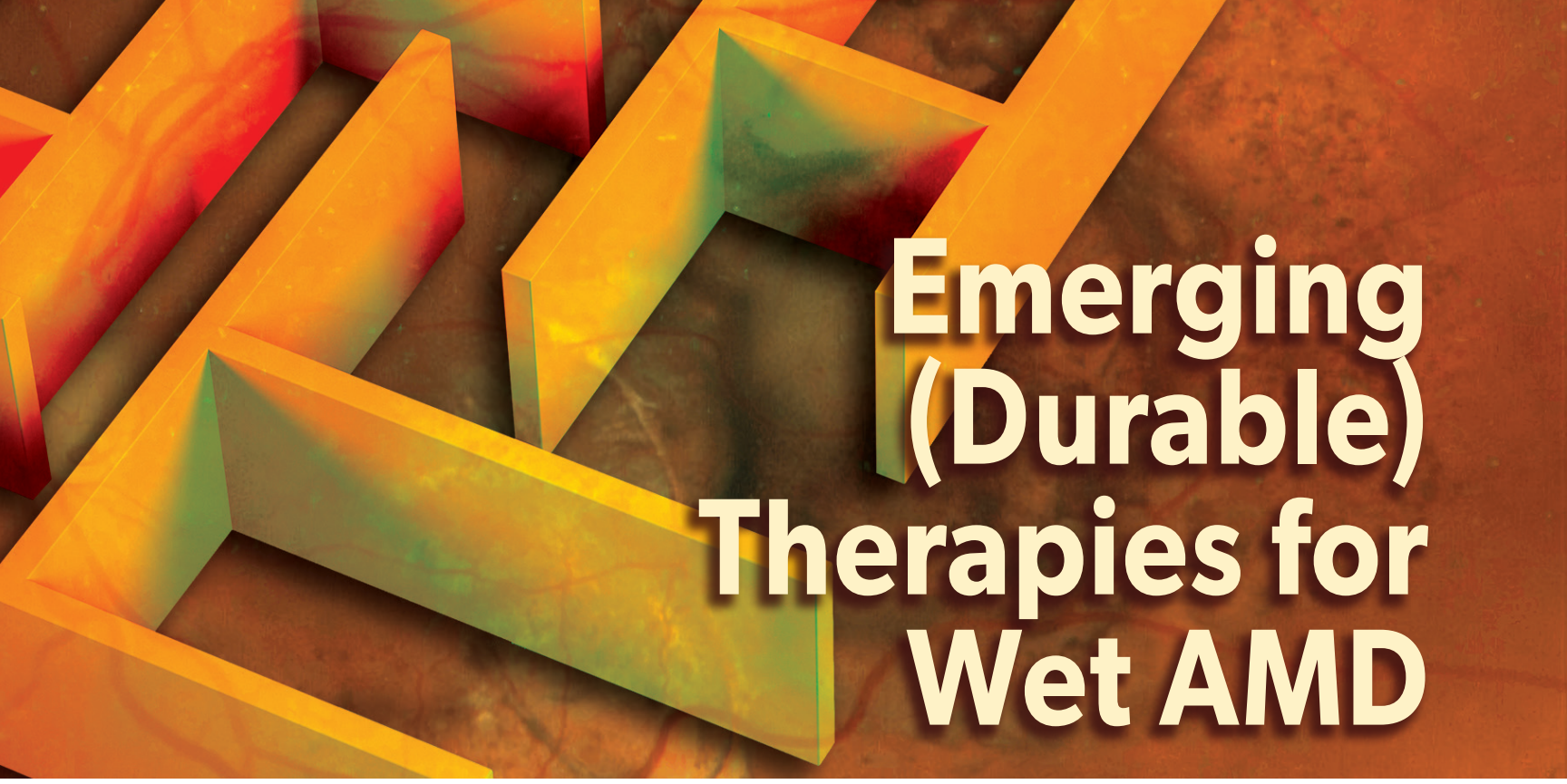

Emerging (Durable) Therapies for Wet AMD

New approaches are helping us care for patients while reducing their treatment burden.

By Jacob S. Heng, MD, PhD, and Adrienne W. Scott, MD


Although anti-VEGF therapy is the mainstay of wet AMD treatment, many patients require sustained VEGF suppression with treatment every 4 to 8 weeks to maintain disease control—a treatment approach that is not always sustainable due to patient circumstances.

