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Neovascular Age-Related Macular Degeneration: Updates on Current Treatment Paradigms and Future Directions

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Age-related macular degeneration (AMD) is a leading cause of vision loss in individuals over the age of 60 years. Neovascular AMD (nAMD) is characterized by the development of choroidal neovascularization and is the main cause of vision loss in AMD patients. Despite remarkable advances in the therapeutic paradigm for nAMD, a high treatment burden and suboptimal response to existing agents in some patients still exist. In this issue of *Ophthalmology Rounds*, we review the current evidence-based treatments for nAMD and explore the future directions for the management of this condition.

Age-related macular degeneration (AMD) is among the most common causes of visual impairment and blindness in the older population across the developed world.[1-3] Our understanding of the pathophysiology of AMD continues to expand, and multimodal imaging has refined our diagnostic approach in this disease. Diagnostic imaging modalities have advanced considerably for both dry and wet (neovascular) AMD (nAMD) and are summarized in Part 1 of the update on AMD that appeared in a recent previous issue of *Ophthalmology Rounds*.[4] The development of new pharmacologic agents has provided more options in the therapeutic paradigm of nAMD. In this review, we evaluate the current treatments and future directions for therapy in nAMD.

Current Treatments in nAMD

As described in Part 2 of the recent AMD update,[5] photodynamic therapy and laser photocoagulation were historically used in the treatment of nAMD. These treatments were aimed at stabilizing progression of disease and avoiding severe vision loss; however, they were unable to offer robust visual improvement to patients.

The advent of anti-vascular endothelial growth factor (VEGF) agents revolutionized the care of patients with nAMD. Those who are treated with anti-VEGF agents often experience improvements in visual acuity and visual quality, as well as a reduction in metamorphopsia. Anti-VEGF agents became the standard of care for patients with nAMD and the ensuing utilization of these agents grew considerably, with a compound annual growth rate of 21.8% from 2012 to 2017 and a total of 49,784 Canadians receiving these medications in 2017.[6]

Ranibizumab, a humanized anti-VEGF-A recombinant Fab fragment, inhibits all active isoforms of VEGF-A. It was approved by the United States (US) Food and Drug Administration (FDA) and Health Canada for the treatment of nAMD based on the results of the landmark phase III MARINA and ANCHOR trials, in which once-monthly ranibizumab demonstrated significant improvement in vision compared to control (placebo and verteporfin, respectively).[7,8] Aflibercept, a soluble fusion protein, inhibits VEGF-A, VEGF-B, and placental growth factor. The phase III VIEW-1 and VIEW-2 trials showed that intravitreal aflibercept administered either monthly or every 2 months after 3 initial monthly loading doses achieved similar efficacy and safety outcomes as monthly ranibizumab.[9] Bevacizumab is a humanized monoclonal antibody that inhibits all isoforms of VEGF-A. Originally approved for metastatic colon cancer, bevacizumab is not approved by either the FDA or Health Canada for nAMD. However, its off-label use in patients with nAMD is widespread and its efficacy and safety

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have been supported in multiple prospective, randomized, controlled nAMD trials.[10-14]

Despite substantial visual and anatomic improvements seen with monthly administration of anti-VEGF agents, the treatment burden on patients and caregivers remains high with this treatment regimen. Most recipients of traditional anti-VEGF agents require frequent injections and follow-up appointments, which can predispose them to procedural risks, pain, and adversely affect compliance, quality of life, and productivity.[15-18] Alternative treatment approaches have been developed for this reason, the most common of which are *pro re nata* (PRN) dosing and dosing with treat-and-extend (T&E) approaches. With a PRN approach, patients undergo a clinical examination each month, but they only receive anti-VEGF therapy in the case of decreased vision, active fluid, or hemorrhage. With a T&E regimen, patients are treated each visit; however, the interval between visits may be extended in the case of disease inactivity. Typical T&E regimens extend the treatment interval in a gradual manner by 2- or 4-week increments until a maximum interval of 12-16 weeks.[19] Large, multicentre, randomized trials have evaluated differences in efficacy and safety between T&E approaches and monthly dosing, including the CANTREAT trial performed at centres across Canada.[20-22] PRN dosing may not be as proactive as T&E dosing, with the possibility of disease activity recurrence in patients treated with this regimen.[23,24] A 2020 Cochrane review found a clinically insignificant difference in the change in best-corrected visual acuity (BCVA) associated with monthly vs. PRN (mean difference 1.7 Early Treatment Diabetic Retinopathy Study letters; 95% confidence interval [CI] 0.6, 2.8) and T&E (-0.5 letters; 95% CI -4.2, 3.1).[24]

