New Age-related Macular Degeneration Injectables

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Modern treatments for wet age-related macular degeneration (wAMD) have progressed tremendously in the last decade, with the rise of anti-vascular endothelial growth factor (anti-VEGF) intravitreal injections as the standard-of-care. However, the treatment burden of monthly injections, and even as-needed treatment protocols, can still be a significant barrier to optimal treatment outcomes. An unmet need also exists for patients who do not respond well to anti-VEGF agents when evaluating their visual acuity improvements or anatomic parameters. New molecules for the treatment of wAMD seek to increase the time between injections, the effectiveness of the molecules and provide new targets for disease treatment. The aim of this editorial is to evaluate these new molecules for their efficacy, durability and safety, to decrease the burden on patients and improve treatment options for this population.

Keywords

Wet age-related macular degeneration (wAMD), brolucizumab, anti-platelet-derived growth factor, anti-angiopoietin-2, receptor tyrosine kinase inhibitors, abicipar, faricimab

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Modern treatments for wet age-related macular degeneration (wAMD) have progressed tremendously in the last decade, with the rise of anti-vascular endothelial growth factor (anti-VEGF) intravitreal injections as the standard-of-care. Both aflibercept (Eylea®, Regeneron, Tarrytown, NY, USA) and ranibizumab (Lucentis®, Genentech, San Francisco, CA, USA) have become the gold standard for anti-VEGF agents. Initially, patients with wAMD receive monthly injections until the disease is controlled, following which, the interval between injections can be extended, using a treat-and-extend protocol, or patients can receive injections as needed (pro re nata; PRN). However, even with PRN or treat-and-extend, the monitoring and treatment burden for these patients is not significantly decreased. Therefore, in the real world, due to missed appointments or lost follow-up, patients rarely achieve the visual acuity outcomes that are seen in clinical trials. Some patients may also show limited positive results from the current standard-of-care, in terms of visual acuity gain or persistent anatomic symptoms. In these cases, patients can be deemed nonresponsive to anti-VEGF agents, creating an unmet need for treatments utilising alternate biological pathways for the treatment of wAMD. New molecules in wAMD treatment seek to elongate the time between injections and increase effectiveness of the molecules, with some also targeting new disease pathways, in an effort to improve the treatment burden on the ageing population and reach the outcomes found in clinical trials.

New molecules in wAMD treatment aim to increase their effectiveness by targeting new molecular pathways beyond anti-VEGF, such as anti-platelet derived growth factor (anti-PDGF), anti-angiopoietin-2 (anti-Ang-2) and receptor tyrosine kinase inhibitors. All of the molecules discussed here are being evaluated for their efficacy, durability and safety, to decrease the burden on patients and improve treatment options for this population.

Brolucizumab

Brolucizumab is a single-chain antibody fragment, with a small molecular weight of 26 kDa. This molecular weight is significantly smaller than other available anti-VEGF agents, which results in more concentrated molar dosing and increased potency of VEGF-A inhibition.[1] The 6 mg molar dose of brolucizumab is approximately 11–12 times higher than a 2 mg dose of aflibercept. Pre-clinical studies revealed that smaller molecular size also results in increased ocular tissue penetration, which increases localised concentrations of the molecule in deeper levels of the retina.[2]

During animal studies, brolucizumab showed a four-fold lower systemic exposure when compared with ranibizumab, while showing tolerability to higher doses and a high affinity to VEGF.[3] Early human studies have also revealed positive findings, where a single dose of brolucizumab was shown to be more potent and longer lasting than a single dose of ranibizumab.[2] OSPREY (ClinicalTrials.gov identifier: NCT01796964) was a phase II, double-masked, active-comparator clinical trial evaluating the non-inferiority of brolucizumab against aflibercept.[4] The trial met its primary endpoint in confirming non-inferiority of brolucizumab to aflibercept when comparing

mean changes in best-corrected visual acuity (BCVA) from baseline to weeks 12 and 16. OSPREY also showed that eyes treated with brolucizumab had more stable central subfield thickness (CST) reductions, received fewer unscheduled treatments and increased rates of fluid resolution.[5]

