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## PCSK9 Antibodies for Dyslipidemia: Efficacy, Safety, and Non-Lipid Effects

Dr. Brown:

You're listening to ReachMD and this is Lipid Luminations sponsored by the National Lipid Association. I am your host, Dr. Alan Brown, and with me today is Dr. Eugenia Gianos. She is Assistant Professor in the Department of Medicine and Co-Clinical Director of the Center for the Prevention of Cardiovascular Disease at NYU School of Medicine. By the way, we are broadcasting live from the Clinical Lipid Update of the National Lipid Association in Amelia Island, Florida and that is why you may hear a little noise in the background. There is a lot of excitement here.

Dr. Gianos, thank you very much for joining us today on Lipid Luminations.

Dr. Gianos:

Absolutely, it is a pleasure.

Dr. Brown:

So I understand you are going to be giving a presentation a little bit later in the meeting about PCSK9 antibodies and talking about their efficacy, their safety, and some of their non-lipid effects. So, I would like to ask you to give our listeners who may not have the privilege of coming to the meeting a little bit of background on your experience with PCSK9 antibodies and tell us a little bit about what you are going to present at your presentation.

Dr. Gianos:

As part of my job at NYU, I do a lot of lipid management in my personal clinic and we have a preventive cardiology fellowship as well and Jamie Underberg leads our Bellevue Lipid Clinic as well, so we have a lot of experience with patients with severe cholesterol disorders aside from patients with advanced cardiovascular disease who really don't get to goal on standard therapy. So, in the past several years, both through clinical trials that we are a part of as well as now that the drugs are on the market, we're getting more and more experience with these drugs and learning more about how we can use them most effectively.

Dr. Brown:

So, as you know, there has been lots of press about the PCSK9 antibodies including a lot of discussion about their relative value versus their relative benefits, much of which, in my opinion, is based on data that is not necessarily accurate. But with that said, maybe you can start by telling us a little bit about the effectiveness of the medications in your hands and some of the things you are going to cover in your talk later.

Dr. Gianos:

Effectiveness is something that I think we just can't argue. They're extremely effective with respect to LDL lowering, up to 60% LDL lowering in many cases. They also happen to lower triglycerides by about 30%, lower LPA, another atherogenic lipoprotein, which is lowered more than 20%, and raise your HDL a little bit as well. So, they have a number of lipid-altering effects, all of which should, in theory, prove to be beneficial in an outcome standpoint if, in fact, we view them as surrogate markers. So, with respect to efficacy, I think they're extremely effective. One of the things that I found out in researching this talk is that there are actually other receptors that PCSK9 affects that we do not know as much about and those receptors are still being looked into. Non-lipid sort of mediated things that

regulate hep. C that have to do with glucose metabolism, fatty acid metabolism, fatty liver, etc., many of which are still being investigated.

Dr. Brown:

That is very interesting that you bring up glucose metabolism because obviously initially the statin effect on blood sugar was thought to possibly be related to LDL receptors. Now I think they have moved away from that, but at least in the basic research on PCSK9 antibodies they didn't see a signal for glucose abnormalities. I wonder, in your research, whether you have found that also or if there is some data that I do not know about.

Dr. Gianos:

Actually, you know, in terms of the trials that have been done to date, they are all pretty short-term, predominantly safety trials that the adverse events in those trials are very low, really impressive compared to placebo and Zetia, very similar in terms of adverse events and I don't think there has been a signal for abnormal glucose levels. The other receptor data that I was mentioning is really through just receptors that are different than the lipid ones and it is really through animal research. There is really not that much in humans that is available about that.

Dr. Brown:

It is interesting in how many organs you find PCSK9 but it does not seem to do anything in other organs. It is still very curious why we evolved the PCSK9 protein and also what triggers it and what makes it regulate our cholesterol levels. It is really fascinating.

Dr. Gianos:

Right. Absolutely.

Dr. Brown:

For our listeners who are not lipidologists and, believe it or not, most of our audience are physicians of

a broad range of specialties, but many are not lipidologists, why don't you give us your insight on what type of patient you might pull out a PCSK9 and use because I think there has been an understandable nervousness by the average physician because, number one, they hear it is expensive and, number two, it is an injectable which a lot of doctors are uncomfortable with, and then, number three, the noise about which types of patients are appropriate for it.

Dr. Gianos:

Absolutely, I think this... we're sort of adapting as we go along and learning who is really ideal for the drug and, as we have more outcomes trials too, we'll probably rethink it again. It's undoubtedly people with familial hyperlipidemia, heterozygous respond very well, even some homozygous, even though they lack LDL receptors more so, some do have a decent response to it so you can use it in those patients. Patients with atherosclerosis who are at high risk, who really aren't at goal on diet and medical therapy really. And in those cases, I think we have to be very responsible that we choose the right patients. If they're almost at goal and they could try another therapy or improve their lifestyle, certainly I think those are things that should be addressed first, but if they are having recurrent events and really are far from goal, then it is important to consider. The reason to be cautious, I think, is because we do not know the long-term effects at this point. They have tremendous promise and I think that for the people who are at high risk, this is the best thing we can give them and we should absolutely advocate for it, but to be cautious in the patients who really don't quite meet full criteria.

Dr. Brown:

As my parents were both old-time general practitioners and they always said never be the first or the last to try something new, which I think was wisdom for many years of practice. In this case, the safety profile looks pretty impressive. So, there is a lot of discussion about cost and value, and most of those discussions are based on a retail price of \$14,300 a year. The information I get is that most pharmacies are actually not paying that much. They are paying somewhere between \$6,000 and \$9,000 but it's a little obtuse, nobody tells you exactly what they are paying for it. What do you think about the outcome data in terms of trying to sort out the cost effectiveness of these relatively expensive medications?

