WHAT'S IN THE WORKS FOR WET AMD

Researchers are pushing forward with novel therapeutics and delivery approaches.

BY MEGHANA KALAVAR, MD; DANTE PIERAMICI, MD; AND NIKA BAGHERI, MD

Although intravitreal anti-VEGF injections have revolutionized our approach to wet AMD, roughly 20% of patients still lose vision and less than half achieve a VA of 20/40 despite ongoing injections (Figure).[1-3] In addition, the initial visual gains seen in clinical trials are often not maintained long-term. Disappointing real-world outcomes may, in part, be the result of undertreatment due to a high treatment burden.[4] Thus, researchers are working to extend the treatment duration of our tried-and-true therapies. In the vein of longer duration therapy, the FDA approved both the port delivery system with ranibizumab (Susvimo, Genentech/Roche) and intravitreal faricimab (Vabysmo, Genentech/Roche) for the treatment of wet AMD. More recently, Regeneron reported results of the use of 8 mg aflibercept for wet AMD from the phase 3 Pulsar trial, in which 79% of study patients maintained 12-week dosing on high-dose aflibercept at 48 weeks, and 77% maintained a 16-week dosing regimen.[5]

Outside of the traditional anti-VEGF space, several other innovations are under investigation, including alternative delivery mechanisms, new targetable molecules, extended-duration drug formulations, and biosimilars that may provide identical safety and efficacy at lower prices (Table).

TYROSINE KINASE INHIBITORS

An alternative targeted for several wet AMD drug candidates is the tyrosine kinase pathway. When VEGF binds to its receptor, it initiates a tyrosine kinase cascade that allows tyrosine kinase inhibitors (TKI) to affect all members of the VEGF family of molecules.[6]

Sunitinib maleate (GB-102, GrayBug Vision) is a TKI delivered via intravitreal injection twice a year. ALTISSIMO, the phase 2b trial, showed similar central subfield thickness but lower BCVA than patients treated with bimonthly aflibercept (Eylea, Regeneron; NCT03953079).[7]

Another TKI in phase 2 is D-4517.2 (Ashvattha Therapeutics), a sunitinib analog that is injected subcutaneously every month (NCT05387837).

Axitinib (CLS-AX, Clearside Biomedical) is a TKI that is delivered via suprachoroidal injection (NCT04626128). The phase 1/2a OASIS trial met its primary endpoint at 3 months, with a favorable safety profile and a 73% reduction in the treatment burden for cohorts 3 and 4.[8]

Vorolanib (EYP-1901, EyePoint Pharmaceuticals), is a TKI that uses the company's sustained intraocular delivery platform, Durasert. The phase 2 DAVIO 2 trial dosed its first patient in August and will be assessing two dosage arms compared with aflibercept (NCT05381948).[9]

GENE THERAPY

Other drugs in the pipeline use gene therapy with the goal of administering one injection to provide sustained expression of an anti-VEGF protein.[10]

Ixoberogene soroparvovec (Ixo-vec [formerly ADVM-022], Adverum Biotechnologies) completed the phase 1 OPTIC trial, showing that one intravitreal injection of the study drug led to robust intraocular expression of an aflibercept-like

AT A GLANCE

- An alternative target for several wet AMD drug candidates is the tyrosine kinase pathway.
- Other drugs in the pipeline use vector-based gene therapy with the goal of administering one injection to provide sustained intraocular expression of an anti-VEGF protein.
- Therapeutics in phase 3 include OPT-302 (Opthea), KSI-301 (Kodiak Sciences), RGX-314 (Regenxbio) subretinal injection, and BAT5906 (Bio-thera).