Brolucizumab

Brolucizumab is a novel humanized single-chain antibody fragment that inhibits all forms of VEGF-A. This agent is notable for having a low molecular weight relative to other anti-VEGF molecules and a high concentration gradient between the vitreous and retina which may enhance retinal delivery of the medication.[19] In the phase III HAWK and HARRIER trials, brolucizumab was noninferior to aflibercept with respect to change in BCVA from baseline, while significantly reducing central subfield thickness (CST) and macular fluid vs. aflibercept.[25] Although the initial HAWK and HARRIER studies noted that adverse events (AEs) were generally similar between brolucizumab and aflibercept, the American Society of Retinal Specialists began to receive reports shortly after FDA approval of episodes of intraocular inflammation (IOI) and rare vision-threatening cases of retinal vasculitis and retinal vascular occlusion associated with brolucizumab administration.[26-28] A *post hoc* analysis of the HAWK and HARRIER trials found that of 49 of 1088 brolucizumab-treated eyes in the trials had evidence of ≥1 episode of IOI.[29] The phase III MERLIN trial, which investigated brolucizumab 6 mg given q4w, was terminated prematurely further to the higher rate of IOI in the brolucizumab group (9.3%) vs. aflibercept (4.5%).[30] Novartis also terminated the RAPTOR and RAVEN trials examining brolucizumab in patients with branch and central retinal vein occlusion (RVO), respectively.[31,32] Thus, although brolucizumab remains indicated by Health Canada for the treatment of nAMD and diabetic macular edema (DME), its use in clinical practice has been limited by these serious AE concerns.

Emerging and Future Treatments in nAMD (Table 1)

Faricimab

Faricimab is a novel bispecific antibody that binds both VEGF-A and angiopoietin-2 (Ang-2) with high specificity and affinity. Ang-2 is involved in the inflammatory cascade of AMD and promotes angiogenesis alongside VEGF.[33] In the landmark phase III TENAYA and LUCERNE trials, treatment-naïve patients with nAMD were randomized to faricimab 6.0 mg extended up to q16w based on disease activity criteria or aflibercept 2.0 mg q8w.[34] The mean change in BCVA in the faricimab group from baseline averaged over weeks 40, 44, and 48 was found to be noninferior to the aflibercept group (TENAYA: +5.8 letters with faricimab, +5.1 letters with aflibercept; LUCERNE: +6.6 letters with faricimab, +6.6 letters with aflibercept). The adjusted mean change in CST at 48 weeks was also determined to be noninferior with faricimab up to q16w vs. aflibercept. At week 48, 45.7% and 44.9% of patients receiving faricimab in TENAYA and LUCERNE, respectively, had attained q16w dosing and 34.0% and 32.9%, respectively, had attained q12w dosing. Ocular AEs were comparable between the faricimab and aflibercept treatment arms in both trials. Overall, faricimab demonstrated high efficacy for nAMD with interval extension of up to q16w between treatments. Based on these outcomes, faricimab was approved by Health Canada in May 2022 for nAMD, as well as for DME based on the results of the phase III YOSEMITE and RHINE trials.[35] The ongoing investigator-driven, real-world, multicentre, prospective TRUCKEE study is evaluating the efficacy, durability, and safety of faricimab in nAMD patients who have received faricimab since FDA approval.[36]

Ranibizumab port delivery system (PDS)

