

MS. GIRAND:

Dr. Ruggenenti, thank you very much. We're back to question time. I can actually turn on some lights here I think or more lights. No, I can turn them off. There, we can, and please give your name before you ask any questions. Go right ahead.

MR. MARLER:

I will start this time, Bill Marler. Dr. Brandt, it's good to see you up here. One of the questions I asked earlier I wanted to get your take on it. As you look over the countries you see different therapies for kids that develop HUS. I see a lot of kids that get plasma apheresis, dialysis and a combination of both.

And I just wondered if you sort of, looking out in the future, what you saw as maybe a coming together of those therapies or choosing of one versus the other.

DR. BRANDT:

I think it's important to differentiate what is a therapy for Hemolytic Uremic Syndrome versus what is a therapy for acute renal failure, because all children pretty much get similar, what we would call "supportive," therapy. They all get fluids if they need them, they get blood pressure medicine, and they get dialysis if they need it.

Now dialysis is not treating HUS. I don't think we now have a good sense of whether we can treat HUS. I think in the future we will know whether childhood HUS should be treated with plasma apheresis. I don't think we know that yet.

So children get dialysis therapy. If they have acute renal failure that presents a danger to them, they get dialysis. Whether plasma apheresis is added on top of that depends on the center you're at and the beliefs of the nephrologists there, the severity of the disease, and whether you have a lot of TTP-like complications, i.e. a lot of brain or CNS involvement.

And to some extent on what country you're in. I think plasma is used quite a bit in some parts of Europe, and they have very good outcomes there but, again, in sort of an uncontrolled way so that it's hard to compare treated to non-treated patients to see if there's a big difference; is that helpful?

MR. MARLER:

Well I think it's just all unfortunately still up in the air.

DR. BRANDT:

I think it's up in the air. I think we don't know whether plasma apheresis is, in particular, needed for a childhood E. coli associated HUS. It's a relatively safe procedure but it's not a simple procedure, and it's not completely safe, and we're reluctant to sort of start it on a massive scale until we have better evidence that it makes the kinds of differences that it clearly makes in adults.

MR. MARLER:

I guess what I've seen is where parents have actually been given a choice: you can have your child on dialysis or plasma apheresis.

DR. BRANDT:

If you do plasma apheresis, it does a lot of the work of dialysis because you're removing a lot of the waste products you need to remove for dialysis. So if someone's going to go on dialysis and has an option of plasma apheresis as well, I'm not aware of people doing that in an organized way.

MR. MARLER:

In Colorado, we had children here who were sick by the same bacteria at Children's Hospital, all on dialysis in Colorado. There was a child--and if you looked at the labs they were identical if you compared the children-- but that child got plasma apheresis as opposed to dialysis.

DR. BRANDT:

And that is an uncontrolled sort of trial. There's nothing wrong with that, it's just that some people, whoever it is in Denver, perhaps Dr. Lumb (phonetic) may believe strongly that plasma apheresis helps.

I think that in order to make a public statement about plasma apheresis, we really need to have stronger data in children to sort of back up what may be an individual's gut feelings about whether it works or not.

And I don't think, again, in a public forum like this I can say, "The data is there to suggest we should be dialyzing all kids with E. coli 0157." In 10 years, I hope we have an answer. I think the German study will help us a lot and we may be saying, "We really should have been doing this," on the other hand we may be saying, "It doesn't help or makes things worse." I don't think we know the answer.

DR. RUGGENENTI:

If I can give a sort of a comment on this important issue. I think that all this, we should remember that there have been two trials, big trials in children in Europe, each showing that plasma therapy does not modify the outcome of children with typical acute HUS.

So I understand that when you have a sick patient, all doctors want to try everything. But we should remind

them that these treatments are not free of risk, particularly in children, you have more complications from infection.

So I think that unless we have the evidence that this treatment improves the response of the children we should not emphasize the use of this treatment unless there are neurological signs. This is the policy we follow in our institute.

MS. SIMPSON:

My name is Christina Simpson, and I have a question for you Dr. Brandt. I had HUS almost about eight years ago. I was on ACE inhibitors for several years and recently was taken off of them.

