to look at it like the battery for the flashlight. It will help create more energy for the system.

Enzymes are specialized proteins in our body that convert one substance into something else. So in this case the enzyme converts phenylalanine into tyrosine, that's the enzymatic reaction, and the enzymes in our bodies require cofactors including vitamins to work correctly, that's in fact why vitamins are so essential. We have to have vitamins in many cases in order to run enzyme reactions in our body, and KUVAN is an essential cofactor for our body. Biopterin is used by the enzyme phenylalanine hydroxylase, and my feeling is that in some cases you can imagine that maybe the enzyme doesn't work quite as well as it should because it doesn't bind biopterin as well as it should, but by giving an extra amount of biopterin, perhaps that could push the enzyme into a more effective functioning state and improve its activity. So that's one way or a simplistic way of looking at how KUVAN helps things, but it is a natural substance, at least biopterin is; Our body does synthesize biopterin, but the patients who respond to KUVAN probably require an even higher level of cofactor than our bodies can provide.

Andrew Schorr:

Okay, we've taught everybody a little bit of science. People have millions of questions now. We're going to take just a brief little break, and then we're going to come back and just start talking to Susan Waisbren in Boston and Corinna as appropriate in Indiana, and you too Dr. Enns with questions as we get deeper into this. So, let's take a brief break. We'll be back in just a second with more of our live webcast understanding the new treatment options for PKU.

Andrew Schorr:

All right, here we go. Dr. Waisbren, have you got your seatbelt on?

Dr. Waisbren:

I sure do.

Andrew Schorr:

All right, let's see. Well, here's the thing, whoever wants to take this and your opinion at your clinics, can everyone that has PKU take the new medication Dr. Enns was just talking about? What's their view in Boston as far as trying it, Dr. Waisbren? What are they saying at your clinic as far as trying it to see if it's effective?

Dr. Waisbren:

It's being offered to all the patients, and it's especially positive for those who are having some difficulties with the diet or who are having some difficulties in school, some anxiety or depression or low motivation. These are the types of things that happen when Phe levels are high. Reading comprehension can be poor or laborious. Attention deficits, especially inattentive types, so some of the children are hyperactive, and math and science might be particularly difficult because of these problems with attending. For those families we are recommending that they give Kuvan a try. Others want to try it because they would like more choices. We are offering it to pretty much all the patients over four years of age and to younger children who are having difficulty adhering to the diet.

Andrew Schorr:

Now we've had people living with PKU for many years and as you reminded me the other day on the phone, we have people who are astrophysicists with PKU, people who where it's been managed and some really smart people where their brains and processing are just fine, but people listen and they say, 'Well okay, I'm not a kid anymore, but I've been living with PKU. Should I try medication? I think I've been doing okay with my diet, but I think my mental processing is okay.' What do you think? Do you have anything to say to those folks?

Dr. Waisbren:

Well, if they're asking the question it's probably a good idea to try it because that means that there's some thought that well, maybe this will make my life a little easier or my responses a little better. The other thing that's very interesting is many times they, especially the adults, will perceive themselves as doing fine. They go on KUVAN and their spouse or partner says. 'I've seen a huge change.'

I heard a story recently of a woman whose husband was doing moderately well on the diet, and he went on KUVAN and became much easier to live with, and a week later he came with flowers for his wife. After hearing the story, everybody in our clinic said we ought to give KUVAN to our husbands.

Andrew Schorr:

That leads to a question that we got in from Tamara. I'm not sure what city Tamara's in. she says her daughter has hyper-Phe. She's not on a special diet, and what they find is she has, she's four years old and otherwise very healthy, and she has temper tantrums, which you know you can see at two years old and some of us sometimes have it older. How much do you attribute that to the Phe levels?

Dr. Waisbren:

In mild hyper-Phe occasionally there are individuals who are having difficulties related to their blood phenylalanine levels, so that would be a child that we'd definitely want to have evaluated by a neuropsychologist to see if there's anything else going on and also to talk to the family and see if there are any other issues that might be setting her off. After such an evaluation, it might be worth a try.