The objective of the ranibizumab PDS is to provide sustained intravitreal anti-VEGF therapy via an implantable device.[19] The PDS is slightly longer than a grain of rice and is implanted via a scleral incision in the pars plana. The ranibizumab PDS was evaluated in the phase III, open-label Archway trial, in which patients with nAMD were randomized to ranibizumab PDS with a fixed 24-week refill-exchange procedure or intravitreal ranibizumab 0.5 mg q4w.[37] Ranibizumab PDS was found to be noninferior to monthly ranibizumab, with a comparable adjusted mean change in BCVA from baseline averaged over weeks 36 and 40 (+0.2 letters in the PDS cohort, +0.5 letters in the monthly ranibizumab arm). Supplemental ranibizumab before the first refill-exchange procedure was not required in 98.4% of patients with the ranibizumab PDS. Ocular AEs of interest to PDS were higher in the ranibizumab PDS arm (19.0%) compared to monthly ranibizumab (6.0%), including endophthalmitis (1.6% of PDS cases), retinal detachment (0.8%), vitreous hemorrhage (5.2%), conjunctival erosions (2.4%), and conjunctival retraction (2.0%). Ranibizumab PDS was approved by Health Canada in September 2022.

Table 1. New approved and investigational innovative therapies in nAMD

Agent/device	Mechanism of action	Studies in nAMD	Outcome	Adverse events
Faricimab[a] (Vabysmo™)	Bispecific binding of VEGF-A and Ang-2	TENAYA and LUCERNE;[34] TRUCKEE (real world)[36]	Noninferior to aflibercept (BCVA, CST) at q12-16w dosing	Comparable to aflibercept
Ranibizumab (Susvimo™) port delivery system[a]	Sustained intravitreal anti-VEGF therapy via an implantable device	Archway[37]	Noninferior to aflibercept q8w (BCVA, CST) at q12-16w dosing	Increased risk of endophthalmitis vs. regular ranibizumab injections
High-dose (8 mg) aflibercept	Same as standard-dose aflibercept	PULSAR[38]	Noninferior to aflibercept q8w (BCVA, CRT) at q12-16w dosing	Comparable to standard-dose (2 mg) aflibercept
Tarcocimab tedromer (KSI-301)	Anti-VEGF antibody biopolymer conjugate	DAZZLE[44]	Inferior to aflibercept; study discontinued	Comparable to aflibercept

[a]Approved by Health Canada
Ang, angiopoietin; BCVA, best-corrected visual acuity; CRT, central retinal thickness; CST, central subfield thickness; nAMD, neovascular age-related macular degeneration; q12w, every 12 weeks; VEGF, vascular endothelial growth factor

High-dose aflibercept

High-dose (8 mg) aflibercept has been investigated as a way of improving treatment durability compared to standard therapy while maintaining VA gains. The international, multicentre, phase II/III PULSAR trial assessed the efficacy, durability, and safety of aflibercept 8 mg intravitreal injections for the management of nAMD.[38] The q12w and q16w regimens were found to be noninferior to aflibercept 2 mg q8w with respect to mean change in BCVA at 48 weeks (+6.7, +6.2, and +7.6 letters, respectively). Central retinal thickness was likewise noninferior with high-dose aflibercept q12w and q16w vs. 2 mg q8w. The q12w and q16w dosing intervals were maintained in 79% and 77% of patients, respectively. The safety profile of aflibercept 8 mg was consistent with that of standard aflibercept 2 mg. Based on these data, the FDA accepted high-dose aflibercept for priority review.[39]

Tarcocimab tedromer (KSI-301)

