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Update on Age-Related Macular Degeneration – Part 2: Current and Future Treatment Strategies

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Age-related macular degeneration (AMD) is a leading cause of vision loss in older patients and in patients in the developed world. The number of patients with this disease is expected to rise as the population ages. The previous issue of *Ophthalmology Rounds* reviewed the current and future diagnostic options. The current issue outlines the evidence-based therapies for dry and wet AMD and discusses options that are showing promise in clinical study.

Age-related macular degeneration (AMD) is among the most common causes of blindness in patients in the developed world and the fourth most common cause worldwide.[1-5] Recent additions to the diagnostic tests, such as swept-source optical coherence tomography (SS-OCT) and OCT angiography (OCT-A), have improved the rapid, accurate, and noninvasive options for the identification of dry and wet AMD. Advances also continue to be made in the therapeutic options for both dry and wet AMD.

Current Treatments for Dry AMD

The Age-Related Eye Disease Study (AREDS) provided natural history data over the course of 5 years.[6] Patients with early AMD had a 1.3% chance of progression to advanced AMD — i.e., foveal geographic atrophy (GA) or choroidal neovascularization (CNV) — at 5 years. The rate of progression at 5 years was 18% among patients with intermediate AMD, defined as extensive intermediate drusen, ≥1 large drusen, or nonfoveal GA. Within this intermediate AMD group, the likelihood of progression among patients with ≥1 large drusen in each eye or nonfoveal GA in at least 1 eye was 4.5 times that of patients with neither of these features (27% versus 6%). Finally, the patients with unilateral advanced AMD had a 43% chance of progression of the fellow eye to advanced AMD by 5 years.

The AREDS trial demonstrated that micronutrient supplements consisting of 500 mg vitamin C, 400 IU vitamin E, 15 mg β-carotene, 80 mg zinc oxide, and 2 mg cupric oxide reduced the progression to advanced AMD in patients with intermediate AMD or unilateral advanced AMD.[6] No benefit was observed in patients with no AMD or early AMD. There have been reports of possible unfavourable responses to micronutrients depending on the *complement factor H* (*CFH*) or *age-related maculopathy susceptibility 2* (*ARMS2*) genotypes; however, these were *post hoc* analyses.[7-10] The American Academic of Ophthalmology, in their Preferred Practice Pattern for AMD (last updated in 2019), do not recommend genetic testing when considering micronutrients for patients.[11]

The AREDS2 trial demonstrated that the addition of lutein/zeaxanthin (10 mg/2 mg) and/or the addition of Ω-3 long-chain polyunsaturated fatty acids (eicosapentaenoic acid [EPA] 650 mg and docosahexaenoic acid [DHA] 350 mg) was found to be of no additional benefit in reducing the risk of progression to advanced AMD compared to the original AREDS formulation.[12] Secondary analyses indicated that lutein/zeaxanthin could replace β-carotene, which was associated with increased risk of lung cancer in former smokers, and the dose of zinc could be reduced to 25 mg without affecting the efficacy of the formulation.[12]

As most patients with early and intermediate AMD are asymptomatic, it is important to screen all patients aged 50 years or over for this disease. A dilated ophthalmological examination

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should be performed looking for drusen or changes to the retinal pigment epithelium (RPE). Optical coherence tomography (OCT) can be obtained if there is suspicion for wet AMD. Intravenous fluorescein angiography (IVFA) and/or OCT angiography (OCT-A) can then be used to confirm CNV. Patients with no AMD or early AMD can be simply observed. In these patients, supplementation with micronutrients has not been shown to decrease progression to intermediate or advanced AMD.[6] It is reasonable to have these patients evaluated annually as one-third of patients with early AMD will progress to intermediate AMD within 5 years.[6]

Patients with intermediate AMD or unilateral advanced AMD should take AREDS supplements. These patients should be followed regularly to screen for CNV thereby allowing for early treatment with anti-vascular endothelial growth factor (VEGF) agents. Smokers and former smokers should be warned to avoid formulations with β-carotene as there is a risk for lung cancer.[6]

In patients with bilateral advanced AMD, supplementation could be considered if the visual acuity (VA) is at least 20/100 in one eye in the presence of CNV;[6] however, if the patient is undergoing bilateral treatment with an anti-VEGF, the role of micronutrient supplementation is unknown as these agents were not available when the AREDS and AREDS2 studies were designed.