Andrew Schorr:

Greg, go ahead.

Dr. Enns:

There are certainly different responses for different patients. It's just fascinating if you look back at the literature in PKU. You might have two children in the same family with the same gene mutations and the same blood levels of phenylalanine as we measure them but have a very different cognitive outcome or very different behavioral outcomes and that's because ultimately what we really want to know really is what is the phenylalanine level in the brain? That's not so easy to measure on a day-to-day basis, and certainly the blood is the best surrogate marker that we have nowadays, but it's certainly possible that somebody's phenylalanine level is relatively low in the blood but somewhat higher in the brain, or they might just be more sensitive to phenylalanine levels for whatever reason. We're very complicated creatures genetically. We focused on this one gene, the phenylalanine hydroxylase gene, but it's really in a sea of 30,000 others that we have to think about, and everybody's a bit different so it doesn't surprise me if somebody has a relatively low or well-controlled level of phenylalanine that maybe they can't have some sort of an effect.

Andrew Schorr:

Okay, we're going to try to get to as many questions as we can. So here's a question from Eileen in Rochester, New York. Dr. Enns, maybe you can answer this quickly. She just says for age is KUVAN FDA approved? Is there an age limit?

Dr. Enns:

There is not an age limit that I know of as far as the approval goes. The clinical trials have mostly dealt with patients who are four years of age and older, so many people in many centers are starting with that as a reasonable time to start treatment, but I happen to know in North America there are a number of infants who have been started on KUVAN. I think in time there's going to be a trend towards using it earlier

and earlier. Of course it bioplerin has been used as a form of testing for responsiveness in neonates in Europe for a number of years.

Andrew Schorr:

Okay, let's go on. We have a caller. Maria joins us from Arizona. Maria, my producers tell me you have a son who is 45 years old affected with PKU. Is that right?

Caller:

That's correct.

Andrew Schorr:

And your question is?

Caller:

Basically I'm just now hearing about this medication. Craig has not been on a diet since he was 14 years old, and he's mildly retarded, but he does extremely well. He just needs assistance. He is on medication for behavior because he does have explosive, but it is a controlled behavior so in that sense he's doing extremely well. His last lab was done in 2004, and it was 22.

Andrew Schorr:

So that was the Phe level was 22?

Caller:

Pardon me?

Andrew Schorr:

The Phe level was 22?

Caller:

Yes, so my question is...

Andrew Schorr:

Let's find out from Dr. Waisbren should he try the drug.

Caller:

This isn't going to reverse anything I'm sure, but what's the potential for us doing this, or should we do this?

Andrew Schorr:

Let's find out. Dr. Waisbren, what are they saying in your neck of the woods related to adults?

Dr. Waisbren:

I think in adults who have that situation, particularly those who are having emotional disturbances, it's very much worth a try. It may bring down the level far enough to control behaviors. We found before KUVAN was even available that by putting people back on diet and reducing blood phenylalanine levels, they were able to cut back or stop taking medications that were prescribed to control behavior.

Potential Side Effects

Andrew Schorr:

Okay, let's go on. Dr. Enns, Carrie from Haydenville, Massachusetts, writes in, 'What are some of the known side effects of using KUVAN because it's new, and even though I'm excited about the possibilities and options they give my daughter, she's very young and I wonder about what do we know long-term or how to evaluate pros and cons?' How do you help people with that because I'm sure you get asked that ten times a day?