Fortunately, much progress has been made to address durable VEGF suppression (Table 1). In addition, therapies that may provide even more durable VEGF suppression are being developed (Table 2), including tyrosine kinase inhibitors (TKIs) and gene therapies (see *Gene Therapy Approach*).

DURABLE ANTI-VEGF THERAPIES

The port delivery system (PDS; Susvimo, Genentech/Roche) is a surgically-implanted, refillable device that allows sustained release of ranibizumab. In the phase 3 ARCHWAY study, patients with wet AMD were randomly assigned 3:2 to treatment with the PDS with refill-exchanges every 24 weeks (Q24W) or intravitreal ranibizumab (Lucentis, Genentech/Roche) every 4 weeks (Q4W).[1] PDS Q24W showed noninferior BCVA gains compared with ranibizumab Q4W. Of patients with the PDS, 98.4% did not require supplemental injections before the first refill-exchange procedure. However, 19% of PDS patients had pre-specified ocular adverse events compared with 6% of patients receiving ranibizumab.[1]

Another new therapy promising extended duration of effect is 8 mg aflibercept (Eylea HD, Regeneron). In the phase 3 PULSAR study, patients with wet AMD were randomly assigned 1:1:1 to 8 mg aflibercept every 12 weeks (Q12W), 8 mg aflibercept every 16 weeks (Q16W), or 2 mg aflibercept (Eylea, Regeneron) every 8 weeks (Q8W) following three monthly loading doses of each respective

AT A GLANCE

- When first-generation anti-VEGF agents do not provide satisfactory outcomes, consider switching to faricimab (Vabysmo, Genentech/Roche) or 8 mg aflibercept (Eylea HD, Regeneron).
- The port delivery system (Susvimo, Genentech/Roche) is a promising approach for treatment intervals of 6 months or more.
- Many therapies touting longer treatment effect are under investigation, including EYP-1901 (Duravyu, Eyepoint Pharmaceuticals), OTX-TKI (Axpaxli, Ocular Therapeutix), CLS-AX (Clearside Biomedical), AR-14034 (Alcon), and KHK4951 (Kyowa Kirin).

TABLE 1. APPROVED THERAPIES FOR WET AMD

Agent (Company)	Target	Type of Molecule	FDA Approval	Target Dosing Frequency
Bevacizumab (Avastin, Genentech/Roche)	VEGF-A	IgG1 antibody	Off-label	4-8 weeks
Ranibizumab (Lucentis, Genentech/Roche)	VEGF-A	Antibody fragment (Fab)	2006	4-8 weeks
2 mg Aflibercept (Eylea, Regeneron/Bayer)	VEGF-A and -B; placental growth factor	VEGFR-1 and -2 ligand domain and IgG Fc fusion protein	2011	4-8 weeks
Brolucizumab (Beovu, Novartis)	VEGF-A	Single-chain variable fragment	2019	8-12 weeks
8 mg Aflibercept (Eylea HD, Regeneron/Bayer)	VEGF-A and -B; placental growth factor	VEGFR-1 and -2 ligand domain and IgG Fc fusion protein	2023	8-16 weeks
Faricimab (Vabsymo, Genentech/Roche)	VEGF-A; Ang-2	Bispecific antibody	2022	4-16 weeks
Port Delivery System (Susvimo, Genentech/Roche)	VEGF-A	Antibody fragment (Fab) with sustained release from refillable device	2021	6 months

TABLE 2. DURABLE THERAPIES IN DEVELOPMENT FOR WET AMD

Agent (Company)	Target	Type of Molecule	Route of Delivery	Target Dosing Frequency	Trial phase
EYP-1901 (Eyepoint Pharmaceuticals)	VEGF-A, -B, and -C; platelet derived growth factor receptor	TKI (vorolanib) in bioerodable implant	Intravitreal	6 months	Phase 3
OTX-TKI (Ocular Therapeutix)	VEGFR-1, -2, and -3	TKI (axitinib) in hydrogel implant	Intravitreal	9-12 months	Phase 3
CLS-AX (Clearside Biomedical)	VEGFR-1, -2, and -3	TKI (axitinib) suspension	Suprachoroidal	12-24 weeks	Phase 2b
AR-14034 (Alcon)	VEGFR-1, -2, and -3	TKI (axitinib) in bioerodible polymer implant	Intravitreal	10 weeks or more	Phase 2
KHK4951 (Kyowa Kirin)	VEGFR-1, -2, and -3	TKI (tivozanib) in nanocrystals	Eye drop	3 times daily	Phase 2

treatment.[2] Patients receiving 8 mg aflibercept Q12W and Q16W achieved noninferior BCVA gains compared with those receiving 2 mg aflibercept Q8W, with a similar incidence of ocular adverse events across all groups.[2]

