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In the Pipeline: New and Emerging Therapies for Dry Macular Degeneration

Narrator:
Welcome to the CME-certified activity, “In the Pipeline: New and Emerging Therapies for Dry Macular Degeneration,” on ReachMD. This activity is co-provided by Med-IQ and Duke University Health System Department of Clinical Education and Professional Development.

In this segment, Dr. Scott Cousins of the Duke Eye Center reviews recent and emerging therapies for dry macular degeneration. In addition, he discusses what is currently known about the natural history of age-related macular degeneration and the paradigms contributing to the development of geographic atrophy. Investigational strategies for the management of geographic atrophy are also explored.

Your host is Dr. Adrienne Scott, who is Assistant Professor of Ophthalmology at Wilmer Eye Institute, Johns Hopkins University School of Medicine in Baltimore, Maryland.

Dr. Scott:
According to the National Eye Institute, AMD is the leading cause of vision loss in the United States. What do we know about the natural history and causes of AMD, and what are the new and emerging therapies?

I am your host, Dr. Adrienne Scott, and we are recording live from the American Academy of Ophthalmology Meeting in Chicago, and today with me I'm pleased to have Dr. Scott Cousins, Professor of Ophthalmology and Vice-chair of Research in the Department of Ophthalmology at Duke University School of Medicine - Duke Eye Center.

Dr. Cousins, welcome to ReachMD.

Dr. Cousins:
Thank you, Dr. Scott. It's a pleasure to be here.

Dr. Scott:
Wonderful. Well, let's get to our topic. We're discussing age-related macular degeneration today. And, Dr. Cousins, can you explain a little bit about what we know about the natural history of AMD?

Dr. Cousins:
So, AMD starts out as early or intermediate disease, often called dry macular degeneration, and over time progresses to the late stage of dry, known as geographic atrophy, and at any stage in dry disease can convert to neovascularization. It begins after age 50, but by age 80 to 90, the majority of patients in modern societies have some manifestation of macular degeneration.

Dr. Scott:
Well, thanks, Scott. So, given that we know there are varying degrees of severity of AMD, can you explain a little bit about the causes of AMD and what we know about which patients are most likely to progress to advanced disease?

Dr. Cousins:
So, there are two ways to look at that. One is by the morphology of macular degeneration; the other is by genetic risk factors. So,

clinically, most useful way of assessing risk is assessing the degree of drusen and pigment changes in early or intermediate disease. The more soft drusen, the more pigment that is present, the higher risk of converting to either geographic atrophy or choroidal new vessels, but we also now know that there are genetic and environmental and systemic health factors that also control, at least the onset of disease, if not the natural history. What we know about genetics, surprisingly, is that the greatest genetic risk factor for the disease falls in the complement pathway, a pathway that traditionally was thought to be related to inflammation and killing pathogens. Well, that pathway has now been genetically tied towards a cause of age-related macular degeneration. In addition, we know that genetics of lipid biochemistry such as in the lipid transport proteins and also in the extracellular matrix protein family are all the related to progression of AMD.

Dr. Cousins:
I think it's a little premature to do genetic testing until we have a treatment for the early stage of disease. What genetic testing can tell you is if you've got the risk genes, but because you have the risk genes doesn't mean you're actually going to get the disease.

Dr. Scott:
You mentioned the staging of AMD reliant upon varying degrees of drusen. Can you tell us about what are drusen and how are they formed?

Dr. Cousins:
Drusen are lipid-rich deposits that form under the RPE. Most of us believe that they are debris or byproducts of dysfunctional metabolism of the RPE, but we disagree about the specific abnormalities of the RPE that give rise to drusen. There's also a debate that whether drusen are simply a marker of dysfunctional macula or they actually are partly causal to the progression of the disease. Absolute knowledge of that is unknown, but I would bet that probably both is going to be true.

Dr. Scott:
And can you tell us a little about any sort of ongoing trials to address the drusen? Are there drusen therapeutics in the works?