Dr. Enns:

Oh absolutely and it's a very important question too because our experience with using KUVAN on a daily basis for a number of years obviously is just starting, and we have to follow the use of KUVAN and any side effects that can occur very carefully. I have had the privilege of taking part on a data safety monitoring board monitoring the effects of KUVAN and especially looking for significant side effects, or adverse events as they're called. In patients who are taking KUVAN when you compare it to those who are taking a sugar pill, the side effects or the complaints are really relatively quite similar. There seems to be perhaps in some individuals a tendency to have headache. Perhaps that is related to another mechanism of KUVAN action, but it's not clear why this happens, but for the most part the side effect profiles when you compare the sugar pill or what's called a placebo to KUVAN, are really quite similar.

There have been some serious adverse events in patients who are taking KUVAN, but it's hard to understand how it would be related to KUVAN. Like appendicitis has occurred, for example, or a bad sore throat, or another infection of the urinary tract, but it's hard to know how that would really relate to KUVAN and these issues need to be studied much more carefully and will be done so in the future. But again, overall in the period of study so far, the KUVAN has appeared really quite safe.

Listeners' Questions

Andrew Schorr:

Okay, and certainly there are people living with serious concerns right now. Here's an e-mail question we got from Owen in Remington, Virginia, and Dr. Waisbren, maybe you can help us with this one. Owen is 30 years old, and he said he's weighed approximately just 100 pounds since age 13. He says, 'I know KUVAN will help me with my levels and allow me to eat more. Will it help me put on weight?'

Dr. Waisbren:

I'm not sure there's been a lot of experience with that, but it certainly will allow, if he's a responder, more variety in the foods that he's able to take, and it very well may help him gain weight.

Andrew Schorr:

Yes, I think, and so let's talk about the whole diet thing. This is not a sort of take the pills and it's permission to eat potato chips and chocolate chip cookies and just eat anything, but it sounds like within reason with a well managed diet, it helps kids be kids, and I'm sure it has developmental advantages just socially as well, doesn't it Dr. Waisbren?

Dr. Waisbren:

Well certainly if you're able to eat the same things as your peers you feel a little better in the social situations, and that's been mentioned many times by families and patients, so I think that's a positive aspect of it.

Andrew Schorr:

Dr. Enns, when we think about this though and think about a new medication, the first one approved, the big deal though is preventing toxicity to the brain. Now how do you assess that? You say you're measuring the blood, but we really, that's a surrogate for what's going on in the brain, and so when you put someone on a new medication like this, help us understand about what you're really trying to do as far as preventing retardation and all those terrible things you said of the people you see now who were diagnosed with PKU long after they were growing up.

Dr. Enns:

Right, as has been stated quite a bit already in the conversation, it is really all about protecting the brain any way we can, and the diet has been an absolute success story overall. That being said, even a success story can be improved upon, so KUVAN offers yet another way to perhaps improve levels of phenylalanine. Again these are levels of phenylalanine we're measuring in the blood, but for the most part it's been really quite clear that the measurement of phenylalanine levels in blood has correlated and corresponded very nicely to developmental outcomes, and the lower or more normal you can keep the phenylalanine level, the better off or the better chance you will have of having an excellent developmental outcome.

Andrew Schorr:

I want to give Corinna a chance to sound off here. So Corinna, you think about this every day, the development of your kids. You've found out that your older boy was not doing the diet, and so you've kind of had to reeducate him and get him to take more responsibility for himself. Your hope for the future as far as their mental abilities, processing, growth, dancing at their weddings, and them giving you grandchildren, what's your hope for the future by managing the Phe levels with a

combination of the medication KUVAN now and also them helping take responsibility for a well-managed diet?

Corinna:

Given that I have one child who is extremely compliant both with diet and KUVAN and now have experienced one child who wasn't compliant for a short period of time but now is, I think it's actually turned out to be kind of a blessing in disguise because it was a good lesson for him while he was off diet, he really felt terrible, and he didn't understand why. His sister is now eating more in a day than he is, and he's quite a bit older than she is, so it turned out to be kind of a blessing in disguise, and I my hope for the future is just continued research.

