Update on Management of Age-related Macular Degeneration

Announcer:
Welcome to "Update on Management of 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.

The faculty for this activity is 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, and Regeneron Pharmaceuticals, Inc.
This CME activity is supported by an independent educational grant from Regeneron Pharmaceuticals, Inc.

After listening to this activity, participants should be better 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 scientific literature regarding the National Eye Institute Age-Related Eye Diseases 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 their future applications for the treatment of age-related macular degeneration.

Neil Bressler, MD:
Age-related macular degeneration left untreated is one of the leading causes of blindness, not only in the United States, but also throughout many parts of the world. There have been numerous new clinical trial reports that impact our management of age-related macular degeneration over the last year, and I would like to review those, so that we can have a better understanding how to treat our patients with this very common condition.

I will be presenting this information on behalf of my colleagues throughout the world who have participated in these trials. The objectives of this program are to evaluate and utilize current and new diagnostic testing modalities that allow us to evaluate both the earlier stages, and advanced stages of macular degeneration. We will be reviewing the scientific literature including the National Eye Institute’s Age-Related Eye Disease Study reports that just came out this year. We also will review evidence based information regarding the use of therapies, including pharmacologic therapies for the treatment of the neovascular form of age-related macular degeneration, and we will develop a practice management model that improves our efficiency and quality of care, we hope, for many of our patients with macular degeneration. And finally, I will be discussing some of the clinical innovations and discuss their future applications as they may apply to the treatment of macular degeneration.

When we suspect that someone is losing vision from macular degeneration, the most common cause of rapid vision loss is the neovascular, or exudative phase of macular degeneration. This is the development of choroidal neovascularization and fluorescein angiography can facilitate our ability to distinguish this neovascular, or exudative form, from the non-neovascular form of macular degeneration.
degeneration. The non-neovascular form includes the formation of drusen, which can lead to atrophy of the choriocapillaris, the pigment epithelium, and photoreceptors and this, indeed, can cause vision loss, but we want to know when someone is having vision loss from macular degeneration, could it be the choroidal neovascular form. Fluorescein angiography is particularly helpful in patients who may not have any clinical signs, and yet complain of vision loss because it may be difficult to visualize the choroidal neovascularization without fluorescein angiography.

In addition, we can look at the neovascularization on angiography, and we can sometimes classify the appearance as whether it is predominantly classic, or whether the angiography shows us occult with no classic choroidal neovascularization. While all patterns of choroidal neovascularization benefit from antivascular endothelial growth factor therapy, these patterns might tell us which eyes need be treated promptly, and which eyes perhaps if they have excellent visual acuity, would have choroidal neovascularization might be monitored carefully. An eye with occult with no classic neovascularization with 20/20 vision and perhaps little, if no, symptoms, may not need immediate intervention. But any eye with choroidal neovascularization where the fluorescein angiographic pattern shows a predominantly classic pattern of bright fluorescence in the early phase, with leakage from that bright area in the later phases, should indeed be treated promptly.

The angiography also may be useful in identifying eyes that might require retreatment when initiating anti-VEGF therapy. Fluorescein angiography indeed may be helpful in about 10% of the cases where OCT following anti-VEGF therapy shows no VEGF activity. About 10% of these cases that show no VEGF activity on OCT indeed may show speckled hyperfluorescence on fluorescein angiography, suggestive of the development of additional choroidal neovascularization for which anti-VEGF therapy would be indicated even though the OCT showed no evidence of activity.

We have various cameras that we can use and various imaging systems to help us evaluate macular degeneration. Confocal scanning laser ophthalmoscopy cameras use monochromatic light and can use autofluorescence to perhaps better delineate the identification of geographic atrophy. These same cameras might be used with Indocyanine green angiography that may be able to detect certain patterns of choroidal neovascularization not easily visualized otherwise on fluorescein angiography. These may be patterns of polypoidal choroidal vasculopathy, a pattern of choroidal neovascularization.

And of course, OCT has become critical to use in the management of macular degeneration because of its ability to detect subtle areas of thickening of the retina from VEGF activity, to detect subretinal fluid, and more recently, to be able to evaluate the elevation seen from pigment epithelial detachments.