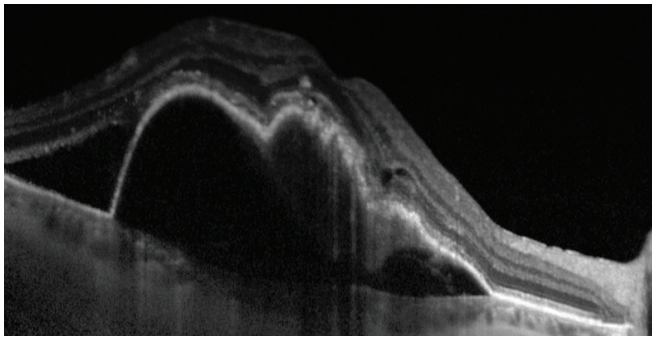

Figure. OCT imaging of a patient with wet AMD in the right eye demonstrates macular edema, subretinal fluid, and a large pigment epithelial detachment.

protein that was comparable with standard anti-VEGF injection therapy over 24 weeks (NCT03748784).[11] The phase 2 LUNA trial launched with the first patient dosed in September (NCT05536973).[12]

4D-150 (4D Molecular Therapeutics) is a dual-transgene intravitreal gene therapy designed to inhibit four angiogenic factors. A one-time dose of 4D-150 will be compared with regularly dosed aflibercept injections in a phase 1/2 trial that is currently recruiting (NCT05197270). This gene therapy codes for an aflibercept-like protein and a small inhibiting RNA that blocks VEGF-C.

RGX-314 (Regenxbio) is a gene therapy that uses adeno-associated vector 8 that promotes native production of a ranibizumab-like protein as an attempted one-time treatment for wet AMD. In the phase 2 AAVIATE trial, RGX-314 is delivered suprachoroidally via a microinjector (Clearside Biomedical) at various doses. Regenxbio announced complete enrollment of cohort 5 of the study in July.[13]

RGX-314 is also being delivered as a subretinal injection in two phase 3 trials, ASCENT (NCT05407636) and ATMOSPHERE (NCT04704921), that are comparing two dosing arms of RGX-314 with intravitreal ranibizumab (Lucentis, Genentech/Roche) or aflibercept. In both trials, which are currently enrolling, eyes undergo pars plana vitrectomy to allow intraoperative access to the subretinal space.

A ONE-TWO (OR THREE) PUNCH

Several therapeutics are targeting multiple pathways. OPT-302 (Opthea) is a Fc-fusion protein designed to inhibit VEGF-C and VEGF-D. In the phase 2b trial, OPT-302 with ranibizumab had a significant increase in BCVA at 24 weeks compared with ranibizumab monotherapy (NCT03345082).[14] Two phase 3 trials, ShORe (NCT04757610) and COAST (NCT04757636), are currently recruiting.

IBI302 (Innovent Biologics) is a recombinant human anti-VEGF and anticomplement (C3b and C4b) bispecific fusion protein in a phase 2 trial.[15] The study compares IBI302 dosed every 8 or 12 weeks with aflibercept dosed monthly (NCT05403749). The phase 1 trial showed improved visual function and good tolerability after 6 weeks of injection.[16]

PHASE 1 TRIALS TO WATCH

- OTX-TKI (Ocular Therapeutix), an intravitreal implant that releases the TKI axitinib, is currently in a phase 1 trial with final results pending (NCT03630315). Interim safety and efficacy data, presented at AAO 2022, indicated that 80% of study subjects were rescue-free up to 6 months.
- BD311 (BDgene Co) is a suprachoroidal gene therapy that increases VEGF-A antibody expression in retinal pigment epithelium cells to neutralize VEGF activity and decrease retinal angiogenesis. The company is recruiting for a phase 1 trial (NCT05099094).
- AIV007 (AiViva BioPharma), an intravitreally administered gel suspension that targets VEGFR, PDGFR, and FGFR and modulates TGFβ1 mRNA expression and TGFβ1 levels, completed phase 1 with results pending (NCT04422899).
- AR-13503 (Aerie) is a rho-associated protein kinase inhibitor sustained-release intravitreal implant with phase 1 results pending (NCT03835884).
- ASKG712 (AskGene Pharma) is an anti-VEGF antibody/angiopoietin 2 antagonist peptide fusion protein delivered via intravitreal injection. The company has not started recruitment for its phase 1 trial (NCT05456828).
- RO7250284 (Hoffmann-La Roche) is a bispecific human antigen-binding fragment form of faricimab delivered via a port delivery system. The company is currently recruiting for a phase 1 trial (NCT04567303).
- MHU650 (Novartis), administered as a single intravitreal injection, completed a phase 1 single ascending dose study with results pending (NCT04635800).
- HMR59 (Hemera Biosciences/Janssen Pharmaceuticals) is an AAV2 vector gene therapy that is delivered via a single intravitreal injection. The phase 1 proof-of-concept study is complete with data pending (NCT03585556).