KSI-301 is an investigational anti-VEGF antibody biopolymer conjugate that blocks all isoforms of VEGF-A and is currently being studied for the treatment of patients with nAMD.[40,41] The size (950 kDa) and molar dose of KSI-301 are designed to provide optimal intraocular durability. A phase Ia study of KSI-301 in 9 patients with DME found that rapid improvements in BCVA and OCT parameters were maintained at 12 weeks after a single dose, and no drug-related AEs or dose-limiting toxicities were observed.[42] A phase Ib, open-label, randomized study was then conducted in 121 treatment-naïve patients with nAMD, DME, and RVO to evaluate 2.5 mg or 5 mg of KSI-301, administered as 3 monthly loading doses followed by monthly evaluation and retreatment based on specific criteria.[43] The first retreatment was at ≥4 months in 82% (40 of 49) and at 6 months in 49% (20 of 41) of patients with nAMD. Overall, 29 serious AEs were observed across 546 injections, and none were deemed to be drug related; both of the reported cases of IOI resolved completely. The prospective, multicentre, randomized, phase II/III DAZZLE study compared KSI-301 5 mg at 3 treatment intervals – q12w, q16w, and q20w – to aflibercept in 557 patients with nAMD.[44] DAZZLE was terminated in 2022 because the primary endpoint of least-square means change from baseline in BCVA at an average of 48 and 52 weeks was not met (KSI-301: 1.0 [95% CI -0.5, 2.5]; aflibercept 7.0 [5.5, 8.5]); however, mean gains in BCVA among the 59.4% of patients in the KSI-301 group who achieved q20w dosing were noninferior to those in the aflibercept group. KSI-301 was well tolerated; ocular AEs occurred in 45.8% and 36.4% of KSI-301- and aflibercept-treated patients, and 6 KSI-301 patients experienced a serious AE vs. none in the aflibercept group. Phase III trials in DME and macular edema secondary to RVO are ongoing.

Abicipar pegol

Abicipar pegol is a designed ankyrin repeat protein whose characteristics are different from traditional antibodies. Abicipar has high specificity to all soluble isoforms of VEGF-A, a long ocular half-life, a pegylated molecular structure, and a high affinity for target binding.[45] Pooled data from the phase III SEQUOIA and CEDAR trials found that abicipar 2 mg q8w and q12w improved BCVA from baseline to week 104 by 7.8 and 6.1 letters, respectively, compared with 8.5 letters with ranibizumab q4w (control).[46] VA was stable (<15-letter loss) to 104 weeks in 93.0% (396/426), 89.8% (379/422), and 94.4% (470/498) of patients in the abicipar q8w, abicipar q12w, and ranibizumab groups, respectively. The mean changes in CRT were equivalent between groups (-147 µm, -146 µm, and -142 µm, respectively). IOI was detected in a higher proportion of eyes treated with abicipar (16.2% for q8w and 17.6% for q12w) than in the ranibizumab group (1.3%) by week 104. While these studies showed that abicipar q8-12w had similar visual and anatomic outcomes to monthly ranibizumab at 2 years, the FDA did not approve abicipar for clinical use, citing an unfavourable risk-benefit ratio with respect to the higher risk of IOI events.[47] Allergan subse-

Table 2. Approved and investigational biosimilar anti-VEGFs for the treatment of nAMD

Reference agent	Biosimilar	Status
Ranibizumab	Byooviz™	Approved by Health Canada
	FYB201	Approved by FDA; submitted to Health Canada
	CKD-701	Phase III study completed
	SJP-0133/GBS-007	Phase III study completed
	Xlucane™	Phase III study completed
	LUBT010	Phase III study in progress
Aflibercept	SB15	Phase III study completed
	ABP-938	Phase III study completed
	FYB203	Phase III study in progress
	SOK583A1	Phase III study in progress
	CT-P42	Phase III study in progress
	OT-702	Phase III study in progress

quently withdrew similar applications to regulatory bodies in both Europe and Japan.

