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Preventing Blindness, Protecting Vision Health: A Focus on Age-Related Macular Degeneration

Announcer:
Welcome to "*Preventing Blindness, Protecting Vision Health: A Focus on Age-related Macular Degeneration*," a CME activity on ReachMD. This activity is jointly presented by the Johns Hopkins University School of Medicine and the National Eye Institute of the National Institutes of Health. It has been developed in collaboration with Prova Education. Additional program collaboration has been provided by the Society for Women's Health Research.

Your host is Dr. Matt Birnholz. Dr. Birnholz will speak with Dr. Neil Bressler, The James P. Gills Professor of Ophthalmology and Chief of the Retina Division at the Wilmer Eye Institute and the Johns Hopkins University School of Medicine in Baltimore, Maryland.

Dr. Bressler receives research grants from Bayer Healthcare Pharmaceuticals Inc., Genentech, Inc., Novartis Pharma AG, Bayer, and Regeneron Pharmaceuticals, Inc.
Dr. Birnholz has nothing to disclose.

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After listening to this activity, participants should be able to:
• Effectively evaluate and utilize current and new diagnostic testing modalities to assist in the early diagnosis of the age-related macular degeneration patient
• Review the specific literature regarding the National Eye Institute Age-Related Eye Disease Study and its findings regarding AMD
• Review evidence-based information regarding the use of pharmacologic, photodynamic, and laser therapies for the treatment of age-related macular degeneration
• Develop a practice management model that improves efficiency and quality of care for the age-related macular degeneration patient
• Review clinical innovations and discuss the future applications for the treatment of age-related macular degeneration

Dr. Matt Birnholz:
Age-related macular degeneration, or AMD, is the leading cause of severe irreversible vision impairment in the world. In persons older than 40 years of age, AMD causes approximately 46 percent of cases of severe visual loss. Several risk factors can increase the chances of developing AMD. They include smoking, hypertension, ethnicity, age, and family history.

This interview will discuss the diagnostic methods as well as the therapeutic approaches to managing the spectrum of AMD. Dr. Bressler, welcome to the program.

Dr. Neil Bressler:
Thank you for having me.

Dr. Matt Birnholz:
In managing the choroidal, neovascular, or wet form of AMD, otherwise termed CNV for choroidal, neovascularization, what are the results demonstrated in randomized controlled trials evaluating aflibercept, bevacizumab, or ranibizumab?

Dr. Neil Bressler:
The real breakthrough in treating macular degeneration was around 2005 when ranibizumab, also known as Lucentis, was found to be far superior to our standard care, which either was unfortunately no treatment, or in some cases a treatment called photodynamic therapy using a drug called verteporfin. Photodynamic therapy with verteporfin was slightly better than no treatment in some cases, but by being slightly better, the difference was people on average lost two lines of vision instead of on average losing perhaps three or four lines of vision. Very rarely did people have improvement in vision.

The big breakthrough in 2005 was when ranibizumab was shown to be far superior not only by halting vision loss in 90 to 95 percent of the people that walked in, but in addition, what happened was about 30 to 40 percent of the people actually had substantial vision gain. In the past, we saw substantial vision gain maybe in five percent of the people. So these outcomes were far superior and quickly became the standard care for treating choroidal neovascularization.

Bevacizumab became just as popular because it's chemically similar to ranibizumab. It was not the drug that was evaluated in randomized trials, but rather because it was similar, but required compounding because the drug was used initially to treat metastatic colon cancer, so a small amount of it would then be used instead of giving intravenously for metastatic colon cancer, it was given intravitreally into the eye. And this appeared to also be effective.

However, it wasn't until a few years ago that definitive studies were performed that showed in some cases bevacizumab could be indeed equivalent with respect to vision outcomes to ranibizumab. So that brought bevacizumab on the scene and in certain circumstances that maybe we can discuss in a few minutes, was clearly effective as well.

Finally, yet another chemically similar drug, aflibercept, also known as Eylea, was recently shown also to be far superior to no treatment in the wet or neovascular form of macular degeneration. So now we have three drugs to consider for the treatment of the wet or neovascular form of macular degeneration. Aflibercept, bevacizumab, and ranibizumab.

Dr. Matt Birnholz:
And subsequently, what has the research study shown as the followup for CNV in year one, in year two, and in years after year two?