ALTENATIVE PATHWAYS

UBX1325 (Unity Biotechnology) is a small molecule Bcl-xL inhibitor that increases apoptosis of diseased senescent cells in the retinal pigment epithelium, subsequently suppressing inflammation and neovascularization.[17] The company announced in September that enrollment is complete for its phase 2 ENVISION trial (NCT05275205).

AXT107 (Asclepix Therapeutics) works on the Tie-2 signaling pathway and is designed to be a yearly intravitreal self-assembling depot. The phase 1/2a study of 18 patients is complete with data pending (NCT04746963).

TABLE. WET AMD TREATMENT PIPELINE					
Drug (Company)	**Mechanism**	**NCT #**	**Estimated Study Completion**	**Recruitment Status**	**Last Update Posted**
PHASE I					
OTX-TKI (Ocular Therapeutix)	Intravitreal implant with tyrosine kinase inhibitor	NCT03630315	December 2022	Active, not recruiting	August 2022
RO7250284 (Hoffman-La Roche)	Bispecific human antigen-binding fragment of faricimab via the port delivery system	NCT04567303	November 2025	Recruiting	November 2022
BD311 (BDGene Co)	Gene therapy	NCT05099094	September 2023	Recruiting	August 2022
AIV007 (AiViva BioPharma)	Intravitreal gel suspension	NCT04422899	Complete		May 2022
MHU650 (Novartis)	Intravitreal injection	NCT04635800	Complete		September 2022
AR-13503 (Aerie)	Rho kinase inhibitor sustained release intravitreal implant	NCT03835884	Complete		June 2022
ASKG712 (AskGene Pharma)	Anti-VEGF antibody and ang-2 antagonist fusion protein	NCT05456828	April 2024	Not yet recruiting	July 2022
PHASE II					
IBI302 (Innovent Biologics)	Intravitreal injection of a bispecific fusion protein	NCT05403749	June 2024	Not yet recruiting	June 2022
UBX1325 (Unity Biotechnology)	Intravitreal injection of a Bcl-xL inhibitor	NCT05275205	January 2023	Active, not recruiting	May 2022
AXT107 (Asclepix Therapeutics)	Intravitreal self-assembling depot	NCT04746963	Complete		November 2022
4D-150 (4D Molecular Therapeutics)	Dual-transgene intravitreal gene therapy	NCT05197270	September 2026	Recruiting	October 2022
GB-102 (GrayBug Vision)	Intravitreal injection with sunitinib	NCT03953079	Complete		January 2022
EYP-1901 (EyePoint Pharmaceuticals)	Intravitreal implant with a tyrosine kinase inhibitor	NCT05381948	December 2023	Recruiting	August 2022
D-4517.2 (Ashvattha Therapeutics)	Intravitreal tyrosine kinase inhibitor	NCT05387837	May 2023	Recruiting	September 2022
CLS-AX (Clearside Biomedical)	Suprachoroidal injection of a tyrosine kinase inhibitor	NCT04626128	Complete		July 2022
PAN-90806 (PanOptica)	Topical tyrosine kinase inhibitor topical drop	NCT03479372	Complete		July 2019
MG-O-1002 (Theratocular Biotek)	Topical ophthalmic drop	NCT05390840	February 2023	Not yet recruiting	May 2022
AKST4290 (Alkahest)	Oral CCR3 inhibitor	NCT04331730	Complete		October 2021
RBM-007 (Ribomic)	Anti-fibroblast growth factor 2 aptamer intravitreal injection	NCT04895293	Complete		August 2022
Ixoberogene soroparvovec (formerly ADVM-022, Adverum Biotechnologies)	Intravitreal gene therapy	NCT05536973	February 2024	Recruting	September 2022
RGX-314 (Regenxbio)	Suprachoroidal gene therapy	NCT04514653	January 2024	Recruiting	October 2023
PHASE III					
OPT-302 (Opthea)	Fc-fusion protein	NCT04757610, NCT04757636	December 2024	Recruiting	September 2022
KSI-301 (Kodiak Sciences)	Antibody biopolymer conjugate	NCT04964089	April 2023	Active, not recruiting	June 2022
RGX-314 (Regenxbio)	Subretinal gene therapy	NCT04704921, NCT05407636	March 2024 December 2024	Recruiting	May 2022 June 2022
BAT5906 (Bio-thera)	Recombinant anti-VEGF intravitreal injection	NCT05439629	June 2025	Not yet recruiting	June 2022