A recent 24-hour urine test came back normal, which surprised me, but they changed my blood pressure medication to a non-ACE inhibitor. And I was wondering about the possibility that the ACE inhibitor did help bring the normal test --

DR. BRANDT:

This is a question not for me but for Dr. Ruggenti. This type of response is associated with improvement in the GFR. And so it may be that the disappearance of proteinuria was related to the ACE inhibitor use.

MS. SIMPSON:

I'm wondering since I was taken off of the ACE inhibitor if there will be an increase or return in problems.

DR. BRANDT:

I don't know. I would talk to your doctor about it and say I went to this conference and "A" I want to get checked and "B" I want that ACE inhibitor back.

MS. SIMPSON:

I guess I will look into it. Thank you.

DR. BRANDT:

Thank you.

MS. SHERWIN:

Hi, my name's Charlotte Sherwin. Dr. Brandt, you spoke to us about the process of filtration and the importance of continued follow-up with blood pressure check, urinalysis and GFR and creatinine. In a practical sense, is there any information for us as parents or evidence concerning a low protein diet in our children to help protect the health of the kidneys?

DR. BRANDT:

I don't think there's evidence, to answer your question, that children should be on a low protein diet. There is some evidence in adults in different diseases that low protein diets may slow the progression of renal disease. And in children I think we're reluctant to prescribe low protein diets for two reasons. One, the studies have not really been done in children and are not strong enough in adults to really make us believe that it makes a significant difference. And two, kids need more protein for adequate growth, and we're hesitant to restrict protein intake because of concerns about just general nutrition.

So, again, I think that the answer is not yet in on children and HUS and protein intake. But normal protein intake is probably not harmful is my guess for kids with HUS. Excessive protein intake might be harmful for someone with some renal damage.

So your kids maybe should not eat meat three times a day but probably should have it once a day.

DR. LINGWOOD:

Dr. Brandt, I was struck by the age-related GFR development, GFR rate in the kidney. And really, as someone pointed out to me before and, if it's common knowledge, that really mirrors the incidence of HUS in the level of --

DR. BRANDT:

Yes, it's a very interesting point that the maturing kidney corresponds with the time we often see HUS in the young child with HUS.

DR. LINGWOOD:

So what we know about verotoxin susceptibilities in soft cultures is the growing cells are more susceptible than non-growing cells. So what may be happening is that we're looking at vascular development within the first two years in those cells that are primarily sensitive to verotoxin and it's the growing cells.

MR. MARLER:

And that's what we see in cancer as well, that when you have a cancer it's vasculature, the new endothelial cells lining of the blood vessels.

DR. BRANDT:

Well it's very interesting. I think it brings up an important point about hopefully the eventual appearance of some sort of agents to block verotoxin Gb3 binding that may be particularly important in the young child.

MR. SANTONI:

Paul Santoni, from Scotland, two questions. First of all, for Professor Ruggenenti, in your studies of ACE inhibitors in 372 people is there anything about children I don't know?

DR. RUGGENENTI:

Should I answer now?

MR. SANTONI:

Yes.

DR. RUGGENENTI:

Because when we look at the sample size of the study we found that in children, we should have a very big number of patients to make the study of the disease prevalence more authoritative.

So we decided to look at what we call, technically, end point not end stage renal failure but an induction in the GAF. So doing this, we have the possibility of 200 to 400 children or more because probably we would need more than 400.

MR. SANTONI:

So it's actually back to the study, a study of 18 months in which 372 people. In that first study, in THAT 18 months did you have any children in that study?

DR. RUGGENENTI:

In the study I showed you?

MR. SANTONI:

Yes.

DR. RUGGENENTI:

No, it wasn't a study of children. The youngest patient is at least 18 years. Anyway, we have not seen a different course in different ages. So even if the patient is younger they have the same problems as the older patient.

And in the limited experience we have with children, studies show that these drugs decreased proteinuria and the same as in all drugs.

