Dry to Wet Age-Related Macular Degeneration:
The Importance of Early Detection

Image courtesy of the National Eye Institute

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The recent addition of Medicare coverage has made it possible for just about every patient at high risk for progression from dry to wet age-related macular degeneration (AMD) to have access to advanced technology that some retina specialists say is a game-changer in AMD treatment.

The ForeseeHome AMD Monitoring Program (Notal Vision), a sophisticated yet easy-to-use system designed for at-home use, enables patients to monitor for signs of choroidal neovascularization. By detecting signs of conversion from dry to wet AMD earlier, often before patients notice changes in their vision, the ForeseeHome device enables clinicians to diagnose and treat choroidal neovascularization at its earliest stage.

We asked several retina specialists who have been prescribing the ForeseeHome device—some since it was cleared by the US Food and Drug Administration in 2009 and completion of the National Eye Institute HOME study\(^1\) in 2013—why they believe its widespread use will have a significant impact on treatment outcomes in AMD.

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Optimizing Outcomes in Age-Related Macular Degeneration

Advanced self-monitoring technology is an important adjunct to anti-VEGF therapy for preserving good vision.

EARLY PREDICTORS OF TREATMENT OUTCOMES

Considered a major breakthrough in the treatment of wet age-related macular degeneration (AMD), anti-VEGF therapy preserves vision in most patients and significantly improves vision in 30% or more.2-5 Since its introduction, anti-VEGF therapy has reduced vision loss and blindness by 43% among patients newly diagnosed with wet AMD.6 Despite these encouraging statistics, AMD continues to be a leading cause of vision impairment among older adults in the United States,7 begging the question: Are there early signs and characteristics of choroidal neovascularization (CNV) that are predictive of better results in anti-VEGF therapy for AMD?

“Pivotal trials of anti-VEGF therapy for AMD as well as subgroup analyses from key studies such as the CATT have shown that the best predictor of final visual outcome is baseline visual acuity (Figure 1),” says Byron S. Ladd, MD.8-13 “The better the vision at diagnosis, the better the final vision will be after treatment. Unfortunately, only 13% to 36% of eyes diagnosed with CNV have 20/40 or better visual acuity (Figure 2), indicating that most patients diagnosed with CNV have already lost significant vision.”10,14-17

These data suggest that even though anti-VEGF therapy will improve vision for a majority of patients, many who are diagnosed when their vision is below 20/40 will not achieve that critical 20/40 visual acuity over the long term, which is generally considered “good” functional vision.

“When we follow the treatment regimen from the clinical trials, roughly 80% of patients will have stable or improved vision at the end of the treatment interval,” says Jeffrey S. Heier, MD. “Patients who start with good vision will continue to have good vision, but their gains may not be significant. If visual acuity is already 20/30, for example, there is not much room for improvement. Patients whose baseline vision is poor, on the other hand, may gain 2 or more lines, but their final visual acuity may still fall short of the good vision they desire.”

Poor baseline visual acuity has been the norm for patients with AMD; studies have shown that about 40% of eyes are in the 20/50 to 20/200 range, and as many as 40% have worse visual acuity at diagnosis.9,13-16

“For years, clinical studies of AMD have focused on vision improvement, because by the time we detect wet AMD, visual acuity, on average, has already dropped to about 20/80,” says Carl D. Regillo, MD. “Certainly, it is important to improve vision when a patient has already lost vision, and gaining 2 lines is good, but what patients really want is good functional vision that allows them to see well enough to read small print and to drive.”

A recent retrospective case review focused on patients who had baseline visual acuities of 20/40 or better and were treated using a treat-and-extend regimen of ranibizumab (Lucentis, Genentech) or bevacizumab (Avastin, Genentech).18 These patients maintained
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vision, lost fewer than 3 lines of visual acuity, and achieved anatomical improvements over a 2-year period.

“This study, which was designed to look specifically at early detection and good vision, demonstrates just how effective our therapies can be when we detect and treat wet AMD while vision is still good,” Dr. Regillo says. “If we initiate treatment when visual acuity is 20/40 or better, the probability that we can maintain that vision through 2 years or more is over 75%.”

Lesion size has also been identified as an early predictor of treatment success in AMD. As early as the TAP and VIP trials of photodynamic therapy, investigators determined that better visual acuity outcomes are achieved when CNV lesions are smaller at baseline. Subsequent studies and retrospective analyses of anti-VEGF therapy for AMD had similar findings.