Patients with dry AMD with visual impairment, whether it be foveal GA, nonfoveal GA, non-GA, or drusenoid pigment epithelial detachment, should be referred for low-vision rehabilitation. A comprehensive list of low-vision options is beyond the scope of this article but include services and devices that help patients optimize their remaining visual function. Implantable miniature telescopes have been shown in a prospective, open-label, multicentre clinical trial of 217 participants to increase both the distance and near vision by 3 lines in 53% of eyes implanted with the device versus 10% of the fellow eyes, which were used as a control.[13] Potential limitations include a 5% risk of 2-line VA loss at distance or near, endothelial cell death of 25% at 1 year, difficulty in viewing the peripheral retina, and the absence of a control group in the study to control for the effect of the intensive rehabilitation. This device has been approved by the United States (US) Food and Drug Administration (FDA) and Health Canada, and the first device was implanted in Canada in February 2019.

Future Treatments for Dry AMD

Future treatments for dry AMD include therapies that will slow down the progression of GA. Potential targets include lipid deposition and metabolism, inflammation through the complement cascade, and autophagy.

Lampalizumab, an anticomplement factor D monoclonal antibody fragment, inhibits the activation and amplification of the alternative complement pathway. It showed benefit in Phase 2 study; however, the primary endpoint of reducing GA enlargement was not met in its 2 Phase 3 studies SPECTRI and CHROMA.[14,15]

Emixustat hydrochloride, which inhibits the visual cycle isomerase to reduce the concentration of vitamin A toxins such as N-retinylidene-N-retinylethanolamine (A2E), also showed promising Phase 2 results but was not shown to reduce the growth rate of GA in AMD patients compared to placebo in SEATTLE, a Phase 2b/3 study.[16]

Other agents such as complement inhibitors, mitochondrial targeted drugs, visual cycle therapeutics, and antiamyloid agents are currently being investigated but are early in their development. Cell therapy is currently in its infancy but could theoretically allow for the replacement of injured retinal cells with functional cells to restore vision.

Subthreshold nanosecond laser (SNL) was studied in the 36-month LEAD study where 292 patients with bilateral large drusen without OCT signs of atrophy were randomized to receive Retinal Rejuvenation Therapy (2RT) SNL or to a sham procedure. The primary outcome was the development of late AMD as defined by multimodal imaging. Overall, SNL was not shown to slow down progression to late AMD; however, a *post hoc* analysis found that the presence of reticular pseudodrusen had a significant effect modification.[17] The 70 patients with reticular pseudodrusen actually trended towards increased progression rates (adjusted hazard ratio [HR], 2.56; 95% confidence interval [CI], 0.80–8.18; P=0.112) while the 222 patients without reticular pseudodrusen had statistically significant decreases in progression rates (adjusted HR, 0.23; 95% CI, 0.09–0.59; P=0.002). While more studies are needed, SNL could be a potential option for patients with intermediate AMD without reticular pseudodrusen.

Current Treatments for Wet AMD

Historically, laser photocoagulation and photodynamic therapy were the standard of care for the treatment of wet AMD. Neither of these treatments offered good visual improvement outcomes, with the therapies being reasonably effective at stabilizing lesions and delaying progression to severe vision loss. The era of anti-angiogenic intravitreal agents has dramatically improved patient outcomes with wet AMD.

Bevacizumab is a humanized monoclonal antibody that selectively inhibits all isoforms of VEGF-A. It was originally approved for metastatic colon cancer, and its use in AMD is off label. Multiple prospective, randomized clinical trials with large sample sizes support the efficacy of bevacizumab for wet AMD.[18-22] Ranibizumab is a humanized anti-VEGF-A recombinant Fab fragment that inhibits all active isoforms of VEGF-A. The landmark MARINA and ANCHOR trials demonstrated significant improvements in VA with a monthly regimen.[23,24] Aflibercept is a soluble fusion protein that, in addition to inhibiting VEGF-A like bevacizumab and ranibizumab, also inhibits VEGF-B and placental growth factor (PlGF). The VIEW-1 and VIEW-2 studies demonstrated that after 3 monthly loading doses, intravitreal injections every 8 weeks (q8w) were equivalent to aflibercept injections every 4 weeks as well as equivalent to ranibizumab injections every 4 weeks.[25]