What we don't know, I think, that we don't know the safety of these drugs in children. So this is why we think we should do a study before nephrologists start to use these drugs also in children two or three years old. They don't know what can be done by these drugs in a small child that is growing.

So this is the reason why I think that we should do trials also in children.

MR. SANTONI:

When will the second study be concluded, when will the second study involving the children be finished?

DR. RUGGENENTI:

When will we finish? It has not started yet. This is a proposal because at the moment we are running an immunology study, and we are starting an immunological evaluation.

I told you now the major problem we have is to find the money to do this study because it is quite expensive. So we have made an application to the European community and we are exploring the possibility of doing something here also in the United States because a multi center trial for so many years costs a lot of money.

So we have the possibility of partnering with a company that is interested in studying the effects of this in children.

MR. SANTONI:

Thank you. Dr. Brandt, one question for you. You twice said that when children leave the hospital, you don't know which ones are going to be the ones with long term problems. What is your hunch or gut feeling of what would give that indication?

DR. BRANDT:

I think the kids that would leave the hospital with an elevated creatinine level and a significant amount of proteinuria or hypertension are the ones that are probably going to be in trouble.

Most kids with HUS, by the time they leave the hospital, have their creatinines back to normal or back to normal within a couple of weeks. And their acute blood pressure problems and protein in urine are usually resolved in large part when they leave the hospital.

So I think that, for kids that leave the hospital, it's clear that for some kids, the HUS has quieted down but they may still have significant renal abnormalities, and these are the ones that we really are most worried about.

And there's another population for which I think we don't know exactly how much to worry about them. Those who have very few abnormalities or those who develop some abnormalities later on.

But a lot of the kids who develop end stage renal disease from HUS do so relatively quickly. They don't get better so you know it.

MR. SANTONI:

Thank you.

MS. DAY:

Laura Day. I was wondering if either of you could speak about potential problems for pregnancy for HUS survivors? And since I know both groups are represented here, for people who may have had kidney failure at the time but haven't had any major problems with their kidneys since then and also people who have recurring problems.

DR. BRANDT:

If you could field that?

DR. RUGGENENTI:

I think that if a patient has had HUS and was a child and it is due to renal toxemia there is no reason to believe that you should have a major problem during pregnancy, unless there is a renal failure.

If there is a renal insufficiency or advanced proteinuria in the early stage of pregnancy, it would be a risk not of HUS, but of conditions such as pregnancy, hypertension and complications like these.

If on the other hand there is some evidence that the child had HUS because of the congenital problem such as usually happens when the child or when other members of the same family have HUS, pregnancy could be an additional risk factor that could trigger again the recurrence of the disease.

So I think that we should be looking at two things. Whether renal function is normal or not normal at the time when the pregnancy was planned, and second, whether the disease, what the child suffered, was a typical HUS or was an atypical in order to determine the risk.

MS. GIRAND:

We're going to take two more questions, please.

MR. HAMMOND:

William Hammond. The ACE inhibitors. If a child has got abnormal kidney function, protein in the urine, yet the blood pressure is okay, would the ACE inhibitors still be applicable to prevent the scarring?

DR. BRANDT:

I think as Doctor -- I'm going to get your name wrong -- has pointed out, you know, the way their study is set up actually you can have a normal blood pressure or high blood pressure and still get an ACE inhibitor.

And, in fact, the use of ACE inhibitors is used with proteinuria, particularly in diabetics who do not have high blood pressure. You have to be careful you don't get too much ACE inhibitor once you've dropped your blood pressure because there's a fairly wide range of dosing you can give that will affect the proteinuria but not really change the blood pressure if it's normal.

MR. HAMMOND:

Any difference in prescriptions of one versus another?

DR. BRANDT:

I think we generally found they're about the same.

MR. HAMMOND:

They're about the same.

DR. RUGGENENTI:

They're all about the same. You can start short-acting ACE inhibitors then move to long-acting ACE inhibitors, which are more easy to use. And you should monitor because I think nephrologists in a patient with this condition should start to look not only at blood pressure but those with the renal insufficiency.

