Eyes Toward the Future in AMD: What's New on the Horizon?

Narrator:
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Your host is Dr. John Russell and he is joined by Dr. Peter Kaiser, the Chaney Family Endowed Chair for Ophthalmology Research and a Professor of Ophthalmology at the Cleveland Clinic Lerner College of Medicine.

DR. RUSSELL: Even though age-related macular degeneration, or AMD, is the most common cause of vision loss in patients age 60 years and older, the good news is that introduction of anti-vascular endothelial growth factor or anti-VEGF drugs in ophthalmology has revolutionized its treatment. However, gaps still exist in the diagnosis, treatment, and management of AMD. As new clinical evidence of novel treatment options continue to emerge, there is now more potential for individualizing therapy and optimizing outcomes.

This is CME on ReachMD, and I am Dr. John Russell. Joining me to today to talk about age-related macular degeneration is Dr. Peter Kaiser. He is Chaney Family Endowed Chair in Ophthalmology Research, Professor of Ophthalmology at the Cleveland Clinic Lerner College of Medicine. Dr. Kaiser, welcome to the program.

DR. KAISER: Thank you for having me.

DR. RUSSELL: To start off, what is age-related macular degeneration?

DR. KAISER: Age-related macular degeneration is the number one cause of blindness in older patients. In fact, when you look worldwide, it is the leading cause of vision loss in people over the age of 50 years old. It is a very big problem. As the baby boomers get older, this is a problem that is only getting worse throughout the industrialized world.
DR. RUSSELL: I have a lot of older patients, who have macular degeneration. I know there is more than one type. How should I, as a primary care doctor, start thinking about macular degeneration?

DR. KAISER: I think that is a very good question because there are patients who are diagnosed with macular degeneration, and they think, this is it. I am going to go blind. I need to sell my car. I need to learn Braille. It is not a death sentence. It is very important to understand that there are actually two different forms of macular degeneration. The more common form is called dry macular degeneration, and this is less severe. Most patients have this. The less common form is wet macular degeneration, and this is the bad form. This is more severe, and more patients lose vision. If you break it down, about 85% of patients with macular degeneration have the dry form. The hallmark of dry macular degeneration is the formation of these little yellow deposits that an ophthalmologist or even a primary care doctor can see on an eye exam. These can progress very slowly. In general, the dry-form macular degeneration does not lead to any loss of vision. That is why I say to my patients who come in and they are first diagnosed with this, in general, you are going to do just fine. About 15% of patients will develop the bad form. We call this wet macular degeneration, and it is called wet because patients develop new blood vessels in their eye. These new blood vessels bleed and leak fluid. This leads to a very sudden loss of central visual acuity. Almost 80% of all cases of legal blindness are due to this wet form of macular degeneration.

As I mentioned, in the wet form, new blood vessels grow into the eye, and these new blood vessels are very different than our regular blood vessels that do not leak fluid and do not bleed. These are very fragile vessels, and they do bleed, and they do cause fluid to accumulate. That is what the loss of vision occurs from in wet macular degeneration.

DR. RUSSELL: You talked about vision loss. Are there other signs and symptoms that I can wrap my head around to really differentiate a patient I am seeing who might have dry versus wet macular degeneration? If I have someone who has wet macular degeneration, is that someone that needs to be in your office today, tomorrow, this week?

DR. KAISER: Sure. Most patients with macular degeneration have the dry form. Most of those patients actually have no symptoms, whatsoever. They may not even notice that they have any problems, whatsoever. They are only given the diagnosis when they go in for a routine eye exam. Some patients with dry macular degeneration may notice that they have more trouble seeing at night or in a dark restaurant, for instance, because their dark adaptation goes down. It usually would affect both eyes. Anytime you have something that is only affecting one eye, that is usually not dry macular degeneration.

As you correctly pointed out, if you have a patient who has a very sudden change in vision, and in particular, somebody who has trouble suddenly reading or recognizing faces or driving, these are patients that may have developed this new blood vessel that I just talked about. In general, we want to see someone with wet macular degeneration pretty quickly within days to at most about a week after they notice the symptoms of a sudden change in vision.

DR. RUSSELL: Is there something involved with central vision? When they talk about visual loss, are they going to mention that more often to me?

DR. KAISER: We have many things in ophthalmology that can cause vision loss, but macular degeneration is unique in that it really affects the center part of your vision the most. For instance, someone with glaucoma, their vision loss is going to be on the sides of their vision, in the peripheral vision. That may be very hard to notice out in the side of your vision. When it happens in the center of your vision, this is what we use every day. This is what we use to see fine print when we are reading. This is what we use to see people's faces. With macular degeneration, if it develops the wet form, that central area becomes wavy and distorted. It is a pretty sudden and pretty significant change. That is why patients notice it and need to be seen pretty quickly by an ophthalmologist.