The success of phase II trials led to the phase III, double-masked, randomised trials HAWK and HARRIER (NCT02307682 and NCT02434328, respectively), which examined 2,824 patients with treatment-naive wAMD. Patients in these studies were randomised to either brolucizumab or aflibercept; the brolucizumab cohort received three monthly doses of brolucizumab and subsequently received a dose either every 8 weeks or every 12 weeks, based on their disease activity assessment, and patients in the aflibercept arm received three monthly doses and a subsequent dose every 8 weeks, per the label. Both HAWK and HARRIER met their primary endpoints of non-inferiority of brolucizumab to aflibercept in mean change of BCVA from baseline to week 48.[6] Patients gained +6.6 (6 mg dose) and +6.1 (3 mg dose) letters with brolucizumab versus +6.8 letters with aflibercept in the HAWK study, while patients in HARRIER gained +6.9 (6 mg) with brolucizumab versus +7.6 letters with aflibercept. Other key endpoints in the studies included patients maintaining 12-week dosing periods until week 48, and anatomic outcomes at week 16 and week 48. Fifty-six percent of eyes in HAWK and 51% in HARRIER maintained the every-12-week dosing until week 48. Anatomic outcomes were also successful, as patients with 6 mg brolucizumab injections had significantly less intra-retinal fluid and/or sub-retinal fluid and sub-retinal pigment epithelium fluid at week 16 and week 48.[7] Brolucizumab treatment also resulted in approximately an additional 35% of patients with no fluid when compared with aflibercept at the same timepoints. The overall safety of brolucizumab was comparable to aflibercept, but in the HAWK and HARRIER studies, patients treated with brolucizumab had a higher rate of intraocular inflammation compared with aflibercept. The US Food and Drug Administration (FDA) approved brolucizumab in October 2019. Early experience with brolucizumab in the real world has shown rare events of retinal vasculitis and retinal artery occlusions, limiting the usage of brolucizumab.[8,9] More work is being done to identify the cause of these events and also the rate in the HAWK and HARRIER studies.

Abicipar

Abicipar pegol is a novel designed ankyrin repeat protein (DARPin) that can bind to targeted proteins with notable precision and affinity.[10] As a new molecule functioning against retinal neovascularisation, abicipar targets VEGF-A_{165}, an isoform of VEGF-A that is primarily expressed in humans and is associated with pathologic angiogenesis.[11] Compared to ranibizumab and aflibercept, abicipar has 100-fold increased affinity for human VEGF-A_{165}. Abicipar also has a small molecular weight of 32 kDa and contains a polyethylene tail, which increases the drug's intravitreal half-life. The 2 mg dose of abicipar is roughly equal to 3.4 times the 2 mg dose of aflibercept and demonstrates a longer period of effectiveness when compared with ranibizumab at equal molar doses.[9] The phase II study, REACH (NCT01397409), was a double-masked, randomised trial that evaluated 1 mg or 2 mg abicipar against 0.5 mg ranibizumab and found that the investigational agent demonstrated central retinal thickness (CRT) reductions and BCVA improvements similar to ranibizumab, at week 16 and 20. These improvements were 8 and 12 weeks from the last abicipar injection (respective to 1 mg and 2 mg doses), confirming its durability.[12] In contrast, the previous injection for the ranibizumab group was only 4 weeks prior. All adverse events reported by the abicipar group were resolved without sequelae or permanent vision loss, with no reported serious adverse events.

In the phase III double-masked, randomised studies, CEDAR and SEQUOIA (NCT02462928 and NCT02462486, respectively), 1,885 treatment-naive wAMD eyes were randomised to either 2 mg abicipar (every 8 weeks [Q8W] or Q12W) or ranibizumab (Q4W). Patients received either 0.5 mg ranibizumab monthly; 2.0 mg abicipar every 8 weeks after three monthly doses; or 2.0 mg abicipar doses every 12 weeks after doses at baseline, week 4 and week 12. The primary endpoint at week 52 was non-inferiority to ranibizumab, which was successfully met. A total of 91% and 96% of each abicipar arm, respectively, lost fewer than 15 letters at week 52 compared with baseline.[13] However, ocular safety was a major concern, as around 15% of patients in the abicipar cohorts in both CEDAR and SEQUOIA experienced inflammatory events.[14] The open-label MAPLE study (NCT03539549) was conducted after the amendments to the purification processes were put into practice, in an effort to study the safety of the improvements. MAPLE resulted in some improvements in the inflammation rate, with the rate of inflammatory events dropping to 8.9% from the 15% reported in CEDAR and SEQUOIA.[15] Recently, the FDA issued a complete response letter about abicipar due to safety concerns with the drug.