Dr. Neil Bressler:
The treatment regimens and followup have now become very important, not only within an individual drug, but when comparing across these three drugs. First of all, the initial trial showed giving ranibizumab every month for two years worked far superior to no treatment at all. However, giving an injection every month for two years and maybe thereafter, can be quite a burden on the patient, on the physician, and on the healthcare system.

So studies were done sponsored by the government called The CATT Investigation which showed that actually you could monitor someone monthly for two years, and if you used ranibizumab while monitoring monthly and only used it when you thought there was neovascular activity, typically on an optical coherence tomography image, but sometimes on fluorescein angiography were other features as well, when you saw activity and you injected and if you saw no activity you withheld injection while these people still were monitored every month, at the least, they did not need treatment every month and ended up getting far fewer than 12 treatments in a year. In fact, they got about eight to nine treatments in the first year and maybe five to six treatments in the second year. So this was less injections that were given.

Now that same CATT trial showed that if you give bevacizumab, or Avastin, every month, you also got equivalent vision outcomes to giving ranibizumab every month. The one concern was that when bevacizumab was given as needed, when you monitor monthly, it was inconclusive as to whether you could get similar vision outcomes as you might get with ranibizumab every month.

So while we are comfortable giving ranibizumab as needed with monthly monitoring for the first two years, we don't have the same confidence that we can give bevacizumab or Avastin as needed, even with monthly monitoring.

Finally, aflibercept was also shown to be effective and similar to ranibizumab every month when given less frequently than every month. And specifically in the first year, it was given three times monthly followed by every other month treatment for a year. And then, the patients again were monitored every month and only treated as needed. And this was shown to be equivalent to giving ranibizumab every month in the first year and in the second year to giving ranibizumab as needed with monthly monitoring.

All of these treatments showed that if you give either aflibercept or ranibizumab as needed with careful monitoring, that is with monthly monitoring for the first two years, that would be equivalent to giving ranibizumab every month. And these studies showed that if you given bevacizumab every month for two years, you can get equivalent outcomes to ranibizumab every month. And the one caveat is that giving bevacizumab as needed with monthly monitoring, may not be equivalent to giving ranibizumab every month.

So if we decide to give aflibercept or ranibizumab we tell the patients we will need to monitor them frequently, ideally every month. That might not be feasible for the patient or the physician or both, but ideally in the first two years to monitor every month and then give whenever we see activity. And if we're going to give bevacizumab, ideally, you not only want to see the patient every month, but probably inject them every month, if we want to be confident that we'll get the same vision outcomes.

Now, none of these trials have given us definitive data as to how to monitor or treat the patient beyond two years. That is, do we still need to see them monthly. So many physicians may look back on that first year or two to see how the patient did and try to make a judgement as to whether they really need to continue to see the patient monthly, or could they stretch some people to five weeks or six weeks, or occasionally eight weeks, or even occasionally up to three months. And that is how we approach these treatments at this time.

Finally, the most popular regimen is the regimen that has not been tested definitively in randomized clinical trials. This is a treatment approach called Treat and Extend. In this case, patients are treated monthly until they no longer show VEGF activity and then they're treated at that time, but the treatment followup is extended by a small amount, and as long as there is still no VEGF activity, the patient is still treated, but the treatment interval is extended longer and longer.

What we don't know is does that cause some risk where some patients may have a rebound in between one of the visits that we fail to see. And if you have a rebound of VEGF activity with scar tissue formation, this may not be reversible. This is very different from treating diabetic macular edema where if we do miss some new VEGF activity in a month or two, there is not likely going to be permanent vision loss. There could likely be permanent vision loss if we miss VEGF activity when treating the neovascular or wet form of macular degeneration.

Dr. Matt Birnholz:
Could you give us some additional clarification as to just what factors need to be accounted for when you talk about as needed therapy?

Dr. Neil Bressler:
Well certainly the easiest one is looking at the OCT or optical coherence tomography. Most, if not all physicians will use this when monitoring to see if there's evidence of thickening of the retinal tissue, to see if there's evidence of subretinal fluid, to see if there's evidence of elevation of the retinal pigment epithelium, and to see if there's cystoid abnormalities.