DR. RUSSEL: For those just tuning in, you are listening to CME on ReachMD. I am Dr. John Russell, and today I am speaking with Dr. Peter Kaiser about age-related macular degeneration, or AMD. What would be my patient's risk factors for developing AMD?

DR. KAISER: Macular degeneration has numerous risk factors. Some of them we cannot change, and some of them we can. The biggest risk factor for macular degeneration is the first word of the name, age-related. Patients will develop this with increasing prevalence as they get older. It has been estimated that about a third of patients over the age of 75 and about half the patients over
the age of 85 years have some form of macular degeneration. As I mentioned before, usually the dry form.

If you get older, you are going to have a higher risk of macular degeneration. Obviously, that is a good thing to get older but nothing you can do about it. The other thing you cannot do about it is genetics. There are definitely genetic risk factors for macular degeneration. Interestingly, in patients who are African-American and Hispanic, the more darkly pigmented individuals, macular degeneration is actually very rare. They have other things that they need to worry about. For instance, they have a higher rate of glaucoma and diabetic retinopathy. Caucasians are unique in that they have the highest risk of developing macular degeneration. There are certain genetic markers that one can test for to see how high your rate is. If you have a family member who has macular degeneration, you have a higher risk than someone who does not have a family member. It is important that if you have members of your family who have this to be seen relatively regularly to make sure that there is nothing you can do about this. The final area of risk factors for macular degeneration is certainly something that you can do something about. Some of the major, major risk factors are cigarette and cigar smoking, so someone who smokes cigarettes has an incredibly high risk. The reason for that is macular degeneration is thought to be related to a decreased ability to fight the oxidative damage that we see in the eye. Smokers already reduce your body's ability to fight oxidation. Light exposure is another big one. If you are outside, it is a good idea to have UV protection of both your eyes as well as to protect your skin, so a hat and sunglasses in the bright sun is a good idea. Many traditional glasses, if you are like myself, I wear glasses. They have clear UV protection on it, and that is a good idea. The final risk factor that you can adjust, that you can modify, is anything that is bad for your heart is also probably bad for your eye. High lipid levels, high blood pressure, and other cardiovascular risk factors are known to increase one's risk for macular degeneration.

DR. RUSSELL: For those modifiable risk factors, is there evidence that if someone quits smoking that they can fall back into a lower risk category?

DR. KAISER: Absolutely. Whenever I see a patient who walks into my office, and they have been diagnosed with macular degeneration and I smell the telltale signs of a cigarette smoker, this is really one of the biggest carrots out there for these patients to stop smoking. In fact, it is a very powerful reason to stop smoking because within about five years of quitting smoking, your risk for macular degeneration goes down to pretty much baseline. That is a huge reason to quit smoking.

DR. RUSSELL: If you are seeing my patient for a routine exam and you see the telltale signs of dry macular degeneration, how are we going to go about treating that patient?

DR. KAISER: The only treatment that has been found in a randomized clinical trial to help in dry macular degeneration is the use of antioxidants and zinc. The dosages of these vitamins, even though they are very common vitamins often found in our diet, is well above what any one individual can eat. Taking these high-dose vitamins as supplementation to a good diet would be beneficial. The study that proved this was sponsored by the National Institute of Health. It was called the Age-Related Eye Disease Study, which we abbreviate as AREDS. Someone with dry macular degeneration and I smell the telltale signs of a cigarette smoker, this is really one of the biggest carrots out there for these patients to stop smoking. In fact, it is a very powerful reason to stop smoking because within about five years of quitting smoking, your risk for macular degeneration goes down to pretty much baseline. That is a huge reason to quit smoking.

DR. RUSSELL: If you are seeing my patient for a routine exam and you see the telltale signs of dry macular degeneration, how are we going to go about treating that patient?