So, let’s look at the typical case that might walk in, and discuss how, indeed, we would manage this, what evidence there is to decide on our management. Here we see in the left-hand side of the slide,
the fundus photograph of the left eye of a 77-year-old man, who first came in, in April 2008. He previously had lost vision in his right eye from choroidal neovascularization, which went on to a disciform scar, and left him with visual acuity of approximately 20/800. More recently, he noted vision loss in his left eye, and when he presented with this picture, he had 20/80 vision in his left eye, and we can see this leakage in the later phases of the angiogram, suggestive of choroidal neovascularization surrounded by staining of drusen.

Now it’s easy to know that we should initiate anti-VEGF therapy to treat this patient. The problem is which anti-VEGF therapy should we use? We now have three anti-VEGF therapies that have been shown to be quite effective. This includes Aflibercept, or Eylea, bevacizumab, also known as Avastin, and ranibizumab, also known as Lucentis. And so the question is, which one should we use?

In addition, and perhaps just as importantly, what retreatment regimen should we use? Should we just apply one of these anti-VEGF therapies monthly, and for how long, a year, two years, forever? Should we perhaps initiate this therapy and then do monthly monitoring for at least two years, and perhaps then decide if we can extend the follow up beyond monthly. And do p.r.n. injections with this monthly monitoring, that is, inject when the monitoring suggests that there is VEGF activity, and withhold injections when we do not see any VEGF activity. Another alternative is to give some set number of injections, let us say three monthly injections and then perhaps give the anti-VEGF therapy every two months for a year, and then perhaps go to monthly monitoring with p.r.n. injections if VEGF activity is seen. And some people say if you are going to do p.r.n. injections, perhaps do them as a capped p.r.n. injection. In other words, only treat when we see activity, but perhaps cap that withholding and treat as often as every three months, so that you never go more than three months without treatment. One of the most common approaches to treatment is the treatment extend regimen, but we have no randomized clinical trials that compare a treatment extend regimen to just monthly treatment. So, we hope that this might work well, but we really do not know the benefits and risks of a treatment extend regimen at this time, and maybe we might choose something else.

The way we decide how to approach these, is we use evidence-based medicine. Now, evidence-based medicine does not mean only randomized clinical trials. We put randomized clinical trials at the top of the hierarchy of evidence-based medicine because it is least likely to buy us our results, and give us a false validity of some conclusion.

But in addition to randomized clinical trials, we might have prospective case series, or even retrospective case series that give us some evidence. They may be biased, maybe they look like they had good results, but half of the patients who did very poorly failed to come back for follow up. Such a retrospective study might suggest good outcomes of the 50% who came back, but in reality, if those
other 50% who did poorly also had come back, you might conclude that the treatment in this retrospective case series is really not as good as what was reported.

And we not only have to decide this hierarchy of evidence, putting randomized clinical trials at the top of it, but we have to take that evidence, and then consider the patient's values, and the patient's resources across alternative management strategies. So, the patient has to weigh for themselves what the benefits and risks may be, what the inconvenience might be of different treatments, and what the costs may be as well.

The CATT results were the first randomized clinical trial to show us definitively different treatment regimens and different anti-VEGF drugs to determine the outcomes for macular degeneration. This slide shows the main outcome from that result. This is a non-inferiority trial. In a non-inferiority trial, we ask what is the difference in outcome between one treatment and another treatment. For example, on the top line, we have bevacizumab given every four weeks, and we compare that to ranibizumab given every four weeks. Now, if the outcome, let us say the mean change in visual acuity, from initiation of therapy to one year, if the main outcome was exactly the same, it would fall on the 0 line. And in this first row, the mean difference in the outcome is shown by the hash line, and it is just a 0.5 letter difference. Now we would say, that is almost 0, aren't those treatments truly equivalent. Well, it is not the point estimate, it is not the 0.5 letter difference that we have to look at. We have to look at the 95% confidence interval if we are asking just one question, or in the CATT investigation, they looked at six analyses, so they looked at the 99.2% confidence interval, and that gives you what the likely truth is in the difference between the two regimens. And here we see that the 99.2% confidence interval ranges from a 4 letter, or 3.9 letter difference in favor of ranibizumab, to a 2.9 letter difference in favor of bevacizumab.

We look carefully at the lower bounds of the confidence interval, and we ask ourselves, does it cross a threshold beyond which we would say it's truly not equivalent, it is possibly inferior. And the CATT investigators chose a mean change of 5 letters, because once you get beyond a give letter difference, previous trials in macular degeneration actually had suggested that, that was probably a real difference. That is, one was probably superior than the other.

