Long-Term Care Updates

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Treatment Options for Wet Age-Related Macular Degeneration

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Introduction

In developed countries, age-related macular degeneration (AMD) is the leading cause of severe vision loss. Among cases of severe vision loss in people over the age of 40 in the United States, AMD is responsible for 46%.[1] Aging is the number one risk factor for AMD and predominately Caucasian patients experience AMD. The number one modifiable risk factor for AMD is smoking.[1,2]

AMD occurs when sections of the retina, called the macula, are damaged. The macula plays a role in seeing detailed images, so when the macula is damaged, patients have a loss of central vision, and their ability to see fine details is lost. There are two types of AMD, dry and wet. Dry AMD, also known as atrophic or non-neovascular, is the most common form of AMD and is characterized by the accumulation of protein and lipid clumps, called drusen, under the retina. The onset of dry AMD is gradual and tends to have a slow progression to severe vision loss.[1,2]

Wet AMD is known as neovascular AMD because its onset is caused by new, abnormal blood vessel growth under the retina. These new blood vessels leak blood or other fluids and cause damage and scarring to the macula. The onset and progression of wet AMD is rapid. Patients can be diagnosed initially with dry AMD that progresses to wet AMD or advance straight to wet AMD.[1,2]

Treatment Options

Currently, there is no treatment for dry AMD. The disease's progression can be slowed by using supplements, such as products like the Age-Related Eye Disease Study (AREDS) formulation which contains proven vitamins and antioxidants.[1,3] For a review of the suggested products for dry AMD, refer to the November 2019 PharMerica newsletter.

Previously, treatment of wet AMD included photocoagulation and photodynamic therapy.[1,3] Laser technology is used to seal blood vessels in photocoagulation.[4] Photodynamic therapy (PDT) uses verteporfin (Visudyne) alongside laser therapy.[3] Verteporfin is given to the patient intravenously and accumulates in the affected eye's vascular portion.[1,4] Verteporfin is activated by a specific light frequency, which highlights areas of leaking vasculature.[3,4] A laser is then used to destroy the damaged blood vessels while avoiding healthy ones.[3] The success of laser treatment is limited. Many patients undergoing photocoagulation or photodynamic therapy usually need repeat treatments due to the treated vessels' rebleeding. Too many laser treatments can often lead to more scarring and further vision loss.[1,3]

Current treatments for wet AMD include various anti-vascular endothelial growth factor (anti-VEGF) agents. VEGF is a molecule that contributes to the growth of new blood vessels. As we get older, VEGF malfunctions and allows the growth of weaker blood vessels behind the retina. Anti-VEGF agents inhibit VEGF and diminish the development of new blood vessels, and various agents have been developed for the use of wet AMD.[2,3]

Ranibizumab (Lucentis) was approved in 2006 and was the first agent to be approved to treat wet AMD. Ranibizumab is a monoclonal antibody that binds to and disrupts VEGF-A and suppresses blood vessels' growth under the retina. Ranibizumab is injected into the eye. Initially, injections are needed every 28 days, and after the first three doses, patients may reduce injection frequency to 4 or 5 injections over nine months.[4] The Anti-VEGF Antibody for the Treatment of Predominantly Classic Choroidal Neovascularization in AMD (ANCHOR) trial looked at the efficacy of two different doses of ranibizumab compared to verteporfin PDT.[2,5] The outcome of the ANCHOR trial showed that 10% of patients on 0.5mg of ranibizumab had a visual loss of 15 letters or more compared to 66% of verteporfin PDT. Similarly, the ANCHOR trial showed that 41% of patients on 0.5mg of ranibizumab had a visual gain of 15 letters or more compared to 6% in the verteporfin PDT group. The ANCHOR trial also showed a lower rate of severe ocular adverse events in the ranibizumab group.[2,5]

The FDA initially approved bevacizumab (Avastin) for use in various types of cancer. Bevacizumab is an IgG monoclonal antibody that binds to and inhibits VEGF, and its use in AMD is off-label.[4] Its use for wet AMD began in 2005 and it was the first anti-VEGF agent used.[1] Bevacizumab is administered via an intravitreal injection with injections given monthly for three months, and then monthly or as needed.[4] Its low cost is a benefit to patients and is one the main reasons it became a popular choice.[5] Despite the fact that it still does not carry an FDA indication for wet AMD, its efficacy is often used as a comparator for newer treatment options. The National Eye Institute funded the Comparison of AMD Treatment Trials (CATT) which examined the effectiveness of bevacizumab versus ranibizumab.[5] The outcome of that study showed bevacizumab and ranibizumab were similarly effective at preventing vision loss after two years. When patients were analyzed five years post-study, efficacy was similar between bevacizumab and ranibizumab; however, visual acuity was decreased compared to two-year post-study.[5,6] Even though visual acuity decreased from year two to year five, more than 50% of the patients still had good visual acuity.[6] Another study, The Inhibition of VEGF in Age-Related Choroidal Neovascularization (IVAN), showed that bevacizumab was non-inferior to ranibizumab; many other studies since have also supported the similar efficacy of bevacizumab compared to ranibizumab.[5] It is notable, that based on the data from these various studies, as needed dosing of bevacizumab has demonstrated decreased efficacy compared to monthly dosing of bevacizumab and as needed dosing of other VEGF agents.[2]