“In other words, the smaller the lesion, the better the outcome,” says Michael J. Elman, MD. “And this makes sense. If a lesion is small, there is less scar tissue, less damage, less obstruction of the visual architecture of the photoreceptors and the like.”

The evidence is overwhelming: early detection of CNV is critical to preserve and potentially improve vision in eyes with wet AMD. The challenge, however, is detecting what can be a sudden and unpredictable change in an eye with dry AMD.

“There is no drug in the pipeline, no therapy that looks promising that would reduce the risk of progression from dry to wet AMD,” Dr. Regillo says. “So the next best step is early detection of neovascular transformation via periodic examinations in our offices and frequent monitoring at home by patients.”

WHO IS AT RISK FOR PROGRESSION?

The Age-Related Eye Disease Study (AREDS) Research Group has produced a comprehensive body of work that has proven invaluable to clinicians. The grading scale developed from their analysis of risk factors for AMD progression has several applications. For example, it is a guideline for determining which patients would benefit from using the AREDS formulation dietary supplement. Of the 8.1 million patients currently diagnosed with dry AMD, approximately 7.1 million are at high risk, making them candidates for AREDS supplementation.

“Most clinicians do not realize how small the signs indicating high risk can be,” Dr. Elman says. “An eye with just one druse 125 microns in diameter (Figure 3)—the size of a vein width—is considered high risk. I suspect that many clinicians do not detect these drusen during an examination, yet these patients are at high risk of progression and should be taking AREDS supplements. They should also be monitoring their vision at home, preferably with the ForeseeHome device.”

SELF-MONITORING STRATEGIES

For more than 60 years, the Amsler grid has been the standard of care for patients with AMD to monitor their vision at home to detect changes. Although the Amsler grid is readily available and inexpensive, research has shown it has variable sensitivity, and it does not provide precise, quantifiable measures of visual field defects, making it an ineffective tool for monitoring disease progression.

“Basically, the Amsler grid is a piece of graph paper,” Dr. Ladd says. “At best, it will detect progression to wet macular degeneration with visual acuity of 20/40 or better in only about one-third of eyes. It does have some value, however, in that it encourages patients to check the vision in each eye individually.”

Checking each eye independently is particularly important for patients with good vision. “That is a key aspect of self monitoring,” Dr. Regillo says. “Patients often try to pick up visual changes by viewing familiar objects in their environment, such as bathroom tiles or grids in a window pane. Those who have good vision in both eyes may not be able to discern subtle changes—in the nondominant eye in particular—because the brain is simply not tuning it in.”

Another concern is that patients who have been diagnosed with wet AMD in one eye may or may not perceive changes in the fellow eye. “CNV development can be insidious,” Dr. Elman says. “A patient may become accustomed to a slight change in vision, perhaps attributing it to cataract. We know the Amsler grid has drawbacks, and indeed, because of the reliance on subjective change, it often fails to detect early neovascular disease when vision is still excellent.”

Given the critical need for early detection of CNV to achieve maximum benefit from anti-VEGF therapy and the limitations of self-monitoring with the Amsler grid, the development of the ForeseeHome AMD Monitoring Program (Notal Vision) was a welcome advancement.

“Very few things that we use in medicine retain efficacy after 60 years,” Dr. Elman says. “I am not suggesting we abandon the

Figure 3. An eye with just one druse 125 microns in diameter is considered high risk.
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Case No. 1
By Michael J. Elman, MD

This 72-year-old woman with intermediate dry age-related macular degeneration (AMD) had visual acuities of 20/25+1 OD and 20/25 OS. Because of her risk for progression to wet AMD, I prescribed the ForeseeHome AMD Monitoring Program, which she used an average of 5 times per week, starting in May 2011.

At the patient’s regularly scheduled appointment on November 17, 2011, her right eye showed no sign of a neovascular membrane (Figure 1), and we scheduled her next appointment for several months later.

One week later, we received an alert from the Notal Vision Data Monitoring Center (Figure 2) and had the patient come in for testing. She remained asymptomatic, detecting no change in her vision. Upon examination, I observed no blood, and the patient’s visual acuity was still 20/25.

We performed optical coherence tomography and fluorescein angiography (Figures 3 to 6). When I compared those images with the corresponding images from the patient’s previous examination, it became apparent that in the week between the examination and the alert, choroidal neovascularization (CNV) had developed and was threatening the patient’s vision. If not for the ForeseeHome alert, I highly doubt the patient would have maintained her 20/25 visual acuity, which she was able to preserve with the institution of proper treatment at that time.