My hope for the future is that we find a cure obviously, and I think we're still a fair ways off from that, but I certainly am interested now in the development of a national organization that perhaps is going to raise some funds for research and continued treatments like KUVAN that are cutting edge therapies for the management of the PKU diet that help my children live more normally. If they go to a birthday party they can have a regular cupcake perhaps like their friends rather than to have to take a special cupcake or to eat something completely different. In school it's become very important because we reward our children as a nation with food, and I guess I didn't pay any attention to that until I had children that were on a special diet, and that obviously becomes a very big part of my day when I have to plan around birthday parties and honor roll awards and those kinds of things, so this treatment has become a very big part of our lives in helping normalize the way my kids deal with their peers and deal with family dinners and those kinds of things. Something that you wouldn't think was such a big deal really is a huge deal in your life when you're 13 years old, I think though by keeping those phenylalanine levels down that keeps my children active and healthy, and I can't ask for more than that.

Andrew Schorr:

Well said. Now I want to skip to a different area that people wonder about, and that is someone who has been diagnosed with PKU who is leading a good life and then gets to the point where they want to have kids. So someone with PKU who maybe has been managing a special diet and also taking KUVAN, what about that Dr. Enns? I know we got basically that question from Tracy up the road from me, I'm in Seattle, and they're in Bellingham, Washington, wanting to know about their 12-year-old daughter and as she gets older about having kids.

Dr. Enns:

Right, this is a very important issue as well. Thank you for asking that question. As far as our knowledge goes on how safe or whether or not KUVAN is safe to take during pregnancy, we simply don't have enough information. There has been a report that I think where Dr. Koch down in Children's Hospital Los Angeles reported the use of biopterin at a very low level in a pregnant PKU patient who had a child without any problems at all, but this is certainly an area that needs clear investigation. To that

extent there is a registry of PKU patients that is being established that will be looking at such important questions.

My feeling as a clinician, however, is that the blood phenylalanine itself is the real toxin here. Blood phenylalanine is a known teratogen. You can almost compare it to the fetal alcohol syndrome, where a woman who is drinking alcohol during pregnancy has a risk of the fetus developing multiple problems; mental retardation, small head circumference, and even heart defects. Similar things are found with PKU patients who have uncontrolled levels or very high levels of phenylalanine, and their offspring can have severe problems because of this. So that being said, I've also followed quite a few patients who have classical PKU, who have had careful monitoring during pregnancy with dietary monitoring who have had absolutely normal children. So, with careful monitoring and careful control of blood phenylalanine levels I think that your daughter will go on and be able to start a family and that should go very well, God willing.

I just want to make one more point; KUVAN could potentially even help in this case. Although we don't have information on how it responds or how it can work in pregnancy, it could potentially again lower the blood phenylalanine and even protect the baby, but we just don't have information on this yet.

Andrew Schorr:

Okay, now we have two leading experts of course, one from Harvard and one from Stanford with us today, and hopefully you have access to PKU specialists in your region, and we'll talk more about that about how to find a specialist in future programs.

Brenda is in, I think it's upstate New York, in Auburn, New York, Brenda? And I am told you have a 3-year-old daughter, so what's your question for your daughter?

Caller:

My question is how old can you be in order to be eligible for the KUVAN?

Andrew Schorr:

Dr. Enns?

Dr. Enns:

Anybody can potentially take KUVAN. There's not a specific age, so this will be discussed with your physician. Do you have a metabolic specialist who's caring for your daughter?

Caller:

Yes.

Dr. Enns:

And how old is your daughter?

Caller:

She just turned three last month.

Dr. Enns:

Three years old?

Caller:

Yes.

Dr. Enns:

Congratulations. I love that age as well. As I've said, patients have been started in North America on KUVAN who have been in their infancy, so less than one-year old. So typically we haven't started patients that early, at least in our clinic. The first few years have been the easiest because it's relatively easy in controlling what the child's intake is going to be. After that time, especially if they're going to daycare settings or schools or preschools and getting into snacks and friends' foods, things can become quite a bit more difficult, although control of blood phenylalanine levels is still possible. So I think at age three it certainly can be considered, and that should be discussed with your metabolic specialist.