Faricimab

Faricimab is the first bispecific antibody designed for intravitreal use and was developed via CrossMAb technology to bind VEGF-A on one arm and Ang-2 on the other. Angiopoietin–Tie signalling has been elucidated as a vascular-specific receptor tyrosine kinase pathway associated with later stages of vascular development, complementary to the VEGF pathway in neovascularisation.[16] Pre-clinical studies have shown that Ang-2 levels are elevated in patients with wAMD,[17–19] and that blockage of Ang-2 also reduces VEGF-induced endothelial barrier breakdown.[20] Animal studies also showed that combining VEGF-A and Ang-2 inhibition reduces the choroidal neovascularisation (CNV) lesion number and area, inhibits retinal leukocyte infiltration, and prolongs anti-leakage effect.[17] A phase I study of faricimab confirmed that the drug was safe and well tolerated, along with improvements in BCVA and anatomic parameters for patients with persistent or difficult-to-treat wAMD.[16]

The positive results led to the phase II studies, AVENUE and STAIRWAY (NCT02484690 and NCT03038880, respectively).[20,21] AVENUE was a double-masked, randomised trial that evaluated the safety and efficacy of 1.5 mg and 6.0 mg faricimab doses every 4 and 8 weeks in patients with treatment-naive wAMD, compared with monthly doses of ranibizumab.[20] The trial consisted of five cohorts: a 0.5 mg ranibizumab control every 4 weeks, 1.5 mg faricimab every 4 weeks, 6.0 mg faricimab every 4 weeks, 6.0 mg faricimab every 8 weeks and a 0.5 mg ranibizumab group receiving three monthly loading doses, then switching to 6.0 mg faricimab every 4 weeks. All groups displayed improvements in BCVA and CST, prompting the STAIRWAY trial for further results.

The STAIRWAY study was designed to evaluate the efficacy and durability of faricimab in treatment-naive patients, where patients were treated with four monthly doses of faricimab and subsequently treated every 16 weeks or every 12 weeks based on the disease activity compared to monthly ranibizumab. The primary endpoint was efficacy of faricimab given every 16 weeks and every 12 weeks, as assessed by BCVA.[21] Pre-specified disease activity was performed at week 24, 12 weeks after the last faricimab dose. Sixty-five percent of patients had no disease activity 12 weeks following the last faricimab injection. Vision gains were similar between all three treatment cohorts and were fully maintained through week 52. Patients treated every 16 weeks with faricimab gained +11.4 chart letters from baseline, while patients treated every 12 weeks with faricimab gained +10.1 letters, and patients

treated every 4 weeks with ranibizumab gained +9.6 letters. All three treatment cohorts showed a similar proportion of patients gaining 15 letters and avoiding a loss of 15 letters. Anatomic outcomes were also similar amongst all three cohorts, as evaluated via change in CST, as well as reduction in CNV lesion size from baseline to week 52. No new safety signals were reported and the overall safety profile of faricimab was similar to ranibizumab. Faricimab holds a high potential of extended durability in patients with wAMD, as seen in AVENUE and STAIRWAY. The phase III studies TENAYA (NCT03823287) and LUCERNE (NCT03823300) began in 2019 and are currently ongoing.

KSI-301

KSI-301 is an antibody biopolymer conjugate developed by Kodiak Sciences (Palo Alto, CA, USA) that targets VEGF-A.[22] *In vitro* assays demonstrated that the molecule has increased potency when compared with bevacizumab, ranibizumab and aflibercept. KSI-301 has a molecular weight of 950 kDa, which is much larger than the newer molecules described earlier. The high molecular weight is a result of the phosphorylcholine biopolymer, which leads to an increased ocular tissue bioavailability in both the retina and the choroid when compared with aflibercept (approximately a 30-day increase in both regards). A phase Ia study of KSI-301 met both safety outcomes and demonstrated improvements in vision and retinal thickness in heavily pre-treated patients with diabetic macular oedema.[22] All dose levels were well tolerated, without any drug-related adverse events reported. Twelve weeks following a single dose, median vision change was +9 letters, and median retinal thickness showed an improvement of -121 microns, across all three dose levels.