CONCLUSION
CNV can develop and progress quickly. Home-based telemonitoring detects CNV earlier than the Amsler grid or symptoms, enabling us to initiate treatment at an early stage, at disease onset, before any change occurs in visual acuity. Early treatment resulting from early detection by home-based telemonitoring prevents vision loss associated with CNV.

Amsler grid. In fact, I still give it to patients, because I want them to have as much of a safety net under them as possible. However, the ForeseeHome device represents technology that is consistent with the 21st century.”

THE HOME STUDY
ForeseeHome is the first US Food and Drug Administration-cleared system for home-based monitoring of dry AMD in patients at high risk for progressing to wet AMD. The system uses preferential hyperacuity perimetry (PHP) to detect metamorphopsia and scotoma (Figure 4). Studies have shown that PHP can detect recent-onset CNV resulting from AMD and can differentiate it from intermediate AMD with high sensitivity and specificity.25-27

The HOME study was a phase 3, unmasked, randomized, controlled clinical trial initiated and managed by the National Eye Institute and supported by Notal Vision.1 The study was designed to determine if home monitoring with the ForeseeHome system—comprised of macular visual field testing with preferential...
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hyperacuity techniques and telemonitoring—and standard care results in earlier detection of CNV when compared with standard care alone.

Investigators enrolled 1,520 participants at 44 clinical sites of the AREDS2. Participants were at risk for developing CNV, with large drusen in both eyes or large drusen in one eye (study eye) and advanced AMD in the fellow (nonstudy) eye, and they had BCVA of 20/60 or better in the study eye(s) with no confounding factors of central geographic atrophy, fluid, or scarring. The primary outcome measure was the difference between BCVA at baseline or enrollment into the study compared to when CNV was detected.

The HOME study demonstrated that the proportion of participants who maintained 20/40 or better visual acuity at the time of CNV detection and initiation of treatment was 87% in the device arm and 62% in the standard care arm. Among participants who used the device at the recommended frequency of at least two times per week, the proportion maintaining 20/40 or better visual acuity when CNV was detected was 94% (Figure 5).

Based on a preplanned interim analysis, the independent Data and Safety Monitoring Committee recommended early termination of the HOME study, because, when compared with standard care alone, the ForeseeHome system plus standard care identifies signs of progression to CNV when eyes have significantly better visual acuity.

“I have been engaged in high-level clinical research for more than 30 years, and usually a study is stopped early because of futility,” says Dr. Elman, who was an investigator in the HOME study. “In this study, efficacy was demonstrated by means of earlier detection of CNV, and the committee believed it would be unethical to continue the study with the control arm as planned.” At the study’s termination, patients in the control arm were offered use of ForeseeHome.

In a subsequent evaluation of strategies for improving early detection and treatment of AMD, researchers reported the HOME study provided the first definitive evidence of efficacy for a device allowing early detection and treatment of eyes with neovascular AMD.28

“Anti-VEGF therapy has the potential to stabilize vision in most patients with wet AMD,” Dr. Ladd says. “The HOME study tells us we have the potential to maintain 20/40 or better visual acuity in up to 94% of our patients when their conversion from dry to wet AMD is detected early. Therefore, our best combination therapy for the management of AMD includes regular at-home monitoring with the ForeseeHome system combined with anti-VEGF therapy. This is a game-changer for our patients with AMD.”

PATIENT ACCEPTANCE

Daily monitoring with the ForeseeHome device takes about 3 minutes per eye. Patients view a series of dotted lines with waves or distortions, called “artificial distortions,” that flash on a screen, and they use a computer mouse to click wherever they see a bump or distortion. A person with early-onset wet AMD may not only click where the artificial distortion is but may also denote a “pathological” distortion due to metamorphopsia resulting from early signs of the disease. Results are automatically transmitted to the Notal Vision Monitoring Center, which sends an “alert” to the physician if a statistically significant change is detected (Figure 6).

“I find that most patients are compliant with the ForeseeHome program,” Dr. Heier says. “For many, it adds a level of comfort, because it helps to relieve some of their anxiety about their macular degeneration.”
Case No. 2

By Carl D. Regillo, MD

This 68-year-old woman was diagnosed with dry age-related macular degeneration (AMD) in both eyes. Her baseline BCVA was 20/30 OD and 20/50 OS. Because she is at risk for developing wet AMD—she has large soft drusen and pigmentary changes in both eyes—I prescribed the ForeseeHome AMD Monitoring Program. The patient was following up with me for monitoring twice a year. At her last visit in May 2015, she had stable, dry AMD in both eyes.