Optimal visual outcomes in the above named trials were seen with monthly injections of these agents.[26] However, in real-world practice, monthly visits over the long term present a heavy burden for patients and their caregivers who bring them to their appointments.[27] Therefore, different treatment strategies such as the *pro re*

nata (PRN) and treat-and-extend (TAE) regimens have been developed. In the PRN regimen, patients are evaluated every month but only receive treatment when certain criteria are present, such as decreased vision, new fluid, or hemorrhage on examination or OCT. In the TAE regimen, patients are treated at every visit; however, the interval between visits is gradually increased if the disease is inactive while the interval is decreased if the disease is active. A meta-analysis comparing PRN and TAE from 42 observational studies (N=26 360 patients) has shown that TAE have better visual outcomes (mean VA change at 1, 2, and 3 years of +8.8, +6.7, and +5.4 Early Treatment Diabetic Retinopathy Study [ETDRS] letters, respectively, for TAE compared to +3.5, +1.3, and -1.9 ETDRS letters, respectively, for PRN) and more injections (6.9 compared to 4.7) but fewer visits (7.6 vs 9.2) in the first year.[28] Large prospective studies, including the landmark prospective, multicentre, randomized CANTREAT trial done in Canada, have demonstrated that TAE ranibizumab is noninferior to monthly ranibizumab.[29-31] Therefore, TAE injection protocols have been shown to be similarly effective compared to monthly injections in wet AMD.

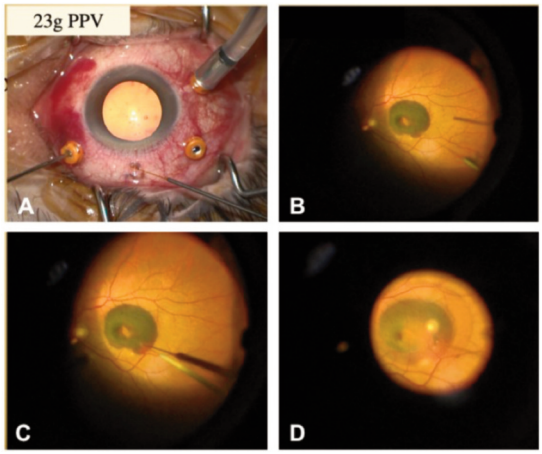
The newest approved anti-VEGF agent is brolucizumab, a small-molecule, single-chain antibody fragment that inhibits VEGF-A isoforms. In the phase 3 HAWK and HARRIER trials,[32] after loading with 3 monthly injections brolucizumab 3 mg and 6 mg q12w (adjusted to q8w if disease activity was detected) were found to be noninferior to aflibercept in mean best-corrected (BC) VA change from baseline. More than 50% of patients on brolucizumab 6 mg were exclusively maintained on q12w dosing through week 48, of whom more than 75% were successfully maintained on a 12-week dosing interval until week 96. Anatomical outcomes in the brolucizumab arms were more favourable than the aflibercept arm, including statistically superior reduction in central subfield thickness versus aflibercept in both the matched head-to-head and maintenance phases (week 48) and significantly fewer patients with intraretinal and subretinal fluid at week 48. The use of brolucizumab offers the potential for longer intervals between injections with fewer total injections, which lessens the treatment burden for patients and retina specialists. Brolucizumab was approved by Health Canada in March 2020, and is also available in the US, Europe, the United Kingdom, Japan, South Korea, and Australia.[33-36] In the US, where brolucizumab was approved in October 2019, there have been some reports of retinal artery occlusion, retinal vasculitis and/or retinal vascular occlusion, or severe vision loss. Following the completion of internal and independent external safety review committee reviews of post-marketing cases, Novartis concluded that there is a confirmed safety signal of rare adverse events of retinal vasculitis and/or retinal vascular occlusion that may result in severe vision loss. Typically these events occurred in the presence of intraocular inflammation (IOI). Based on this review, Novartis has initiated a safety information update to global brolucizumab prescribing information (https://www.brolucizumab.info). Prescribing information has been revised in the US, Australia, and Japan, and revisions have been approved in other countries, including Canada. The independent safety review committee is expected to publish its independent assessment in a peer-reviewed journal in the coming months.

Safety issues with anti-VEGF injections include the more common but less serious ocular adverse events such as subconjunctival hemorrhage, floaters, ocular surface irritation from the antiseptic to the rare but potentially serious endophthalmitis, retinal tears or detachment, vitreous hemorrhage, and sterile inflammation. Systemic adverse events from anti-VEGF agents are also possible as the medication can cross into the general circulation and inhibit VEGF functions such as the formation of new blood vessels in ischemic areas of the heart and brain. Although cardiovascular and cerebrovascular events were monitored in many large studies, the low incidence makes it hard to draw definitive conclusions. However, it is still important for the ophthalmologist to discuss these risks with patients especially those with vascular risk factors.