Dr. Cousins:
So, for those of us who think that drusen are partially causal for the progression of disease, the chaotic quest for drusen Drano, that is a medication that will make them go away, is one of mine and some of my colleagues' dream. As of now there are two drugs that are being evaluated that could treat the drusen stage of the disease. One is MC-1011, which is a small molecule drug that appears to increase blood flow of the choroid based on the theory that if you improve flow that you will improve clearance of the debris, and that program is moving forward. At Duke we are initiating a Phase I trial of another approach using a drug called elamipretide. This is a drug that targets mitochondria. Mitochondria are the organelles that make energy in the form of ATP. Many diseases are associated with dysfunctional mitochondria, and our laboratory research suggests that dysfunctional mitochondria are crucial in driving dry AMD, and if you had a drug that could reset and normalize these sick mitochondria, you could actually at least stop the production of drusen or maybe make them regress. In fact, we've shown that in animals. So, a Phase I clinical trial of using this drug that elamipretide that actually normalizes sick mitochondria will be initiated actually next week at Duke. It's a Phase I study, 40 patients, but if it's positive, it will be the first drug that is directly targeted towards drusen regression and improving vision in these patients.

Dr. Scott:
Well, that's fascinating. So, I don't know that many of us think of age-related macular degeneration as a disease in which the mitochondria are implicated. Can you tell us a little bit about geographic atrophy, another form of advanced AMD causing significant vision loss in our patients?

Dr. Cousins:
So, eventually, most drusen patients will develop areas of focal loss of photoreceptor in RPE. These usually begin as parafoveal focal loss that eventually expand and can consolidate to go subfoveally. And once you have subfoveal extension of atrophy, loss of RPE cones and the underlying choriocapillaris, clearly those patients are going to have severe vision impact. We don't know why the cones in RPE actually die. There are a number of theories out there: one relates to complement; one relates to amyloid.
Dr. Scott:
Thank you, Dr. Cousins. We seem to have a number of agents available that are able to restore vision and stabilize vision in neovascular AMD, but our geographic atrophy patients seem to still continue to progress, and this is a large area of unmet need among our patients. You mentioned some compounds in studies that are going on with geographic atrophy. Can you tell us about some of the therapeutics that are in the works for geographic atrophy, and how close to being ready for primetime are any of these agents?

Dr. Cousins:
So, there are three main areas that pharmaceutical companies are developing therapeutics for late-stage geographic atrophy. Farthest along, perhaps, are the complement inhibitors. Lampalizumab, which is an antibody that inhibits Factor D, which is one of the regulatory

components of the complement cascade, and if this pathway is inhibited, the premise is that complement activation would be decreased. This is currently in a Phase III, multicenter, international trial, and the results should be made available to us in the next year or two.

One step behind in a Phase II trial is a molecule called APL-2, which is another anticomplement. This molecule attacks complement factor 3, which is an intermediate component of the complement cascade. And again, this medicine is given by intravitreal injection. And we should know the results of this Phase II study in about a year and a half.

Dr. Scott:
Switching gears, we talked a little bit about the pathogenesis of geographic atrophy. Dr. Cousins, can you tell us what are amyloid beta peptides, and how can they be used to treat geographic atrophy?

Dr. Cousins:
Scientists have long thought that there was a connection between Alzheimer's and macular degeneration, and in the last five years or so, the connection appears to be these amyloid proteins. In Alzheimer's disease, one of the causes is thought to be a natural protein that is expressed in the brain called amyloid precursor protein, and if it gets cleaved in the wrong way, the cleavage products become toxic, and these are called amyloid peptides. A lot of research has gone into treating these peptides with antibodies or other therapies in terms of Alzheimer's disease and, unfortunately, none of those trials have borne fruit. It turns out that when you look at dry macular degeneration, especially drusen, plaques of these same peptides builds up, so the thought is that maybe these are the toxic component that cause geographic atrophy. So, some of the antibodies that were tested for Alzheimer's disease are currently in clinical trial for the treatment of these peptides in geographic atrophy.