DR. KAISER: The only treatment that has been found in a randomized clinical trial to help in dry macular degeneration is the use of antioxidants and zinc. The dosages of these vitamins, even though they are very common vitamins often found in our diet, is well above what any one individual can eat. Taking these high-dose vitamins as supplementation to a good diet would be beneficial. The study that proved this was sponsored by the National Institute of Health. It was called the Age-Related Eye Disease Study, which we abbreviate as AREDS. Someone with dry macular degeneration would want to take the so-called AREDS vitamins, which are found in any drugstore. This is an over-the-counter treatment with no prescription required. I want to warn the listeners that people who are currently smoking should not take this formulation because there is a slightly higher risk in those patients of lung cancer, taking high-dose beta carotene. Those patients who take the AREDS vitamin formulation have many benefits. It decreases the progression to advanced macular degeneration by about 25%. Those patients who do develop advanced macular degeneration have a reduced risk of vision loss. Most importantly, it reduces the conversion of the dry form, which we consider the good form, to the wet form, which we consider the bad form. For those people who are smokers, there is actually good news. I would first recommend they quit smoking. Since they cannot take the AREDS 1 vitamins, there was a second study that was performed by the National Institute of Health. This one was known as the AREDS 2 study. In that study, they took out the beta carotene and they replaced it with lutein and zeaxanthin as well as some omega-3 fatty acids. It was found that this formulation, which was different from the AREDS 1 formulation, actually works the exact same. A lot of times people say maybe I should take the number two formulation. It has to be better than the number one formulation. In a lot of things in medicine, that is true. In macular degeneration, AREDS 1 formula and the AREDS 2 formula have the same outcome, so you could take either one, depending on which one you liked better. Dry macular degeneration is one of the biggest problems we have in ophthalmology. You could well imagine that we are working on many, many
ways to possibly treat this. I say possibly because there are many clinical studies currently ongoing. Some of the areas we are looking at are neuroprotection, reducing some of these toxic byproducts from accumulating, improving blood flow to the eye, which would help with dry macular degeneration. Stem cells are another area we are working on very closely, and finally preventing some of this oxidative damage that I have talked about. For the listeners, it is important to know that all these different things I just mentioned, including in particular stem cells because I get a lot of questions about stem cells, are all in clinical trials. None of these treatments has yet to be proven outside of the vitamins we talked about earlier.

DR. RUSSELL: The AREDS trials I really think are trials that all primary care doctors should avail themselves to. I think they are very powerful studies. There are lots of different brands. Does it really matter?

DR. KAISER: No, it does not. This is the area where some people kind of scare patients into using a particular brand or not. The vitamins themselves are the formula that matter. If you would get that at your local drugstore, a generic version, or you get a name brand version, or you get one from someone on the internet saying that this is the best, they all are the same. It really comes down to some are easier to take than others. For instance, they are smaller gelcaps, they are easier to swallow. Others are actually dissolvable, so you could actually dissolve them into your food, so you do not have to take a pill. Quite frankly, they all work exactly the same. There is no reason to spend extra money for any of the name brand versions.

DR. RUSSELL: You do not need to buy them from your eye doctor.

DR. KAISER: No. These are freely available from your local drugstore. The version that your local doctor may be selling you is exactly the same as the one that you would get in any drugstore or even online.

DR. RUSSELL: Now that we move onto wet age related macular degeneration, it is a much more complicated treatment regimen. Correct?

DR. KAISER: Yes. In wet macular degeneration, we have the growth of these new blood vessels. Much like we see, for instance in cancer where new blood vessels are very important for the growth of tumors, these new blood vessels require certain growth factors to be activated to allow these blood vessels to grow. One of the most common growth factors for the growth of these blood vessels are something called vascular endothelial growth factor, or VEGF for short. This was one of the first areas that we found that we were actually able to block a growth factor and prevent the growth of the blood vessels, these new blood vessels, in the eye.

Unfortunately, the only way to get these drugs that block VEGF into the eye at a high enough level is to actually do an injection into the eye of these particular drugs. We currently have four different drugs that we use, and they all block the same growth factor, VEGF. People always ask me why can't I take a pill or an eyedrop? It is an eye problem. An eyedrop should work. The problem is to get these growth factor inhibitors at a high enough level in the eye requires us to specifically put it inside the eye. The other issue is these growth factor blockers only last for so long, yet the growth factor itself is being produced by the body for longer than the drug lasts. Because of that, these drugs need to be given at a very frequent interval. In the clinical studies, it was anywhere from every month to every other month. Some of the new drugs are every three months. We have looked at other treatment regimens to reduce this treatment burden but also hopefully maintain the visual acuity gains that we have seen in the clinical studies. In the U.S., for the most part most doctors will treat until the patient's fluid has disappeared and then try to extend the intervals between treatments while still maintaining a dry retina. We want to dry that leakage and bleeding that these blood vessels produce. I want to let the listeners know that when you say an injection in the eye, that sounds like one of the worst possible things that could happen to you, but it is not the case. Unlike a flu shot where we just give you a flu shot without any anesthesia, for an injection into the eye, we completely numb up the eye before the injection so that the injection itself is actually totally painless. Most of my patients, especially the first time they get the shot, they ask so when are you going to finish, doc? I say we already gave it to you. We are already done. It is really not painful, and I do not want your listeners to think that this is a painful procedure at all. It is not.

DR. RUSSELL: How do you anesthetize the eye?

DR. KAISER: We numb it with just some topical either drops or we can even use a pledget of lidocaine, which is an anesthetic that
we place directly on the eye to numb up the area where we are going to give the injection.