RBM-007 (Ribomic) is anti-fibroblast growth factor 2 aptamer that inhibits angiogenesis and scar formation. Initial results from the phase 2 trial, TEMPURA, in which study eyes received a single intravitreal injection of RBM-007, suggests that it has the potential to improve BCVA in treatment-naive wet AMD eyes (NCT04895293).

Tarcocimab (KSI-301, Kodiak Sciences) uses a new antibody biopolymer conjugate platform. The biopolymer attached to the antibody binds to VEGF, increasing the size of the molecule and allowing for a higher concentration and longer effect duration. Although the phase 2b/3 DAZZLE trial did not meet the primary efficacy endpoint (NCT04049266), the phase 3 DAYLIGHT trial is evaluating tarcocimab dosed every 4 weeks compared with aflibercept every 8 weeks (NCT04964089).[18]

BAT5906 (Bio-thera) is a recombinant anti-VEGF intravitreal injection being compared with aflibercept in a phase 3 trial that is not yet recruiting (NCT05439629).

TOPICAL AND ORAL OPTIONS

PAN-90806 (PanOptica) is a topical VEGFR2 TKI drop. A completed phase 1/2 showed 51% of patients on PAN-90806 were able to complete the study with no rescue injections and demonstrated anti-VEGF biological response at all doses tested (NCT03479372).

Topical MG-O-1002 (Theratocular Biotek) is currently being evaluated for safety compared with placebo in a phase 2 trial that has yet to start recruiting (NCT05390840).

Oral AKST4290 (Alkahest) inhibits chemokine C-C motif receptor 3. AKST2490 is dosed twice daily after three initial loading doses of aflibercept (NCT04331730). Results are pending from the completed phase 2 trial.

BIOSIMILARS UNDER INVESTIGATION

Xlucane (Xbrane Biopharma AB), GNR-067 (AO Generium), and LUBT010 (Lupin) are ranibizumab biosimilars in phase 3 trials. Aflibercept biosimilars in phase 3 trials include ALT-L9 (Alteogen),[19] ABP-938 (Amgen, Parexel), AVT06 (Alvotech), FYB203 (Formycon, Bioeq), SOK583A19 (Sandoz), and SCD411 (Sam Chun Dang Pharm Co).[20,21]

ONS-5010 (Outlook Therapeutics) and TAB014 (TOT Biopharm) are bevacizumab (Avastin, Genentech/Roche) biosimilars in phase 3 trials. The FDA accepted Outlook Therapeutics' biologics license application for ONS-5010 in October with the hope for market approval in 2023.[22]

THAT'S A WRAP

In today's treatment landscape, poor visual outcomes in wet AMD are exacerbated by the high treatment burden of current therapies. Given the large number of clinical trials evaluating novel therapies for wet AMD, there is promise that alternative, more sustainable and effective treatments for the disease are on the horizon. ■

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NIKA BAGHERI, MD
- Vitreoretinal Surgeon, California Retina Consultants and Research Foundation, Santa Barbara, California
- bagheri.n@gmail.com
- Financial disclosure: Consultant/Research Grant Support (Genentech/Roche)

MEGHANA KALAVAR, MD
- Resident Physician, The Ohio State University Wexner Medical Center Department of Ophthalmology and Visual Sciences, Columbus, Ohio
- meghana.kalavar@gmail.com
- Financial disclosure: None

DANTE PIERAMICI, MD
- Vitreoretinal Surgeon, California Retinal Consultants and Research Foundation, Santa Barbara, California
- dpieramici@yahoo.com
- Financial disclosure: Consultant/Research Grant Support (Genentech/Roche)