Ideally, we compare one visit to the next by looking at the old images and trying to superimpose them or register them so we can see if there is, indeed, any new activity. Careful studies have shown though in about 10 percent of cases, even using the most recent spectral-domain OCT devices, we may see no activity and yet when we obtain a fluorescein angiogram, we might see new areas of leakage.

So it might be wise to look at the OCT and if indeed activity is seen, consider treating, and if no activity is seen, maybe consider getting fluorescein angiography in order to confirm or deny whether there is any new activity, and if there is new activity on fluorescein angiography, even in the absence of OCT, one might consider treating.
And if again, no activity is seen and you're within the first one or two years, then even if you do not treat, careful followup is indicated and you still want to see them a month later.

Now obviously, patients may be very sensitive at picking up some change and someone who says their vision appears to be deteriorating, even in the absence of OCT activity or fluorescein angiography activity, because we are so fearful of missing a small amount of VEGF activity that could lead to scarring. In macular degeneration we might want to err on the side of treatment, even though in treating other diseases with anti-VEGF drugs like diabetic macular edema, we might have the luxury of waiting another month to confirm, if indeed, we are correct. And of course, while we err on the side of treatment in macular degeneration, that also means unfortunately, each time we take a small risk of endophthalmitis when we inject.

Dr. Matt Birnholz:
What is the affect of anti-VEGF therapy on geographic atrophy of the RPE? Does it cause it?

Dr. Neil Bressler:
Because we are avoiding growth of scar tissue in macular degeneration, that does not mean we avoid another natural consequence of drusen in the eye. And that is one consequence is the development of VEGF activity and choroidal neovascularization, but the other consequence of drusen is that it can slowly but surely lead to atrophy of the retina.

So if you avoid in patients with drusen, the development of scar tissue from macular degeneration, that does not mean you stop the development of geographic atrophy. Now just because we see geographic atrophy develop in some patients over time while we are giving them anti-VEGF therapy, that does not mean that there's a cause and effect relationship of the anti-VEGF drug to the

development of geographic atrophy.

And so this requires further study, but I think at least for now, we have recognized that in cases in which we are more likely to get rid of neovascularization, which means in cases that we are more likely to have better vision outcomes, we also might have more anatomic appearance of geographic atrophy. For me, I would rather have geographic atrophy form with better vision than have less geographic atrophy form, but scar tissue forms with worse vision.

It's a little analogous to thinking about putting panretinal photocoagulation over laser spots outside of the center of the retina when treating proliferative diabetic retinopathy. Surely when we do that, we cause some damage to the side vision with atrophy from the laser spots; however, we avoid severe vision loss because the neovascularization in that case does not go on to vitreous hemorrhage or detach the retina.

The same situation is true when treating macular degeneration. You might avoid scarring and avoid vision loss. As a consequence, you might see more geographic atrophy when you're successful at saving vision and avoiding neovascular growth.

Dr. Matt Birnholz:
But with an incomplete anatomic response, are there controlled studies suggesting improved outcomes when switching anti-VEGF drugs?

Dr. Neil Bressler:
There are no carefully controlled trials so far that show us whether switching from one anti-VEGF drug to another will result in resolution of VEGF activity or thickening of the retina when you fail to get complete resolution using one drug perhaps monthly for up to a years' time.

What we have seen are case series that have proven if someone fails to have resolution of edema despite multiple injections, and by multiple, I mean at least six if not 12, we have case reports where that edema can indeed go away rapidly when you switch to a different drug. The temporal relationship of rapidly going away when you just switch drugs suggests that indeed you might be able to use these other drugs when you fail to get a complete response with one drug.

The difficulty is we have seen every situation happen, and we don't know which is more likely. That is, we've seen the fluid or the activity go away in the retina, but the vision fails to improve. We've see the food and the activity go away and the vision does improve. We've seen cases where we switched drugs, the fluid goes away, there's no improvement in vision, and then over time, the fluid comes back on the new drug and perhaps we want to switch again.

So we need further study on what are the benefits to switching drugs and not be satisfied with just individual case series that have shown us you can get resolution of the anatomic incomplete response without definitive vision improvement. We need to determine what will we do to maximize vision improvement when we fail to get any further response. Do we need to switch at all, or did we reach the maximum response in most people?