Large submacular hemorrhage cases can be treated with anti-VEGF monotherapy or additionally with intravitreal injection of tissue plasminogen activator and gas bubble and face-down position to displace the blood, or pars plana vitrectomy with subretinal injection of tissue plasminogen activator (Figure 1).[37-41] Presently, there are no prospective studies to demonstrate the superiority of any one of these options.

Patient education is an important part of AMD management. Patients should be told to regularly check central vision monocularly and to contact their ophthalmologist promptly if they notice any change. Additionally, patients should be informed that while AMD can severely affect their central vision, total blindness is rare. Finally, patients should be reassured that reading and other routine visual tasks will not harm their vision and therefore they should be encouraged to pursue any visual activity that brings them enjoyment.

Figure 1. Injection of subretinal tissue plasminogen activator (tPA) in an eye with a massive submacular hemorrhage



A. Pars plana vitrectomy. **B.** Insertion of a 39-gauge cannula. **C.** The cannula pierces the retina and injects tPA into the subretinal space. **D.** The subretinal tPA blister extends beyond the borders of the submacular hemorrhage.

Images courtesy of Dr. Berger

Referral to low-vision services, as in end-stage dry AMD, is important to allow patients to best use their remaining vision.

Future Treatments for Wet AMD

Several new intravitreally administered drugs are currently being investigated for the treatment of wet AMD.

Abicipar pegol is a designed ankyrin repeat protein (DARPin®). In contrast to antibodies, these smaller molecules have better tissue penetration, have great thermal stability, have low immunogenicity due to the absence of a Fc antibody portion, and are relatively easy to produce. In the Phase 3 trials CEDAR and SEQUOIA, patients were randomized to receive either 3 monthly loading doses of abicipar followed by 2 mg q8w, 2 monthly loading doses of abicipar followed by 2 mg q12w, or ranibizumab 0.5 mg q4w.[42] Both arms of abicipar were shown to be noninferior compared to ranibizumab. The primary outcome was percentage of stable vision as defined by a loss of less than 15 ETDRS letters and was found to be 94.6%, 91.3% and 96.0% in CEDAR and 91.7%, 91.2 and 95.5% in SEQUOIA. Mean change in vision was a secondary endpoint and was found to be +8.3, +7.3, and +8.3 ETDRS letters, respectively, in SEQUOIA and +6.7, +5.6, +8.5 in CEDAR. The abicipar groups had a higher rate of ocular adverse events (15% versus 0.3% of ranibizumab); these events primarily involved IOI, most episodes were classified as mild or moderate, and 80% responded to topical steroids. A modified manufacturing process was evaluated in the Phase 2 MAPLE study involving 123 patients with nAMD.[43] The incidence of IOI was 8.9% and 1.6% for severe IOI, with1 reported case each of iritis and uveitis. Despite this reduction in the incidence of IOI versus Phase 3 outcomes, the FDA rejected Allergan's application, citing an unfavourable benefit:risk ratio.[44]

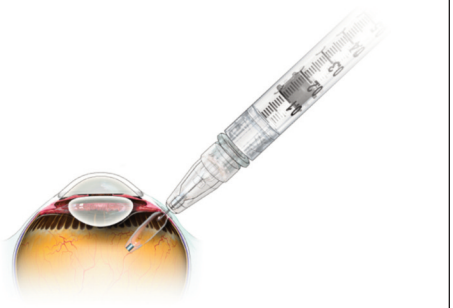
Faricimab is a bispecific antibody for Ang-2 and VEGF. Ang-2 works with VEGF to promote angiogenesis. Ang-2 also plays a role in the inflammatory component of AMD.[45] The Phase 2 STAIRWAY trial showed that faricimab injected every 12 weeks or 16 weeks was equivalent to monthly ranibizumab.[46] The global Phase 3 studies LUCERNE and TENAYA are ongoing.[47,48]