A phase Ib trial was initiated in 2019 to evaluate the safety, efficacy and durability of multiple doses of KSI-301 in treatment-naive patients with wAMD, diabetic macular oedema and retinal vein occlusion (NCT03790852). Interim data from the phase Ib trial revealed that, in the wAMD cohort, patients gained an average of +5.8 letters from baseline and showed a -73 micron improvement in median retinal thickness at week 44.[23] This was achieved with a mean of only 1.32 injections after the three loading doses, meaning that fewer treatments are needed with KSI-301 to control disease activity, highlighting the durability of KSI-301. Sixty-eight percent of patients have also been able to meet the maximum duration of 6 months between injections. The positive results influenced both an extension of the phase Ib trial and a phase II trial, DAZZLE. DAZZLE (NCT04049266) is a double-masked, randomised trial comparing KSI-301 to aflibercept, and seeks to evaluate injection intervals of 3–5 months with KSI-301 after the loading doses, compared with on-label aflibercept every 8 weeks. DAZZLE is currently on-going and will confirm the safety and efficacy of KSI-301 in patients with wAMD.

Sunitinib

Sunitinib malate, from Graybug Vision (Redwood City, CA, USA) is a multiple receptor tyrosine kinase inhibitor that is approved as an oral agent for solid tumours, including renal cell carcinoma, imatinib-resistant gastrointestinal stromal tumour and pancreatic neuroendocrine tumours. Bevacizumab, ranibizumab and aflibercept all function to inhibit VEGF receptors (VEGFR)-1 and -2, while sunitinib selectively inhibits VEGFR-1, -2, and -3; PDGF receptors α and β; stem cell growth factor receptor KIT; colony stimulating factor receptor; and FMS-like tyrosine kinase receptor. These receptors are all implicated in angiogenesis, proliferation, vascular permeability and fibrosis.[24] Sunitinib is formulated as injectable intravitreal poly-lactic-co-glycolic acid molecules that aggregate to form a depot in the inferior vitreous out of the visual axis. As a result of the depot, the drug is being hailed as a potential treatment that is necessary only twice a year; a massive reduction from monthly injections.

Preclinical animal studies support biannual dosing following a single intravitreal injection of sunitinib.[25] A phase I/IIa study of a single injection of sunitinib with dose-escalating cohorts revealed that sunitinib maintained BCVA and CST equivalent to patients receiving standard-of-care intravitreal anti-VEGF agents with 6-week dosing.[26] The majority of the adverse events noted in the phase I/IIa study were the result of migration of the bio-absorbable particles into the anterior chamber of the eye, as a result of the incomplete aggregation of the depot. These events were described as self-limited and reversible as the formulation biodegrades within the eye. At month 6, there were no observed sequalae. An optimised version of sunitinib was manufactured to eliminate the particle dispersion for the phase IIb study, which was initiated in the third quarter of 2019. The phase IIb study, ALTISSIMO (NCT03953079), compares 1 mg and 2 mg doses of sunitinib biannually to a 2 mg dose of aflibercept administered every 2 months in patients with wAMD. Prior to the phase IIb study, an open-label safety study (NCT04085341) was also initiated with sunitinib in patients with diabetic macular oedema and retinal vein occlusion to evaluate the safety of the optimised version.

Conbercept

Conbercept is a recombinant fusion protein developed by Chengdu Kanghong Biotechnology (Chengdu, China) targeting VEGFR-1 and -2.[27] The molecule is composed of the second immunoglobulin G (IgG) domain of VEGFR-1 and the third and fourth domains of VEGFR-2 to the fragment crystallisable region of human IgG. Conbercept has a molecular weight of 143 kDa and *in vitro* assays revealed that the drug has a 30-fold increased affinity for VEGF than either ranibizumab or bevacizumab.[28] The biochemical functionality of conbercept allows it to target both VEGF-A, -B and -C, along with placental-derived growth factors (PlGF).