So we look at the point estimate, that is the 0.5, we look at the confidence interval and the lower bounds of it, that is 3.9 in this first row, and we say it does not cross that 5 letter boundary, so we are pretty confident that the truth likely is that bevacizumab every four weeks is equivalent to ranibizumab every four weeks.

But one of the problems is if you look at bevacizumab given as needed on the bottom row, and you compare this to ranibizumab every four weeks, our gold standard out to one year, the concern is that
now the confidence interval crosses five, so the truth may include the possibility that bevacizumab as needed may indeed be inferior to ranibizumab every four weeks.

So, we have to consider this when we are deciding which drug and which regimen. If we are going to use bevacizumab, we might only want to use it every four weeks in the first year, rather than giving it as needed, even if we see no VEGF activity. Because the p.r.n. regimens in this trial monitor the patients monthly. And if any VEGF activity was seen, typically on OCT, retreatment was given. So these patients given bevacizumab as needed were watched very carefully, only treated when there was VEGF activity, and yet we cannot be confident that bevacizumab as needed is, indeed, definitely equivalent to ranibizumab every four weeks. And we have to discuss this with our patients, when we are deciding which treatment we might recommend.

In addition, at one year, when that bevacizumab as needed was questionably equivalent to ranibizumab every four weeks, that was just at one year. What happens by the time we get to two years? Well this slide shows the mean visual acuity change from baseline to two years. And you can see that the ranibizumab as needed regimen remained close to the ranibizumab every four week regimen, suggesting that ranibizumab as needed likely is equivalent to ranibizumab every four weeks. But the bevacizumab as needed continued to decline compared to ranibizumab every four weeks, again making us question if, indeed, not only the point estimate, which is a five letter gain with bevacizumab as needed compared to an 8.8 letter gain using ranibizumab every four weeks, not only the point estimate is different, but very likely the confidence interval goes below a 5 letter difference, making is question if we really could use bevacizumab as needed and be confident that we would get equivalent results. We will get good results, but we cannot be confident they would be equivalent to ranibizumab every 4 weeks, and that is just at 2 years. What happens at 3 years, at 5 years. Hopefully these patients will live at least 10 years after we initiate therapy for someone who perhaps has an average age of 75 or 76 or 77 years old.

The HARBOR study was an additional randomized trial to give us confidence again that monthly monitoring as shown here, and treating only as needed, appeared to be equivalent to ranibizumab given monthly.

Afibercept was looked at in a slightly different way in the first year. Here, afibercept was given every 4 weeks for 3 doses, and then every 8 weeks through the first year. And this was compared with ranibizumab every 4 weeks. Now, the afibercept, when it was given every 8 weeks, was given regardless of whether there was evidence of VEGF activity. So, if the OCT was not thickened, but it was 8 weeks since a treatment, it was retreated. If there was thickening seen in between the 8 week visit, it was not treated. This is a little different from monthly monitoring where you treat p.r.n. or only
treat when we see VEGF activity.

And we can see that in giving this regimen, that the results showed in the first year, that aflibercept 3 doses every 4 weeks followed by every 8 week dosing to 1 year, gave equivalent results to giving ranibizumab every 4 weeks.

Now in the second year, a capped p.r.n. regimen was done for both ranibizumab and aflibercept. So now they are given at the same regimens and again, the results appear to be likely equivalent. If we look at the integrated, or combined results, we can see that the mean change from baseline for both ranibizumab, which now in the second year is given as a capped p.r.n., monthly monitoring, only treated if there is activity, typically on OCT, and treated every 12 weeks even if there is not activity, and aflibercept given the same way likely results in the same outcome.

Now some people have questioned whether the VIEW trial showed that you actually get a longer duration with aflibercept. We do not see that. It is just that the regimens were different in the first year. So in the first year, you had to give ranibizumab every 4 weeks, where you had to give aflibercept less often, so there were fewer injections given, about 12 versus 7 with ranibizumab versus aflibercept in the first year. In the second year, when the retreatment regimens were identical, if one lasted longer than the other, we would have expected perhaps a larger difference in the number of injections given for the same visual acuity outcomes. And yet, in the second year, the number of injections are very close to each other, 4.7 for the ranibizumab group given as a capped p.r.n., and 4.2 for the aflibercept given as a capped p.r.n.

And, in fact, if we look at the CATT trial, where it was given as a p.r.n. dosing for two years of monthly monitoring, we can see again, just doing that regimen we have a similar number of injections and we know that ranibizumab with monthly monitoring, given p.r.n. for 2 years, gives us likely equivalent results to ranibizumab every 4 weeks. So we know that we can monitor monthly, treat only when we see VEGF activity, and this gives us the opportunity to only treat patients if we see activity so that some patients may only need a few treatments. Some unfortunately may need 24 treatments, and some patients can be in between.