Caller:

Thank you.

Andrew Schorr:

All right, we're going to move on. We have another caller, Wendy in New York. Wendy, are you in New York City, or where are you?

Caller:

I'm in Chestertown about 30 minutes north of Lake George.

Andrew Schorr:

Okay. I used to go to Lake George, a beautiful area as we approach the summer. So what is your question?

Caller:

My question is I'm 41-years old, and I have classic PKU. BioMarin, I went to a dinner with them and they told us about the KUVAN, and I started it about two months ago, and what my question is, is how long before we know that it is working because right now I am taking the KUVAN plus my formula and special foods that I get from Cambrooke's.

Andrew Schorr:

Okay, let's find out from Dr. Waisbren. Dr. Waisbren, what's your thinking, and I know you have a very special interest in adults with PKU, so great the drug's new, how do you know when it's working? Also, again, I think we'll stress that nobody's saying you shouldn't following a diet too.

Dr. Waisbren:

I think the first step is, are you responding biochemically? Is your blood level going down at all?

Caller:

It is, yes.

Dr. Waisbren:

Okay. And then when we look for the impact, we look for speed of mental processing. That would be one indication that KUVAN is helping. A second one would be emotional wellbeing. Are your moods more steady? Do you have more motivation? Were you less depressed than before? Is your anxiety going down? Those would be questions to ask, and I also say ask the people around you. Do they notice a difference? Because often it's something you might not notice yourself, but those around you say, 'Gee you're talking more slowly, or you're making more sense when you try to discuss things, or your tolerance for change is a little easier.' The last thing would be, are your blood levels more stable? We recently did a study, again not with people on KUVAN, but looking at blood phenylalanine levels over a lifespan and found that people who were able to keep their blood phenylalanine levels steady did better than people whose blood levels went up and down. So, that would be another thing to look at.

Andrew Schorr:

Okay. Here's a question we got from Cindy from Saint Louis, and she says, 'Is it possible to use KUVAN intermittently, let's say on weekends?' She follows the diet very well during the week, but weekends become difficult. Dr. Enns, do you have a thought about that? About managing the Phe levels and whether you can just do it sometimes but not all the time?

Dr. Enns:

I have never been asked that question, so I am smiling a little bit. I think that's a great one. I honestly don't know. The same approach obviously applies where we try to control our blood phenylalanine levels as best as possible, and if you are, in your specific case, having a difficulty for whatever reason during a specific period, I guess that would be helpful. Anything you can do to control your blood phenylalanine levels would be helpful. But you really have to ask yourself and be evaluated very carefully, are you a responder? Am I responding to this medicine? Is this even worth a

consideration? Then you can take the next step. But as I said, anything you can do to keep your blood phenylalanine levels lower, even for a short period of time, I think would be a reasonable thing to attempt.

Andrew Schorr:

Now what do you do Corinna? Now you're dealing with the compliance with your son, and I know, I have a child with ADHD, and you know they like to not use their ADHD medicine on weekends. Is this a day-in/day-out approach that you do in your house Corinna?

Corinna:

You know, it is. We do find weekends challenging because I have kids who are very athletic, and when you're traveling and you're on the road with soccer and baseball and those sorts of things, you tend to eat on the run just like everybody else does. So we are probably a little more liberal on the weekends than we are during the week just because of schedule. Life kind of gets in the way sometimes, and we take allowance for that, but we still try to maintain some discipline with the diet, and the KUVAN we take every day regardless of wherever are or what we're doing. It travels well. We have a little pill crusher, and we drink it or put it in a little bit of pudding, and so it transports easily enough that we don't vary with the KUVAN. We don't vary with the formula. The diet, we'll kind of fudge on once in a while. If we want to go out for pizza, maybe the PKUs will take the toppings off, and my nutritionist now is about to have a fit because really you shouldn't do that, but again part of this with the PKU is about feeling normal, and I was interested in the behavior question with the 4-year-old.