Dr. Matt Birnholz:
Does a polypoidal pattern or RAP affect treatment approach?

Dr. Neil Bressler:
There are different patterns to choroidal neovascularization and two of the unusual patterns are termed polypoidal in one case and RAP or retinal angiomatous proliferation in the other pattern.

Each of these are ways of describing what is seen on imaging of the retina, but each of them do indeed represent histopathologically choroidal neovascularization. And so the treatment approach should be the same. Choroidal neovascularization is choroidal neovascularization and no study has shown that there is a failure of response. In other words, all studies have shown that you still can get a beneficial response in either a polypoidal pattern of choroidal neovascularization, or a RAP pattern of choroidal neovascularization in the setting of macular degeneration.

While these patterns may look different on imaging, we still recommend that they be approached in the same way. There are anecdotal case series that suggest we might want to consider photodynamic therapy in the case of polypoidal patterns added to the anti-VEGF regimen, or that we might want to consider laser treatment either to the polypoidal patterns or to the RAP lesions, but again, these are fraught with potential bias in the outcomes, and in the absence of any definitive study, I don't think we should be confident about adding other therapies when we see these other patterns.

The mainstay of therapy still, even in these patterns, likely should be initiating anti-VEGF therapy and trying this for at least a year to try to get the lesions under control and stop vision loss.

Dr. Matt Birnholz:
Dr. Bressler, what is the impact of the various therapeutic injections on intraocular pressure?

Dr. Neil Bressler:
We know that intraocular pressure can fluctuate in anyone that you measure it monthly for several years, especially in people as they get over the age of 65. If you're injecting somebody and seeing them monthly, and you keep measuring intraocular pressure, for some of them you're going to see this normal variation or fluctuation. The question is that are any of these fluctuations due to a cause-and-effect relationship of the injection and due to the injection on the intraocular pressure.

And indeed, there are several case series that suggest there might be some increased intraocular pressure, but by enlarge, there's no clinically relevant impact that has been shown definitively to be a problem of these intraocular injections. So if there is a problem on intraocular pressure from anti-VEGF drugs that are injected, the problem is likely very small.

We do need to be very careful when someone has glaucoma, where their optic nerve is sensitive to any increase in pressure. In this case even the slight increase in pressure that occurs transiently during the day when someone has done an intravitreal injection might be enough of an increase to potentially cause some additional damage to that person's optic nerve who has glaucoma. So careful monitoring, of course, is indicated. However, if you don't give the anti-VEGF drug, the person may lose vision from the scarring of the macula.

So in these cases of glaucoma where any increase in pressure might be very sensitively damaging to the optic nerve, it's probably worthwhile doing this in conjunction with a glaucoma expert who can help guide what to do.

Dr. Matt Birnholz:
Now what have we learned about intravitreal injection techniques and endophthalmitis?

Dr. Neil Bressler:
We know that the biggest risk to doing an intravitreal injection that can damage the vision is the development of endophthalmitis. And so we have learned from some very careful studies, both with macular degeneration and in treating diabetic macular edema with intravitreal injections that first of all, the placement of povidone iodine, an antiseptic, directly over the conjunctival area where you're going to inject and letting it dry for at least 30 seconds is critical to preventing endophthalmitis.

So this should never be avoided. If a patient says that they have a sensitivity or allergy to that antiseptic, then I think the decision is it's either no injection or you place the antiseptic on that area and hope that you minimize whatever their discomfort is.

Typically, these are probably not allergies, but more likely just a sensitivity on the cornea to the antiseptic and keratopathy that may develop, and that's no reason to avoid placing the povidone iodine. Now many people use a sterile lid speculum to try to keep the lids out of the way, but we've certainly learned that the povidone iodine is essential.

We've also learned that what's probably not essential is putting on any topical antibiotics either before or after the injection or both. In fact, careful studies have suggested that not only is there is no increased risk when one avoids topical antibiotics, the risk may be decreased when one avoids putting on any pre-op or post-op topical antibiotics.

Why this is? We don't know. It may just be a spurious finding. It's possible that any additional manipulation to the eye might slightly increase the risk of endophthalmitis including putting drops on and there's no scientific rational to give topical antibiotics. It does not get into the vitreous at any concentration that could be effective at killing any bacteria that are introduced during the intravitreal injection and so we recommend topical antibiotic drops both before and after an injection be avoided.