But we see that there is really no difference in the total number of injections, whether you use these fixed regimens, or these p.r.n. regimens, and so many people choose to treat only as indicated, typically from the OCT. But as we said earlier, the fluorescence angiogram may also show evidence to consider therapy, in about 10% of the cases when the OCT shows no evidence of VEGF activity.

Now, safety is also an issue when comparing across these regimens. Here we see the safety results at 2 years comparing ranibizumab and bevacizumab. One concern was that there appeared to be a
greater percentage of people who had one or more serious adverse events, typically resulting in hospitalization in the bevacizumab group, 40% compared with the ranibizumab group, 32%. There were not any increased number of strokes or other risks that had typically been associated with systemic intravenous anti-VEGF therapy, but there were a few greater number of GI disorders seen in the bevacizumab group than the ranibizumab group. And, interestingly, it was the bevacizumab as needed group that had the greatest number of cumulative proportion of serious systemic adverse events.

Now again, this could be due to other confounding factors, and so we look at other studies to see if they confirm or refute this information. The IVAN study that also compared bevacizumab to ranibizumab failed to show any obvious difference in the number of serious systemic adverse events, making is question the differences that were seen for this outcome in the CATT investigation, and making us believe that likely the outcomes could be the same. The VIEW study showed no obvious differences with respect to safety outcomes, looking at aflibercept compared with ranibizumab.

One other item I would like to discuss that has come out over the last year or two involves the safety of the injections with respect to endophthalmitis, the ocular safety. And we can look here at the recent publications from the Diabetic Retinopathy Clinical Research Network.

Indeed, the use of preinjection antibiotics, or postinjection antibiotics were up to the investigator. So it was not randomly assigned, but we can see from this slide, that about half of the investigators used no preinjection nor any postinjection antibiotics. And about half of the investigators for over 11,000 injections used either pre, or more often, postinjection antibiotics.

And if we look at the number of cases of endophthalmitis of these 11,000 injections, there were 8, but 7 of them occurred in the cases that received antibiotics and only 1 among 5,000 injections occurred in the cases that got no pre or postinjection antibiotics, suggesting that giving topical antibiotics certainly does not appear to reduce the risk of endophthalmitis.

And so the current data suggest that it is extremely unlikely that omitting topical antibiotics, either prior to, or after an injection, has a moderate or large increase on the risk of endophthalmitis, because 7 of the 8 cases of endophthalmitis across these 11,000 injections occurred among patients who got either pre or post, or both, pre and post topical antibiotics.

Now, finally, I want to discuss some recent data concerning macular degeneration that came out of Age-Related Eye Disease study. This was designed to evaluate the role of dietary supplements in preventing eyes from progressing from an intermediate stage of macular degeneration, typically large drusen, to an advanced stage associated with vision loss, typically choroidal neovascularization, or less
frequently, the development of geographic atrophy in the center of the macula.

Now we know from the original AREDS publications that were first revealed to us about 10 years ago, that giving a combination of antioxidants and zinc were, indeed, superior to placebo with respect to reducing the chance of having the development of the advanced stage of macular degeneration. There was a 25% risk reduction at 5 years, 28% to the eyes given placebo went from the large drusen appearance in the eye, to an advanced stage of macular degeneration with either choroidal neovascularization, or central geographic atrophy, and a 27% risk reduction was maintained out to 10 years when 44% of the placebo group compared to 34% of the group given a combination of antioxidants plus zinc developed the advanced stage of macular degeneration. This only applied to people at baseline who had the intermediate stage. There was no value seen for people who are healthy and have no signs of the earlier stages of macular degeneration.

Now this slide shows that, that reduction in risk of getting the advanced stage of macular degeneration was mainly driven by the neovascular form of macular degeneration. If we look at cases with geographic atrophy, we see no obvious reduction in risk with the use of antioxidants plus zinc. So perhaps giving these antioxidants plus zinc might reduce the risk of someone going from drusen to choroidal neovascularization, but has no effect, perhaps, on cases with geographic atrophy. We still would consider using this in someone with geographic atrophy to try to reduce their risk of getting choroidal neovascularization.

