Study Examines Genetics Impact on Statin Disposition and Response

Based on guidelines from the American Academy of Pediatrics (AAP), approximately 0.8 percent of adolescents 12 to 17 years old with dyslipidemia may qualify for pharmacological treatment.

That translates into approximately 200,000 adolescents who could be eligible for statin therapy.

With the increasing prevalence of overweight children, the incidence of clinically diagnosed coronary artery disease in young to middle-aged adults is expected to increase by 5 to 16 percent over the next two decades.

Jon Wagner, DO, is here to discuss how he is leading a research study looking at the liver specific protein transporter, OATP1B1, which is the major transporter of statins from the blood to the liver to better understand how children's bodies distribute statins in the body.

Featured Speaker:

Jonathan B. Wagner, DO

Jonathan B. Wagner, DO, is a pediatric cardiologist at Children's Mercy and an Assistant Professor of Pediatrics with the University of Missouri-Kansas City School of Medicine. He graduated from Kansas City University of Medicine and Biosciences before completing his pediatrics residency at Children's Mercy Kansas City. He completed a fellowship in pediatric cardiology at Penn State University – Milton S. Hershey Medical Center before returning to Children's Mercy where he completed fellowships in pediatric cardiology and clinical pharmacology. His special areas of interest include statin pharmacogenomics, personalized medicine and pharmacokinetics.

Learn more about Jonathan B. Wagner, DO (http://www.childrensmercy.org/Clinics_and_Services/Clinics_and_Departments/ doc=14146)

Transcription:

Dr. Michael Smith (Host): Welcome to *Transformational Pediatrics*. I'm Dr. Michael Smith and our topic is, "The Impact of Genetics on Statin Disposition and Response." My guest is Jonathan Wagner. Dr. Wagner is a pediatric cardiologist at Children's Mercy and an Assistant Professor of Pediatrics with the University of Missouri Kansas City School of Medicine. Dr. Wagner, welcome to the show

Dr. Jonathan Wagner (Guest): Thank you very much for having me.

Dr. Smith: So, approximately how many adolescents with dyslipidemia are eligible for pharmacological treatment?

Dr. Wagner: Oh, I think that's a very good question. We are starting to see, with several observational

studies over the last few years, that more and more children are at the cut points to qualify for statin therapy. That actual number is anywhere from 200,000 to 400,000 adolescents based off the studies that were previously done. So, that actually is a large segment of the population in the U.S. that would currently qualify for statin therapy and I think that it's really important, with that increasing number, to really understand how the statins are working in the pediatric population.

Dr. Smith: What about the increase in prevalence of overweight children? How is that impacting these numbers, do you think?

Dr. Wagner: Exactly. It's hard to tell what the actually baseline was for children that would qualify for statin medication because, really, the observational studies started after the year 2000 and, really, in this new millennium. I think that those numbers will continue to rise for two reasons. Number one, we're screening patients more effectively in the United States than what we previously had done. The NHLDI and the American Academy of Pediatrics and the American Heart Association now recommend universal lipid screening patient 9 to 11 years of age and then, again, in late adolescence from 17 to 21 years of age. We are discovering more patients that have asymptomatic dyslipidemia that are otherwise healthy patients. The other big reason is the trend toward childhood obesity in our country. One third of adolescents now are defined as overweight and with that trend, we're seeing more patients that are at risk for coronary problems later on in life and dyslipidemia is a major cause of that.

Dr. Smith: Do you, when it comes to adolescents and when it comes to measuring the lipid profiles with the pediatric population, are you guys going more into some of the advanced lipid analysis? Not just the standard LDL, total cholesterol? I mean, are you guys actually breaking down the LDL sub-types? Are you doing more advanced testing in kids?

Dr. Wagner: At this point, I don't think we've done as much in terms of the advanced testing like our adult counterparts. There are some pediatric centers across the country that are sub-typing the lipid profile to a greater extent. I think, at this point, it's more of a research endeavor as opposed to the actual clinical application but I think it's important to appreciate that because that may refine our guidelines for the future in the pediatric population.

Dr. Smith: What about when pediatricians are speaking to their patients and the family. What about having that conversation about sugar intake? I mean, how important is that conversation to this whole dyslipidemia conversation?

Dr. Wagner: Absolutely. I think the two are very much linked in the sense of what we've already described about the increasing overweight adolescent population in the United States. The harm of a poor diet not only can accelerate the atherosclerotic process, not necessarily in childhood, but in young adulthood; but, it can also lead the patient potentially at risk for other co-morbidities, more specifically, diabetes. We know that when those two diseases processes are linked, meaning the dyslipidemia and diabetes, it places the patient in extreme risk of having a coronary intervention very early on in life.