Farthest along is an antibody that binds the amyloid beta 40 peptide, and yesterday we heard the results of that study and, unfortunately, it was negative, that although they achieved adequate serum concentrations of the antibody and lowered their biomarker in the blood, it did not slow the progression of geographic atrophy, and that was very disappointing. There are several other amyloid drugs currently in early phase trial or being considered for trial, and we'll have to wait and see the results of those trials.

Dr. Scott:
Also, we've looked at the visual cycle as a target, a potential therapy in geographic atrophy. Can you explain a little bit about how the visual cycle of therapeutics are being used to treat GA?

Dr. Cousins:
So, the visual cycle is a part of our residency training where we all fell asleep because that was where the visual scientists came in to give the residents a lecture on how vitamin A gets transformed from its natural state into visual pigment, and then after light strikes visual pigment, the opsin activates a photochemical response and the vitamin A transforms from cis to trans. The trans vitamin A is thought to be toxic, and the photoreceptor and RP have a very complex machinery to remove that toxicity and restore vitamin A into visual pigment. That process is called the visual cycle. And there are multiple steps in the visual cycle where one could consider blocking the visual cycle to slow down the rate of toxic trans vitamin A accumulation.

A number of companies have developed therapeutics to interfere with the visual cycle with the idea that if you decrease trans vitamin A, you decrease lipofuscin and you decrease toxicity of the disease. Farthest along is the drug emixustat, which blocks an enzyme called RPE65, which really slows down the formation of visual pigment. Unfortunately, the results of that trial were released yesterday, and in spite of achieving biochemical evidence that the drug was on board, it failed to decrease the progression of geographic atrophy, and it's unlikely that drug is going to be moving forward into commercial development.

There are also several other visual cycle-targeting drugs currently in early phase trial or being considered for trial. We'll have to wait and see if maybe targeting something, another enzyme in the visual cycle might be more therapeutic than RPE65.
Dr. Scott:
Well, whomever was falling asleep in their physiology class listening to the visual cycle obviously didn't have you to break it down for them as well, so we appreciate that. I do have a question regarding stem cell therapy. There is a lot of media exposure to stem cell therapies. Patients are hearing this. Trade magazines are publishing on it, and other fields have actually started implementing stem cell therapies in their practices. Can you give us a little bit of summary about where stem cells stand in the treatment of age-related macular degeneration?

Dr. Cousins:
So, there are two strategies that use stem cells. One is a cell replacement; that is, you want to grow a new macula. If somebody has end-stage geographic atrophy, they need to grow new rods and cones. The other is to use stem cells for the production of supportive factors. That is, they're going to release factors that will rejuvenate struggling but living cells in the tissue. There's ongoing research

targeting both. In terms of cell replacement therapy, a number of approaches. The most exciting approach is to take embryonic stem cells, grow them in a culture system on a substrate, then implant that substrate under the macula. There are at least two groups that are currently in clinical trial using that, one in the States and one in Europe. So this is a very exciting area. Another strategy is to inject in embryonic stem cells or neuro-derived stem cells as a suspension and then hope that those cells can then differentiate into rods and cones in situ. A number of companies have trials that are doing that, and some of the early-stage research suggests maybe they are becoming functional. But to me, the one that is most likely to work soonest are those trials that are using stem cells to produce supportive factors. Furthest along is the use of umbilical-derived stem cells. The idea is that these cells will be injected subretinally at the edge of geographic atrophy, and they'll release factors that will rejuvenate and stimulate struggling cones at the edge of geographic atrophy and boost them to recover their visual function. This study is currently gearing up for a Phase II, and there will be centers across the United States that will be doing umbilical stem cell therapies. In addition, there are probably, last time I checked, at least 12 single sites that are doing various kinds of stem cell injections into the vitreous cavity, bone marrow-derived stem cells, neuro-derived stem cells, etc. We have to await the results of these trials before we can recommend those therapies moving forward.

Dr. Scott:
Thank you so much, Dr. Cousins. We've come to the end of our discussion. Your insights have been invaluable regarding new and emerging therapies for AMD.

I am your host, Dr. Adrienne Scott. Thank you very much for listening.