Conbercept is a recombinant fusion protein composed of the second immunoglobulin (Ig) domain of VEGF receptor-1 (VEGFR1) and the third and fourth Ig domains of VEGFR2 to the constant region (Fc) of human IgG1. VEGFR1 and VEGFR2 are both closely related receptor tyrosine kinase that play a role in angiogenesis.[49] Similar to aflibercept, conbercept inhibits VEGF-A, VEGF-B and PlGF. It is hypothesized to have a higher binding capacity and longer half-life, and has been approved for use in China since 2013. The PHOENIX trial randomized 125 patients in a ratio of 2:1 to receive either 3 monthly loading doses followed by quarterly doses or to receive 3 sham injections, followed by 3 monthly loading doses, followed by quarterly dosing.[50] Mean change in BCVA at 3 months (primary endpoint) improved significantly in the immediate conbercept group compared to the delayed conbercept group, which had to this point received sham injections (+9.20 ETDRS letters versus +2.02 letters; $P<0.001$). At 52 weeks, the immediate conbercept group gained 9.98 letters compared to 8.81 letters among the delayed conbercept group ($P=0.64$). PANDA-1 and PANDA-2 are ongoing global clinical trials comparing conbercept 0.5 mg q8w and 1 mg q12w with aflibercept 2 mg q8w in a 1:1:1 randomization.[51,52]

Several companies have been working on a method for slow release of anti-VEGF drugs to allow for fewer injections. Port delivery systems (PDS) involve the surgical implantation of a device that would allow for a slow diffusive release of a drug over time. This device could then be refilled in the clinic in a manner similar to current intravitreal injection techniques (Figure 2). The advantages include a longer duration of effect as well as a more constant VEGF suppression. The Phase 2 LADDER study demonstrated that the ranibizumab PDS is associated with visual and anatomic benefits similar to monthly intravitreal ranibizumab but with a reduced total number of treatments.[53] The time to refill was 9–15 months, depending on the concentration of drug used. In the Phase 3 ARCHWAY trial, 98.4% of patients receiving ranibizumab via a PDS achieved a 6-month interval before requiring additional treatment.[54] Visual outcomes were equivalent between PDS and monthly injection groups.

Gene therapy for anti-VEGF is another potential avenue for solving the problem of durability with intravitreal anti-VEGF injections. Adeno-associated virus (AAV) vectors are well suited to gene therapy as they have low immunogenicity and pathogenicity. They can induce long-term gene expression, allowing a patient's own cells to produce proteins with therapeutic effects such as inhibition of angiogenesis, alleviating the need for regular anti-VEGF injections. One target is the soluble form of fms-like tyrosine kinase-1 (sFLT1) also known as VEGFR-1, an endothelial

Figure 2. Refilling a port delivery system implant.



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receptor tyrosine kinase that mediates the angiogenic effects of VEGF. Because sFLT-1 has no transmembrane domains, it has no signal transduction properties and therefore acts as an antagonist of VEGF. In a recent Phase 2a study, 32 patients received ranibizumab injections at baseline, week 4, and afterwards according to prespecified criteria.[55,56] At 1 week 21 of those patients also received vitrectomy and subretinal injection of rAAV.sFLT-1, which is a recombinant AAV (rAAV) encoding for sFLT-1. The study found no serious gene therapy-related ocular or systemic side effects and concluded that rAAV.sFLT-1 is safe when injected subretinally. The change in mean BCVA was +1 ETDRS letters for the rAAV.sFLT-1 group compared to -5 letters for the control group. It is important to note that these patients were not treatment naïve, having received a median of 9 injections beforehand, so the potential for visual gains was diminished. rAAV.sFLT-1 seems to be a safe and promising treatment for AMD, although more studies need to be done. At the time of writing, numerous Phase 1 and 2 trials of AAV are ongoing.[57-60]

Stem cell therapy is another promising avenue. A recent Phase 1 study implanted a fully differentiated, human embryonic stem cell-derived RPE monolayer on a synthetic basement membrane into the subretinal space of 1 eye in each of 2 patients with severe exudative AMD.[61] The patients reported gains of 29 and 21 letters, respectively, over 12 months.

Summary

Ongoing advances in the accuracy and speed of diagnostic testing for both dry and wet AMD has spurred on continued development of safe and effective therapies. Therapies to slow GA progression are being studied and include promising options like subthreshold nanosecond laser. For wet AMD, brolucizumab has recently joined the approved anti-VEGF options in Canada, and abicipar and depot slow-release systems will likely make their way into our treatment armamentarium soon. Gene therapy and stem cell therapy form a promising avenue but are likely farther into the future.

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