One of the challenges that I had as a parent was trying to decide is this PKU related or is he just being four? Because we all know that 4-year-olds sometimes see things a little differently than we do as parents and so that is a challenge, and it is difficult to manage, but typically we try to make the KUVAN and the formula nonnegotiable, and then we can fudge a little bit on the food.

Andrew Schorr:

Okay, I just want to mention a few points. First of all, coming up, we're going to have in June we're going to talk about living with PKU, managing diet, and all these sort of "how to" patient-to-patient, family member to family member tips, so that's June 19, 2008. That will be our third webcast. On May 27, 2008, the one in between, we're going to talk about how you get these medications and diets paid for, and there are support programs to help you. So we'll give you all the ins and outs of that, who qualifies, who can help you, where you call, and all that kind of stuff.

Research for New Treatments

Andrew Schorr:

Going back to treatment options now. So we've talked about medication. We've talked about variability. I want to just talk for a second about research, where things are headed. Corinna, you said you hope there's a cure, and we all do, and I hope for that in my leukemia believe me, and so we see these conditions as chronic, and we have to take medications, be monitored, and we wish we could just be done with it and live well. We all dream for that day.

Dr. Enns, where we with continuing research? You talked about KUVAN working for many people, not all people, and we heard from the adult who said I'm waiting to see is it working for me, so are there yet more exciting medications maybe in development, we don't know where they'll go, we have a great start now. Where are we headed?

Dr. Enns:

The most exciting one on the horizon of course is called phenylalanine ammonia lyase or PAL. This is an enzyme that has the ability to cleave phenylalanine in the blood, so it shouldn't matter what type of defect you have. If your phenylalanine level is high in the blood, this enzyme should be able to cleave it. It certainly works beautifully in animal models, but as you know, people are not animals, or most of us are not. The effect of this enzyme in humans is just going to be starting to be studied this year, and we're all very excited to see whether this can truly help patients who have high levels of blood phenylalanine, and it could be very exciting.

I have a difficult time I think trying to control my excitement over this new development, but I also think it's important to discuss it with my patients as I see them in clinic because as I already said, if you have classical PKU, if you have the most severe form of PKU, you might not and in fact you probably won't respond exceptionally well to KUVAN. It really depends on your own individual circumstance. Of course you should be tried on it and see how you respond, but if for whatever reason you don't, don't give up hope because there are things in the pipeline that I think could really be dramatic. That's my hope. Whether or not this will work in humans, we don't know whether there will be immune reactions or other sorts of responses that will blunt the possibility of it working. We just don't know, but that's what clinical research is all about. We hope to be able to answer those questions, and so I'm quite excited about that.

Andrew Schorr:

Right, and there's a point I want to make, and that is we're all in it together. Now my family is not touched by PKU, but if you're listening to this program, you are, and so with researchers like Dr. Enns, leading centers like Children's Boston, Lucile Packard, and these others where there are people like Dr. Waisbren and Dr. Enns who have devoted their lives to it, you're in partnership with them, and so it's current

treatments and also research, because we all want to get to the goal line of a cure or great management of this condition for everyone.

I want to get some final comments. We might go just a couple of minutes over. I want to give everybody a fair chance to make a final comment. Dr. Waisbren, you've been listening to this and you've been participating, and you have devoted your life to this over many years. You've seen lots of changes. So, again, how would you characterize where we are now and how people need to be in an active dialogue, a proactive dialogue, with specialists such as at your clinic and at others in their region so that they get the best care available to them today?

Dr. Waisbren:

I think I'd like to respond to that with the idea of advocacy of our young adults. I think they're now in a position, this is really the first generation that's been treated for life or that has options to have an easier treatment, and I think if they could get involved and start telling us all what they want, what works, how they feel on these new treatments, participating in the research, it would have a tremendous impact on the field.