With that background the Age Related Eye Disease Study number 2 looked at whether adding lutein and zeaxanthin, and whether adding Omega-3 fatty acids might further reduce the risk of progression of macular degeneration and independently looked at whether these had any effect on cataract. The study design was giving people either lutein and zeaxanthin, or Omega-3 fatty acids, or a combination of both, compared with a control. This was the primary randomization. The initial results were published this year in the Journal of the American Medical Association in May, and what we can see is that there really was no additional benefit of adding lutein and zeaxanthin, or Omega-3 fatty acids, or the combination compared to a placebo, which mainly was people already taking the original AREDS formulation. And we can see that there was no benefit in preventing the advanced stage of macular degeneration.

If we look just at people who took the AREDS formulation without beta keratin, but with lutein and zeaxanthin, and compared those to people who are taking the original AREDS formulation with beta keratin, there was a suggestion in an exploratory analysis, that you might get an incremental benefit substituting lutein and zeaxanthin for beta keratin. And this was only seen for reducing the risk of developing the neovascular form of macular degeneration. However, I will emphasize this is an
exploratory analysis, so we do not have the same confidence that such a substitution indeed will definitively have an incremental benefit in preventing the development in the advanced stage of macular degeneration. And we have less safety information on using this compared with the safety information we have with the original AREDS formulation.

With respect to safety, though, at least out to the time that these patients were followed, there was no increased mortality. There was an interesting effect seen with beta keratin. If we look at people who were former smokers, not people who never smoked, but if we looked at people who were former smokers, we can see that there were 23 cases, or 2% of these patients given beta keratin unfortunately developed lung cancer compared to only 1% of the people who had no beta keratin. Again, this does not definitively say that former smokers will have an increased risk if they take the original AREDS formulation, but this should be discussed with the patient in light of their considering, perhaps, using the new formulation, which substitutes lutein and zeaxanthin for beta keratin.

So in conclusion, there was no additional benefit of adding lutein and zeaxanthin or Omega-3 fatty acids to the original AREDS formulation, so we might stick with the original AREDS formulation, except in people who are smokers because we might want to reduce the risk of having lung cancer that might be increased with the use of beta keratin, but this should not be a concern for nonsmokers. There is no evidence in the literature that giving beta keratin increases their risk of lung cancer.

There are some exploratory analyses that suggest substituting lutein and zeaxanthin for beta keratin might have an incremental benefit at preventing the neovascular form of macular degeneration, but this will require further analysis.

And finally, it was looked at whether these dietary supplements may have an effect on cataract. That would have a huge public health impact, but unfortunately it was also published this past year there is no additional benefit of using any of these dietary supplements when trying to prevent the progression of cataract.

And so we come full circle back to macular degeneration to conclude and say we really have learned a tremendous amount in the last year or two in terms of managing not only the neovascular form, which treatment regimen we should use, it appears that monthly monitoring for at least the first year or two may be equivalent to monthly injections and whether other regimens, such as treat and extend, or some other approach may work, we really do not know. We have very good evidence to suggest that both aflibercept with monthly monitoring and p.r.n. usage and ranibizumab with monthly monitoring and p.r.n. usage, likely gives us equivalent results to giving ranibizumab every month for two years.

With respect to bevacizumab, while the costs are greatly reduced, and while there does not appear to
be any systemic risks associated with this at this time, we have less confidence that giving bevacizumab as needed with monthly monitoring is indeed equivalent to giving ranibizumab every four weeks.

And we have to consider the potential increased risk of endophthalmitis when having to do an extra step to prepare the bevacizumab since it needs to be compounded when it is going to be used in a small aliquot for the eye.

And finally, we have reviewed the Age-Related Eye Disease Study, and the Age-Related Eye Disease Study number 2 to give us confidence again that we should identify people who have large drusen, consider what their primary care provider whether they could take a dietary supplement, such as that used in AREDS. Perhaps there is an incremental benefit of substituting the beta keratin with lutein and zeaxanthin, but certainly in smokers, we might want to avoid beta keratin and offer them the formulation that does, indeed, substitute lutein and zeaxanthin for beta keratin.

Thank you for joining us to hear this update on macular degeneration in 2014.

Announcer:
This segment of Grand Rounds CME is jointly presented by the Johns Hopkins University School of Medicine and the National Eye Institute of the National Institutes of Health in collaboration with Prova Education. To receive your complimentary CME credit, or to download this segment, go to Reachmd.com/grandroundscme, or go to the ReachMD Medical Radio App on your iPhone, iPod touch or BlackBerry smartphone. Thanks for listening.