DR. RUSSELL: Dr. Kaiser, in this time of changing formularies and you mentioned new medicines being introduced to the marketplace, how do our patients navigate individual products, and is there really differences between the different injectable medications you can use?

As you can imagine when you look at wet macular degeneration, there are many, many clinical trials that are currently ongoing. We know that blocking vascular endothelial growth factor works. It goes without saying that there are many other companies looking at blocking VEGF in either a sustained-release manner. One of the first treatments that was approved for macular degeneration was pegaptanib, and this was a treatment that, in general, did not improve visual acuity. Most of us do not use that treatment anymore. The first treatment that actually showed an improvement in visual acuity was ranibizumab. Ranibizumab was given monthly in the clinical studies, and it was approved and is actually the second approved medication for macular degeneration. The same company that makes ranibizumab also makes a drug called bevacizumab. Bevacizumab was designed for the treatment of cancer. It is actually a cancer medication. At the time of ranibizumab going to the FDA for approval, we already had bevacizumab. We started to use bevacizumab off-label in the eye. In the United States, about 40% of treatment is using this off-label bevacizumab, and it works very, very well. In fact, there was a study that showed that the outcomes with bevacizumab and ranibizumab were essentially the same. Aflibercept is the most recently approved product, and the difference between aflibercept and ranibizumab and bevacizumab is that that drug could be delivered every eight weeks whereas ranibizumab and bevacizumab in the studies were delivered every month. We are actually having a very exciting time in wet macular degeneration because we have two new products that are in front of the FDA as we speak. One is called abicipar and the other is called brolucizumab. Both of these passed and had a successful phase 3 study. The nice thing about both these medications is aflibercept is every eight weeks. These drugs are every 12 weeks. You can see that each iteration, each approval, we are basically getting about the same vision results. I do not want your listeners to think that there is a difference in vision between any of these products, but what we are seeing is even longer durability. Currently in phase 3 clinical studies is another drug called faricimab. Faricimab targets another growth factor besides VEGF. This drug appears to work every 16 weeks. Again, you are starting to see the pattern of what we are doing in our clinical research in terms of hopefully getting similar results but extending the interval. The final area that is really very exciting is the use of gene therapy. There are a couple of studies ongoing right now using gene therapy to have your own body produce an anti-VEGF molecule. Theoretically, that would require only one injection and should work for the rest of your life. Very exciting. Again, I want to warn the listeners, these are all in clinical studies, which means we do not yet know if they will work. We do have two drugs in front of the FDA as we speak that will hopefully extend the interval from eight weeks to 12 weeks or maybe even beyond. One company is looking at a surgical implantation of a delivery system that could be refilled in an office and that refilling would occur once every six months instead of getting injected every one, two, or three months. This one would require an every six-month refill.

DR. RUSSELL: Dr. Kaiser, you are doing a lot of exciting things at the Cleveland Clinic, but these are treatments that someone should be able to get in Anytown, U.S.A. Most of the things you talked about, correct?

DR. KAISER: That is correct. The clinical studies unfortunately are being performed at different clinical sites, and those are throughout the U.S. Certainly, if you have macular degeneration, it would be very beneficial to ask your doctor if there are clinical studies that you may benefit from. Once a drug is approved, then it will be available nationwide. You would absolutely not have to go to specialized treatment centers to receive it.

DR. RUSSELL: Dr. Kaiser, before we wrap up, what are the most important takeaways you would like to share without audience today?

DR. KAISER: I think the most important thing is the diagnosis of macular degeneration is not a death sentence. Most patients do just fine and will never lose vision. If you are diagnosed with dry macular degeneration, it is very important that you take the high-dose vitamin combination and have a good diet high in green leafy vegetables and fruits and low in fried foods. When you have wet macular degeneration, in the past we really had no good treatments. When I first started practicing, we had nothing for this, but the use of these anti-VEGF injections not only improves vision in about a third of patients, almost 95% of patients receiving these
treatments maintain and do not lose vision. This is a huge change. In fact, there have been studies that have shown that the incidence of legal blindness has dramatically been reduced with the introduction of this therapy. Not everybody is the same. Like anything in medicine, we need to individualize our treatment regimen for patients with macular degeneration. Your doctor would work with you if you have wet macular degeneration to determine the best treatment for you. At the Cleveland Clinic and other places nationwide, we are working on new treatments, better treatments that will give not only better vision but hopefully extend the interval between these treatments because this is a disease that is only getting bigger in the future.

DR. RUSSELL: Dr. Kaiser, it was great speaking with you today. Thanks for being on the show.

DR. KAISER: Thank you so much. It was my pleasure.

Narrator:

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