Andrew Schorr:

We wish you well. First of all I want to thank you for all you do. A lot of people are just hearing about your for the first time, people in New England know you well, and I want to thank you for all you do, and we'll have you back as we do more PKU programs.

Dr. Waisbren:

Thank you.

Andrew Schorr:

Yes, ma'am. Dr. Gregory Enns, let's go 3,000 miles to you. So you said at the beginning you thought it was an exciting time, and you've given us a window into the research, but now we need action for all these people so we add into the mix a new treatment, an approved treatment, and somewhat without limitation really trying to see can it work for different people, so what would you say they do in conversation with their doctor, their nutritionist, or even to seek out specialists such as clinics like yours?

Dr. Enns:

Educate themselves, talk to your specialists, read the literature. You can even go and read as much as you can. If things are confusing, go and talk to your biochemical geneticist, your geneticist, and also become involved. It's a dialogue, and as a physician, the most important thing as already been stated is to really interact with your team and tell us what your needs are. How is this working and how is it not working? How can it be improved? What's your response to this? We need to learn as everybody needs to contribute to this. So as I look forward to the future, I hope we

continue to interact, and I'm sure that we're going to learn a lot about this new medication, and I just encourage people to learn, to read, and if they have any questions or any concerns, just really bring that up with the treating team because I think as a whole everybody of course wants nothing but the best for the kids and the adults who have PKU.

Andrew Schorr:

Right. Well said. Thank you. I love these providers. They're so dedicated to the PKU community, and then there's Corinna in Indiana, and you have two members of the household who are affected by it, and then you speak and you're involved in the organization there in Indiana. How would you like to leave it with the parents and the adults living with PKU or in the household, what would you tell them where we are now and how they can really take action to make sure they can get the best for themselves or the ones they love?

Corinna:

I would say a couple of things. I think it's important to be an advocate. Don't forget that we're all human and that we all have the same goal in mind and that is to lower those phenylalanine levels, protect the brain. It's all the same things we've saying in the last hour, but you can be an advocate. If you have questions, don't hesitate to ask your nutritionist or your physician. Send an e-mail. Make a phone call. Don't hold back. It's okay to ask the questions. A lot of folks are intimidated by their physicians or nutritionists. My nutritionist is my best friend, and I can call her any time, I can ask her anything, and my physicians are the same way. So be an advocate for your child or for yourself as an adult, but don't forget that there's a child in there. We tend to get really caught up in the diet. An example is that when my middle son is having dinner, sometimes I get so caught up on the weighing and measuring for the PKUs I forget there's another child here that needs some dinner too, and you just get caught up in it, and let's not forget that these are just people, and this is a diet. It's okay.

There's also a national PKU organization that's being formed right now to help with research, and so you'll hear a lot more about that coming up in the very near future. Please be supportive of that and of programs like yours, Andrew, because getting the word out really, really is critical to the research for this disorder.

PKU is a lifestyle, and there are a lot of things out there that are a lot more detrimental to your health than PKU. I encourage people to remember that it's diet for life and just enjoy your life. It's great to be on the diet and feel good and be happy and healthy.

Andrew Schorr:

There you go. Corinna, I wish you were my mom. You sound like a great lady. We're going to meet you in person some time. All the best to you with your three kids, including the one in the middle with the R-E-G after his name. This is what we do on Patient Power. We like to say that knowledge can be the best medicine of all, and now

in PKU we have a medicine, we have an understanding of diet, and we have a community. Remember we've got another program coming up May 27, 2008, helping you with all the reimbursement issues, financial support, and then June 19, 2008, all the sharing of how you can all work together and get tips from other people.

Remember the replay will be posted probably by tomorrow, and we'll add the transcript. Discuss it with folks you know. Tell others.

From Seattle, I'm Andrew Schorr. Have a great evening, and we'll be with you again May 27, 2008.

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