Conbercept was first studied in the AURORA (NCT01157715) trial, where patients were randomised 1:1 to either a 0.5 mg dose or 2.0 mg dose.[29] After three monthly doses, patients were randomised to either a PRN treatment schedule or continued monthly, with no changes to their initial dosage randomisation. At month 3, mean BCVA improvement in the 0.5 mg cohort was +8.97 letters, while the 2.0 mg cohort had an increase of +10.43 letters. At the month 12 evaluation, mean BCVA improvement was +14.31 letters for the 0.5 mg PRN cohort and +9.31 for the 0.5 mg monthly cohort. At the same checkpoint, BCVA improvements for the 2.0 mg cohort were +12.42 for the 2.0 mg PRN cohort, and +15.43 for the 2.0 mg monthly cohort. Statistically significant reductions in CRT were also found. At month 12, CRT reduction was -119.8 microns for the 0.5 mg PRN cohort, -129.7 microns for the 0.5 mg monthly cohort, -152.1 microns for the 2.0 mg PRN cohort, and -170.8 microns for the 2.0 mg monthly cohort. Two serious adverse events were recorded in this trial: a case of endophthalmitis associated with the injection procedure, and cataract development associated with the study drug.

The PHOENIX trial randomised patients 2:1 to two cohorts: treatment and delayed treatment.[30] In the treatment cohort, patients were given monthly injections of conbercept 0.5 mg for 3 months, then extended to quarterly injections of the same dosage. In the delayed treatment cohort, patients received sham injections monthly for 3 months, then moved to conbercept 0.5 mg injections monthly for 3 months, then extended to quarterly injections at the 0.5 mg dosage. By month 12, the treatment group showed a +9.9 letter gain in BCVA, while the delayed treatment group showed a +8.8 letter improvement. Both groups showed reductions in CRT, with no statistical significance between the two cohorts. No ocular serious adverse events were noted in relation to the study drug.

Currently, conbercept is being studied at the global level in two masked, randomised studies known as PANDA-1 (NCT03577899) and PANDA-2 (NCT03630952). Both trials have three cohorts in a 1:1:1 randomisation, of 0.5 mg conbercept every 8 weeks, 1.0 mg conbercept every 12 weeks and 2.0 mg aflibercept every 8 weeks. All three cohorts received three monthly loading doses and were then extended to their respective intervals. PANDA-2 differs from the first trial at week 40, where all patients then begin a capped (maximum interval of 16 weeks) PRN treatment of their cohort. Both studies are ongoing and follow patients through 96 weeks, with the hopes that conbercept proves itself as non-inferior to aflibercept.

OPT-302

OPT-302 is a soluble form of VEGFR-3 developed by Opthea Limited (Melbourne, Australia) and functions as a "trap" molecule that blocks VEGF-C and VEGF-D.[31] When utilising an anti-VEGF agent such as ranibizumab that blocks VEGF-A, the proteins VEGF-C and VEGF-D are noted to be upregulated. OPT-302 is designed to work in conjunction with an anti-VEGF-A agent and provides a more complete inhibition of the four classes of VEGFs by also inhibiting VEGF-C/D.

OPT-302 recently completed its phase IIb trial and met its primary endpoints.[32] Combined OPT-302 and ranibizumab treatment had increased vision gains compared with ranibizumab monotherapy. Along with these results, OPT-302/ranibizumab also showed anatomical improvements, including a reduced CST, a decrease in CNV lesion size and decreases in intra/sub-retinal fluid. Patients in the 2.0 mg OPT-302/ranibizumab therapy group gained +14.2 letters, while the low-dosage cohort of 0.5 mg OPT-302/ranibizumab gained +9.4 letters. The ranibizumab monotherapy group showed an improvement of +10.8 letters. By week 24, the 2.0 mg OPT-302/ranibizumab cohort showed a mean CST reduction of -147 microns, from baseline. The ranibizumab monotherapy showed a -134 micron reduction at the same checkpoint. Due to the positive phase IIb data, two pivotal phase III trials are expected to start in 2021.

The range of molecules currently under investigation shows great potential in broadening the options available to those afflicted by wAMD. The new molecules target VEGF with higher binding affinity or sustained ocular bioavailability. Other molecules target different biological pathways alongside VEGF, such as faricimab and sunitinib, to address the unmet need of alternative pathways for patients not responsive to anti-VEGF. Finally, agents such as conbercept and OPT-302 expand on the VEGF family to address subtypes that may also lead to a more complete inhibition of VEGF for disease control. All of these agents are currently undergoing clinical trials to assess their safety, efficacy and durability as potential treatments for wAMD. ❑

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