The other patient to which I referred before, after a period of treatment, she had no more renal problems. I think you can say that she had achieved remission of the disease and the prognosis really is good.

MS. MCINTOSH:

Sarah McIntosh. I have a couple of questions. First, are there any long-term negative effects of ace inhibitors?

DR. RUGGENENTI:

Major side effects are in (unintelligible), in particular there is increasing blood (unintelligible) and that is very rare, actually, if you imagine it correctly with the patient that means using drugs that do not tend to increase serum potassium correcting metabolic acidosis, that is common in patients with renal insufficiency.

And whether there are problems in the renal artery before you start ace inhibitors this is a risk factor in anemia, this should be quite less frequent in children because there is no reason to believe that they have diseases in the arteries.

So this is why we should explore very carefully, which is the safety of these drugs in children, before deciding that what is working out well in adults is also good for children.

I can't give you examples but many of these drugs are started for proteinuria and then doctors have started using them in other patients. Actually they do not work with diabetes and increase the risk of acute renal failure.

So we must go very much -- must be very careful before adding a new treatment in particular in children, I think.

DR. BRANDT:

I will just comment quickly because I use a lot of ACE inhibitors in children primarily to treat hypertension. And I think that a very good point is made that we need adequate studies to really outline what the risks are.

But from a purely practical standpoint, most children do not have any problems. You do need to watch the potassium, you need to watch the liver function every once in a while, because you will have rare reactions in the liver. And some children develop a very annoying but not harmful cough, that's not uncommon with the ACE inhibitors.

MS. MCINTOSH:

For instance, if a child has been on ACE inhibitors for eight years and they continue to have proteinuria but the blood pressure is stable is that a sign that maybe the ACE inhibitor needs to be changed to a different drug or increased dosage?

DR. BRANDT:

I would say that, if your blood pressure is fine, it's probably an indication to try to increase your dose of the ACE inhibitors if you can get more effect out of it.

And particularly nephrologists will start with a very low dose and see if you get an effect and increase the medicine to either get an effect on the proteinuria or blood pressure or if side effects develop like high potassium levels, then you will have to stop. Particularly they will be increased until you see an effect. If it has been increased as much as you say, and there's no effect, then it may be this is not going to be helpful for that patient.

MS. MCINTOSH:

What would be an acceptable limit of proteinuria?

DR. BRANDT:

Well --

MS. MCINTOSH:

Thirty?

DR. BRANDT:

I think, one, any decrease in your proteinuria is going to be helpful. And two, I think that it may be that in some patients even a sort of plateauing of your protein will be helpful because the proteinuria will with time tend to get worse over the long term.

MS. MCINTOSH:

The long term meaning 10 years?

DR. BRANDT:

Ten, twenty, thirty years, you know, as you get progressive scarring you may have an increase in your proteinuria. So if there are some patients just maintaining it, you can get it down low and if it plateaus, it may be helpful. Not every patient is going to see a disappearance of their proteinuria.

And I do think that we use these, and I even recommend them for kids with proteinuria, but the point is well

taken that they have not been well studied in children because people, parents and doctors together, have been reluctant to do the studies. They're difficult to do.

And I think this is an enormously helpful opportunity for us to find out, one, how helpful they are; two, what the right dose is; three, what the side effects are. And so I think this study will be enormously helpful and I hope we can get an American arm in that.

MS. MCINTOSH:

If you, for instance, have some slight proteinuria, your creatinine's pretty much stable, your blood pressure's pretty much stable for 10 years, are you somewhat out of the woods, so to speak?

DR. BRANDT:

I don't think we know that. Certainly the fewer symptoms you have, the less proteinuria, the less worrisome it is. But I just don't think we have the data to tell you what these kids' kidney function will be like when they're 50.

MS. GIRAND:

Dr. Ruggenti and Dr. Brandt, thank you very much.

MS. GIRAND:

We're going to take a 10 minute break. And I need you all really to be back here in 10 minutes because we're going to whip through the rest of the program. Well, we really don't want to whip through because it's absolutely fascinating so I would like you to be able to be back as soon as you can. Thank you.