On July 20, 2015, I saw the patient on an urgent basis, after receiving an alert from the Notal Vision Data Monitoring Center notifying me that a change had been detected in the patient’s left eye (Figure 1). The patient had not noticed any new symptoms, and her BCVA was unchanged at 20/50 OS. Optical coherence tomography (OCT) showed new central subretinal fluid (Figure 2).

I initiated anti-VEGF therapy with ranibizumab (Lucentis, Genentech) that day and have been following a treat-and-extend regimen. Figure 3 shows reduced subretinal fluid 1 month after the patient’s second ranibizumab injection.

The patient’s visual acuity has remained stable during treatment, fluctuating between 20/40 and 20/50 OS. She has had six injections as of her last visit in February (Figure 4), when her visual acuity was 20/50.

CONCLUSION

The ForeseeHome AMD Monitoring Program allowed for early detection of the conversion from dry to wet AMD, before this patient recognized any symptoms and before her visual acuity declined. Prompt initiation of anti-VEGF therapy resulted in retention of good visual acuity, the level of which was the same as before the eye converted to the wet stage.

Figure 1. In the ForeseeHome Report, the blue bars represent individual tests, which are compared to a normative database taken from an AMD population (green line). This comparison represents the trend score. When the trend score rises above the threshold of a suspected change (red line) an “alert” is issued.

Figure 2. Although the patient’s BCVA was unchanged, OCT showed new central subretinal fluid in her left eye, just 2 months after her regularly scheduled semi-annual visit.

Figure 3. OCT taken 1 month after the patient’s second ranibizumab injection shows reduced subretinal fluid.

Figure 4. The patient’s most recent visit showed stable visual acuity and good control of her macular exudation on anti-VEGF therapy.

Dr. Elman has also found acceptance is high among his patients for whom he has prescribed ForeseeHome. “The good news is that pretty much everyone is accustomed to using computers these days,” he says. “Once patients settle into a routine, their compliance improves. In the HOME study, there was very little fatigue and very little loss to attrition.”

Dr. Ladd adds that the ForeseeHome system is quite user-friendly. “It simply plugs into the wall and automatically connects to any cellular network in the area, which makes it portable,” he says. “Some of my patients who spend the winter in Florida take it with them—it weighs just 3.5 pounds—and plug it in when they arrive.”

ADVANCED TECHNOLOGY FOR IMPROVED OUTCOMES

Now that the ForeseeHome AMD Monitoring System is a Medicare-covered service, utilization is likely to increase significantly.
ForeseeHome: The Test, The Report, an Alert

About 3 min/eye

Comparison to a normative database & patient’s baseline

Identification of new visual defects

Figure 6. ForeseeHome is user friendly for patients. In the HOME Study, the average use of ForeseeHome by the device arm subjects was 4.4 times per week and is aligned with frequency of use seen today outside the clinical study.

"Any tool that enables us to detect neovascular AMD early has significant value, and I believe this device can be helpful in minimizing vision loss from conversion to wet AMD," Dr. Heier says.

Dr. Regillo notes, “The ForeseeHome device has the potential to have a major impact on public health, enabling us to detect progression to wet AMD in more patients with better vision; and better vision at detection translates into better visual outcomes. That is a huge step forward.”

According to Dr. Ladd, the ForeseeHome system has become an extension of his practice into patients’ homes, reinforcing the doctor-patient relationship. “Being able to offer patients a technologically advanced monitoring device has been rewarding for me,” he says. “Over and over, patients tell me they have a sense of security when they use the ForeseeHome device. They all are fearful they will go blind when they have macular degeneration, but this alleviates those fears and provides more peace of mind than anything I have previously offered my patients.”

Dr. Elman notes, “Retina specialists are data-driven. We want to know that a drug or device will help our patients. We have conclusive clinical evidence of the efficacy of the ForeseeHome program from a rigorous, independent, level-one clinical trial of the type that we trust for everything else we do; whether it is the medicines we inject into the eye or the supplements we prescribe. Until now, cost was the major barrier to utilization of the ForeseeHome device. Now that it is a Medicare-covered service, it is affordable for all patients. In my opinion, it should be prescribed to all at-risk dry AMD patients.”