Dr. Gianos:

I think that it will be very useful and, again, because of the mixed effects of PCSK9, there is a small question of whether, through other effects on inflammation or other receptors, etc., will the LDL lowering entirely translate into outcomes or get affected by the mixed effects, etc. But I do expect that there will be tremendous outcomes benefits and maybe further justify the use of the medications, if anything. Apparently, this recent JAMA article reviewed the cost at this point and it is something like \$500,000 per year where about \$100,000 quality adjusted life years is really what would be cost effective. So, based on 2015 expenditure, it seems like they may not be cost effective.

Dr. Brown:

That was an interesting article. They made some assumptions that, number one, that the cost was \$14,300 and then they made what I think was a clever assumption that the amount of events that were saved would be based on the exact amount of LDL lowering, based on prior studies with statins. So, they probably overstated what the actual price is. On the other hand, my guess, and I'd be curious on your thoughts, is once we see the outcome studies, hopefully before the middle of next year, we'll be able to sort out which patients are the highest risk and where it might be cost effective versus those who have some elevated LDL but their risk may not justify the expense of the therapy.

Dr. Gianos:

Absolutely, I 100% agree. I have people who really have heterozygous FH, have had several surgeries, stents every year or two, and for those patients anything we can do to stop that process is key. Whereas, the person who is somewhat intolerant to statins that maybe we can try different things with and really get them to tolerate a better dose or try other therapies, perhaps that is not the person who we should be spending these healthcare dollars on.

Dr. Brown:

So it is worth making the efforts we have made for years to add ezetimibe, add bile acid resin and has tried multiple statins to make sure when a patient is statin intolerant.

Dr. Gianos:

Absolutely, there're tried, true, safe methods that we should absolutely exhaust, I agree.

Dr. Brown:

If you are just tuning in, you are listening to ReachMD. I am Dr. Alan Brown and with me today is Dr. Eugenia Gianos, Assistant Professor in the Department of Medicine at NYU School of Medicine. So, one thing we did not talk about too much was the safety data and, from the standpoint of efficacy, the percent reduction of LDL with these drugs, I wonder if you can comment on that, and comment whether the baseline therapy that the patient is on has any effect on the efficacy of the drug.

Dr. Gianos:

They are extremely effective and when coupled with a statin, actually statins, although they decrease the production of LDL and increase LDL receptors, normally they actually increase PCSK9 indirectly through a feedback loop so by then targeting that, coupling it with a statin, it is actually pretty effective. They have been shown to reduce your LDL by 50 to 60% on top of a statin, which is extremely impressive. One of the issues that some physicians I think are coming across is whether there is a number that is too low because these have such a tremendous effect that we are coming up with LDL levels between 1 and 30 that physicians are sort of not so sure if they should be comfortable with those low levels as well. For the most part, populations that have PCSK9 down regulations that genetically have that disorder do well in the long-term and there aren't really safety concerns, but is lowering it iatrogenically really going to have the same effects or could there be other long-term effects? So far, from the statin data from other cholesterol data trials, there really hasn't been a signal in reviewing all those for hemorrhagic stroke which was a concern, cancer risk, other things. But again, we really haven't gotten them to these really low levels on a larger level.

Dr. Brown:

We certainly do not have ten-year data to look at, at this point. It is interesting, as you pointed out, though that people with a knockout mutation of their PCSK9, where genetics did the experiment for us, are walking around with 12, 14, 17 LDLs and they are in their 50s, looks like they are healthy. So, that is encouraging.

Dr. Gianos:

Exactly, that is what we expect. Granted, same thing with HDL, people with high HDL seem to be protected, although that is still a mixed controversy, but does raising HDL through therapy, this is now a bit controversial between the anacetrapib and other niacin data, etc. things that are targeting that, are they improving outcome is the question we really do not know. How you get there is important.

Dr. Brown:

It seems that way. So, we did not talk much about side effects. We have covered effectiveness with 50-60% LDL reduction. We touched on, although we didn't really go into the fact that no matter what the baseline therapy is, even on max dose statins or statins plus other agents like ezetimibe bile acid resin, there still seems to be an incremental 50-60% additional lowering which is interesting. You sort of think maybe you have already upregulated all the LDL receptors but there must be enough fluff in the system that you can still get that extra 50-60% which is encouraging. And we realized that we do not have outcome data yet, as you pointed out, and hopefully that will come out in the next year or so. Why don't you tell us a little bit about the downsides and what docs have to worry about when they use these medicines.

Dr. Gianos:

On a whole, they really are well-tolerated. In terms of safety and adverse events, the most common things are injection site reactions, maybe some flu-like type symptoms in the beginning and having administered these to a number of my patients who have taken multiple other drugs prior to this, they really seem to tolerate them very well. Having said that, I did have one patient who did have a hypersensitivity-type reaction and it was actually a type IV reaction where she had a delayed response where she first got a rash distal and then at the injection site and then systemic symptoms, etc., and she can't be on the drug. So, with these they are monoclonal antibodies, they are fully human so they are less likely to create a reaction or have immunogenic potential, but there is a potential to have an immediate hypersensitivity reaction or any of the type I through type IV. So, we should be aware of that. Other monoclonal antibodies that are used for rheumatoid arthritis, for cancer, for everything in the long-term seem to have very good overall safety profiles. They do have increased adverse events in terms of minor things but their serious adverse events are very low and those have been around for 10 to 20 years and overall they have done very well for patients.

Dr. Brown:

Thank you very much for a brief, but very thorough review of the PCSK9 antibodies and a review of the types of patients we should use them in, their effectiveness, and some of the potential side effects. I really appreciate you being here today.

Dr. Gianos:

It was a pleasure, no problem.

Dr. Brown:

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