Aflibercept (Eylea) was approved in 2011 and is a fusion protein that behaves as a decoy receptor for VEGF-A. It binds to VEGF and inhibits its function. Like the other anti-VEGF agents, aflibercept is an intravitreal injection. Injections are needed monthly for the first three months, with the frequency of injections decreasing to eight weeks after that.[4] The RIVAL study compared ranibizumab and aflibercept by looking at the change in macular atrophy over two years.[7] The study showed that the mean change from baseline for patients in the ranibizumab group was +0.36mm compared to +0.28mm in the aflibercept group, but there was not a statistically significant difference between the two groups.[7] The VEGF Trap-Eye: Investigation of Efficacy and Safety in Wet AMD (VIEW) trial also compared ranibizumab to aflibercept. However, the VIEW study also looked at different dosing regimens with ranibizumab dosed monthly. Aflibercept was either dosed monthly, or monthly for three doses and then every two months. The results of the VIEW study showed no difference between ranibizumab and aflibercept, including the various dosing regimens.[2,5] Therefore, an advantage of aflibercept is that it shows similar efficacy to ranibizumab but can be dosed less frequently, saving time and money for the patient.

The newest anti-VEGF treatment for wet AMD is brolucizumab (Beovu).[2,4] Brolucizumab was approved in 2019 and is a recombinant monoclonal antibody that inhibits VEGF-A's three major isoforms. Brolucizumab is given through intravitreal injection and is administered once monthly for three months, with one injection required only every 8 to 12 weeks after that.[4] The HAWK and HARRIER studies were phase three trials and compared brolucizumab to aflibercept.[8] Brolucizumab and aflibercept were each dosed monthly for three months, and then the dosing interval could be extended to 12 weeks for brolucizumab and 8 weeks for aflibercept. Both studies looked at the mean change in best-corrected visual acuity at 48 weeks. The HAWK trial examined different doses of brolucizumab (3mg and 6mg). The HAWK results showed a mean difference of +6.1, +6.6, and +6.8 for brolucizumab 3mg, brolucizumab 6mg, and aflibercept 2mg, respectively. The HARRIER showed a mean change in visual acuity of +6.9 for brolucizumab 3mg compared to +7.6 for aflibercept 2mg. Ultimately, both of these studies demonstrated non-inferiority of brolucizumab compared to aflibercept. However, these studies did show decreased disease activity in the brolucizumab patients at 16 and 48 weeks, suggesting a superior anatomic outcome for brolucizumab.[8]

Side effects of intravitreal anti-VEGF are similar between agents and include eye redness or pain, light sensitivity, blurred vision or floaters, dry or itchy eyes, among other issues. More severe effects include infections, detached retina, and cataracts.[4] Cost is an issue to consider with the VEGF agents and prices can range from $50 to $1,950 per dose.[2] Bevacizumab is the least expensive option but use of bevacizumab in AMD is considered off-label treatment. Through various trials, ranibizumab, aflibercept, and brolucizumab have shown similar effectiveness. Dosing differences can impact total cost. Brolucizumab is the newest and most expensive drug on the market, but after three once-monthly doses, it can be given every three months. Aflibercept is more expensive than ranibizumab but both can eventually be given every two months.[2] As needed injection strategies with the different agents have been studied and may be an option to decreases the total amount of injections over time. However, monthly visits are required to monitor disease progression, and frequent visits may be burdensome to many patients.[5] The best treatment option is usually patient specific and is determined by the patient and provider.

Summary

Age-related macular degeneration affects millions of aging patients, and treatment options vary depending on the AMD type. Eighty percent of patients with AMD experience the dry type. However, 90% of severe vision loss related to AMD is attributed to wet AMD.[1] Currently, no treatment exists for dry AMD, but various treatment options are available for wet AMD, decreasing the burden of AMD for some patients.

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