Dr. Smith: Right. Tell us about the cardiology pharmacogenomics repository that's been established at Children's Mercy Kansas City.

Dr. Wagner: Absolutely. The cardiology pharmacogenomics repository, conveniently named the CPR—

and we hope to prevent "CPR" by, really, this type of preventive treatment later on in life, but I developed this bi-repository at our institution during my cardiology fellowship training and pharmacology training. The purpose of this repository is really to collect biospecimens and eventually isolate the DNA on patients that are seen in a number of our clinics—our cardiology preventive clinic, our weight management clinics, our endocrine clinics and nutrition clinic. Any patient that's really at risk of cardiovascular disease can be enrolled in this bi-repository. Once we have isolated the DNA, we're able, then, to run genotype analysis on anything that we're really interested in related to cardiovascular therapeutics. What we have targeted so far in the bi-repository is a specific genotype and that is a gene called "SOCL1B1." This gene is responsible for, basically, laying the framework for a liver-specific protein that takes statin medications from the blood into the liver and that's where statins work. So, the purpose of the bi-repository is really for that DNA so we can run that genetic testing but it's also kind of a living, breathing patient registry by which we identify gene variance or patients that don't have that variation at all, to enroll them into prospective studies related to statin or anti-cholesterol medication.

Dr. Smith: And, what you're identifying are these polymorphisms on this gene, this liver-specific transporter, and, in a sense, those different polymorphisms affect how statins are distributed throughout the body, correct?

Dr. Wagner: That is absolutely correct. It's really well-described with this gene, SOCL1B1, in adult literature; that it can have a profound impact on how a statin is actually going to distribute throughout the body and, thereby, how effective the medication is going to be. In adult literature, when you have a variation of this specific gene, you have decreased expression of the protein on the surface of the liver. You also decrease the functionality of the transporter as well. So, if you're not transporting the medication, like I said previously, there's less drug within the liver to disrupt cholesterol biosynthesis. In adults, when you have this variation, less of the drug makes its way into the liver; the drug levels in the blood are much higher; there's more peripheral exposure of the statin into the muscle tissue and other end organs. Those patients that have that genetic variation are more prone, anywhere from 6 to 16-fold higher, to have increased incidence of myalgia, which is the most common side effect of that medication. It also decreases the effectiveness of the drug because less of it is getting where it needs to go. So, in adults, it's well-described. In pediatrics, it's really unknown and the challenge is, in a developing child, is that same principle occurring in our patient population? That's what we really mean to replicate here.

Dr. Smith: Dr. Wagner, how fascinating is all of this, right? I mean, from a pharmacokinetic perspective, right? When we were in medical school, it was really the kinetics—we thought—mostly influenced by how that drug was formulated and, of course, some of the physiology of the patient, later on. But, now we're actually going to look at the genetics of a patient and how that influences drug kinetics. Where do you see this kind of research going in the future and what do you hope to accomplish?

Dr. Wagner: So, I think the frontier is extremely exciting and I think it can have a profound impact on patient care. There are many of our patients that really read the book in terms of how well they respond to medicine. But, there is a subsegment of our patients that don't respond to medication or they respond too much and are prone to adverse effects. It's really trained to capture those patients that are kind of the outside portions of the bell-shaped curve to where pharmacogenetics really comes in. Is there something else that we need to appreciate when prescribing these medications and many other medications to the developing child? To your point with the pharmacokinetics, I think what we find and

what's fascinating, is where these medicines are going in the patient. It's really taking a really hard look at not only the response to the medicine, but what's happening in the whole pharmacokinetic profile. So, the absorption—what's going on there at a transporter level? How is it getting distributed in the body? Is this medication, like the statin, preferentially going to the brain, which is a very troublesome thing in a developing child that hasn't matured? How is the body getting rid of the medicine? At every one of those points, pharmacogenomics could have a potential impact. Then, you throw in the pediatric population that is developing and some of these transporters might not even be matured. So, is there really an impact of pharmacogenomics in a developing child a moving target? Well, that's really our passion here at our program.

Dr. Smith: Thank you, Dr. Wagner. That's fascinating, fascinating work and I know that it's going to reveal a lot of things that we don't know about pharmacokinetics and, as you said, where these drugs are going and how that can influence dosing and side effects. So, I want to thank you for the work that you're doing and thank you for coming on. You're listening to *Transformational Pediatrics* with Children's Mercy Kansas City. For more information, you can go to ChildrensMercy.org. That's ChildrensMercy.org. I'm Dr. Mike Smith. Thanks for listening.