Finally, I think what we have learned is that when you're considering intravitreal injections in order to try to avoid endophthalmitis, you can't avoid it in all cases. And so each and every time, it's worth reminding patients while their risk is rare, maybe one in five thousand injections in some practices, the risk is not zero and you want to remind the patient to please call if they have substantial pain within a day or two after the injection, as this may very well be endophthalmitis and you want to get them back into the office promptly to evaluate them.

Dr. Matt Birnholz:
Dr. Bressler, can you update us on the results of the NIH National Eye Institute sponsored Age-Related Eye Diseases or AREDS study that examine the role of dietary supplements in managing AMD, specifically when considering dietary supplements such as used in that trial?

Dr. Neil Bressler:
The National Eye Institute's Age-Related Eye Disease Study number two, expanded on the original AREDS study. The original AREDS

study shows us that using a dietary supplement in AREDS could reduce the risk of developing the neovascular form in patient to have the intermediate stage of macular degeneration. Specifically large drusen in at least one eye.

Now the Age-Related Eye Disease Study number two looked at where they're adding lutein and zeaxanthin or adding omega-3 fatty acids would add additional benefit and no additional benefit was seen with those.

The study did show us that for cigarette smokers, where we want to avoid giving beta -carotene, substituting the beta-carotene for...we did find that substituting the beta-carotene with lutein or zeaxanthin might be an adequate supplementation. And so, in cigarette smokers or even perhaps former cigarette smokers, one might want to consider the newer formulation which substitutes lutein and zeaxanthin for beta-carotene.

Finally, while there have been some studies that have suggested that genetic testing might be of value when deciding what supplements to give. This was a secondary analysis that was unplanned and post-talk and probably only worth to be considered as an exploratory study that would require further confirmation, not as a treatment recommendation.

So we certainly do not recommend that any genetic testing be done to determine whether someone should take dietary supplements or what supplements they should take. We do recommend that everyone that over the age of 50 be evaluate for the presence of large drusen in the back of their eyes and the retina. If they don't have this, maybe check again every five years. If they do have it, then they should consider the original AREDS formulation to try to reduce the chance of getting the neovascular or what form of macular degeneration with vision loss and in current cigarette smokers, or in former smokers, we would probably recommend that they consider the newer formulation which substitutes the beta-carotene with lutein or zeaxanthin.

Finally, the Age-Related Eye Disease Study added an additional home monitoring study which suggested that home monitoring was a specific perimetry device might be able to alert the patient and the physician when the neovascular form is developing at an earlier stage. That is when the vision is better and of course, the earlier we treat neovascular macular degeneration, the better the vision when we treat it, the more likely we can preserve good vision.

So it may be in the future that if we see someone with large drusen, we consider these dietary supplements. We might adjust it depending on their cigarette smoking history, and we may indeed be doing home monitoring more often to try to identify at an earlier stage when the vision is better, the development of the neovascular form, and then we can go forward with using our treatment, the anti-VEGF treatment, to prevent substantial vision loss.

Dr. Matt Birnholz:
What should children do if both of their parents had AMD?

Dr. Neil Bressler:
If both of the parents have AMD, even if neither of the parents have AMD, the children should be examined once they're over the age of 50 for large drusen. But regardless of what the parents have, the decision to use dietary supplements and to monitor for the neovascular form is really only indicated if those children indeed have large drusen. Any sort of genetic testing or anything else at this time has not been shown to be of value if looking in the eye and asking us, do they have large drusen.

Dr. Matt Birnholz:
How about the patients who already have vision loss from either CNV and scarring or geographic atrophy, should either of those groups take the supplements?

Dr. Neil Bressler:
If both eyes are involved, then there's no reason to consider the supplements most of the time. If only one eye is involved and the other eye still has large drusen, then we want to consider the supplements.

Dr. Matt Birnholz:
Well, I'd very much like to thank our faculty, Dr. Bressler, for outlining first the overall burden of this disease as well as discussing the available tests and treatment options in the management of age-related macular degeneration.

Again, Dr. Bressler, thanks much for your insights today.

Dr. Neil Bressler:
Thank you for letting me share that information.

Announcer:
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