Biosimilars (Table 2)

The World Health Organization defines biosimilars as biological products that are shown to be highly similar in terms of their quality, safety, and efficacy to already licensed reference products.[48] The advent of biosimilar medications in the US is predicted to reduce drug costs by $100 billion over the next 5 years.[49] As of February 2023, 52 biosimilar agents have been approved by Health Canada.[50] Ten of the 13 provinces and territories have implemented mandatory biosimilar switching policies.[51]

Further to recent patent expirations of Lucentis® (ranibizumab) and Eylea® (aflibercept), biosimilar anti-VEGF medications for these agents have been developed.[19] The first of these agents to be approved by Health Canada is SB11 (Byooviz™; ranibizumab-nuna).[52] In a randomized, parallel-group equivalence study, 705 patients with nAMD were randomized to either ranibizumab or SB11 (0.5 mg q4w for each agent) and were followed for 48 weeks.[53] At the preplanned 24-week interim analysis, SB11 demonstrated equivalent efficacy to ranibizumab, with comparable least-squares mean changes from baseline to week 8 in BCVA (primary endpoint) (SB11: +6.2 letters; ranibizumab: +7.0 letters; adjusted difference -0.8 letters; 90% [CI] -1.8, 0.2 letters) and to week 4 in CST (SB11: -108 µm; ranibizumab: -100 µm; adjusted treatment difference -8 µm (95% CI -19, 3 µm). Ocular adverse events, serious adverse events, and immunogenicity profiles were also similar between these 2 agents. The equivalence of efficacy and safety were maintained when patients were followed until 52 weeks.[54] In a *post hoc* analysis of the same randomized trial, the serum antidrug antibodies as a marker of immunogenicity of both SB11 and ranibizumab were analyzed, and no association was found between these antibodies and efficacy or safety parameters in both the SB11 and ranibizumab groups.[55] As a cost comparison, the current list price of Byooviz in the US is $1,130 for a single-use 0.5-mg vial, which is ~40% lower than the $1,850 list price of Lucentis.[56] It should be noted that the same price differential may not be applicable in Canadian provinces and territories.

Other ranibizumab biosimilars are in various stages of development and regulatory approval. FYB201 (ranibizumab-eqrn) was approved by the FDA in August 2022. The randomized, evaluation-masked, parallel-group phase III COLUMBUS-AMD study investigated the clinical equivalence of FYB201 to reference ranibizumab (0.5 mg q4w for both agents) in 477 patients with nAMD over 48 weeks.[57] The mean BCVA improvement at 8 weeks (primary endpoint) of +5.1 letters in the FYB201 group and +5.6 letters in the ranibizumab cohort, and the 90% CI of -1.6 to 0.9 was within the predefined equivalence margin. Adverse events and immunogenicity profiles were comparable between the 2 treatment groups. The cost of Cimerli™ in the US is $1,360 for a 0.5-mg vial, which is 26% lower than Lucentis.[56] Phase III studies of other biosimilar ranibizumab agents have been completed (CKD-701, SJP-0133/GBS-007, Xlucane™) or are ongoing (LUBT010).[58]

Several aflibercept biosimilars are in phase III trials. Phase III study data showed that patients with nAMD who received SB15 experienced equivalent changes from baseline to week 32 in BCVA and CST to those receiving reference aflibercept.[59] No new safety signals were identified and the adverse event profile was similar to reference aflibercept.

Three biosimilars of bevacizumab – Mvasi® (bevacizumab-awwb), Zirabev™ (bevacizumab-bvzr), and Almysys® (bevacizumab-maly) – have been approved by the FDA for the management of various types of cancer.[60-62] There are no robust data supporting the use of these biosimilars in nAMD, and the American Academy of Ophthalmology has expressed concern that these agents will be con-

sidered by payers to be biosimilar to compounded bevacizumab in this patient population.[63] It also remains unclear whether compounding pharmacies will repackage bevacizumab biosimilars for intravitreal administration.[64]

Summary

Anti-VEGF treatments have saved the sight of millions of patients with nAMD; however, the treatment burdens on patients, caregivers, and the healthcare system remain high. New and emerging agents aim to reduce this burden on patients by increasing the injection interval while maintaining the safety of these agents. In 2023, we are likely in the beginning of a paradigm shift with the introduction of effective and safe biosimilar anti-VEGF agents which aim to reduce the healthcare cost of treating nAMD and make anti-VEGF therapy accessible to more patients. It is important that ophthalmologists continue to practice evidence-based medicine and make decisions that optimize patient outcomes, as well as serve as stewards of healthcare resources.

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