Faricimab (Vabysmo, Genentech/Roche) is a bispecific antibody targeting VEGF-A and Ang-2. Ang-2 is a soluble protein associated with vascular destabilization by binding to the Tie2 receptor on vascular endothelial cells. Faricimab was evaluated for wet AMD in the TENAYA and LUCERNE trials, where patients with wet AMD were randomly assigned 1:1 to receive intravitreal faricimab up to Q16W (after four loading doses) compared with 2 mg aflibercept dosed Q8W (after three loading doses).[3] Faricimab dosing intervals up to week 60 were fixed at Q8W, Q12W, or Q16W based on strict protocol-defined disease activity criteria; between week 60 and week 108, a treat-and-extend regimen was used. BCVA change and ocular adverse events were comparable between the faricimab and aflibercept groups. At week 112, 74.1% and 81.2% of patients receiving faricimab achieved Q12W or longer dosing, while 59.0% and 66.9% achieved Q16W dosing in TENAYA and LUCERNE, respectively.[3]

EXTENDING THE TREATMENT INTERVAL

The most common first-line anti-VEGF agent is off-label bevacizumab (Avastin, Genentech/Roche).[4] Recently, many payers, including Aetna,[1] have mandated step therapy, which dictates that patients first be treated with bevacizumab and switch to ranibizumab (or a biosimilar such as ranibizumab-nuna [Byooviz, Samsung Bioepis/Biogen]) or 2 mg aflibercept only when there is an inadequate therapeutic response. The CATT trial found similar visual acuity gains between wet AMD patients treated with bevacizumab compared with those treated with ranibizumab.[2] However, no prospective study has compared aflibercept with ranibizumab and bevacizumab in wet AMD.

In diabetic macular edema (DME), however, the DRCR Retina Network Protocol T found that 2 mg aflibercept resulted in better visual gains compared with ranibizumab and bevacizumab when the presenting BCVA was 20/50 or worse.[3] Furthermore, DRCR Retina Network Protocol AC found that step therapy starting with bevacizumab and switching to 2 mg aflibercept achieved similar visual acuity gains at 2 years compared with aflibercept monotherapy

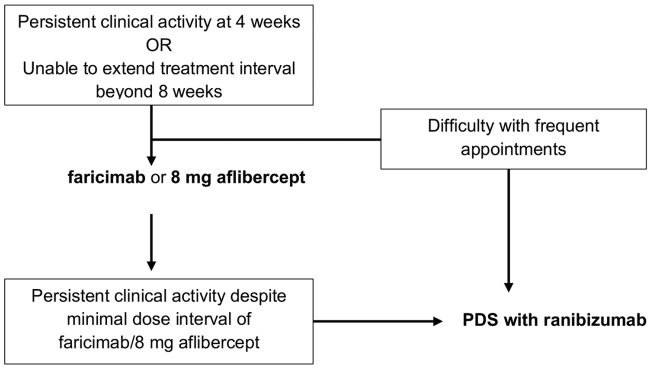

Figure 1. This is our approach to extending the treatment interval for patients with wet AMD.

in DME patients.[5] Extrapolating these results to wet AMD and considering the CATT trial, step therapy starting with bevacizumab and switching to 2 mg aflibercept would seem to be a logical choice.

When treatment with these first-generation agents every 4 weeks does not result in satisfactory drying of the retina, switching to faricimab or 8 mg aflibercept may be considered (Figures 1 and 2). Of note, faricimab can be given as frequently as every 4 weeks after four monthly doses, whereas 8 mg aflibercept can only be given every 8 weeks after three monthly doses.[6,7] In addition, switching therapies may also benefit patients who cannot be extended to treatment intervals of 8 weeks and beyond. However, no head-to-head study has compared farcimab with 8 mg aflibercept, although a network meta-analysis using data from the phase 3 clinical trials (TENAYA/LUCERNE and PULSAR) suggests that faricimab may have a superior drying effect.[8]

Finally, for patients already receiving faricimab or 8 mg aflibercept at the minimum dosing interval with persistent disease activity, the PDS may offer more consistent and durable VEGF suppression. The PDS could also be considered for patients with a high treatment burden who cannot attend frequent injection appointments.

DURABLE THERAPIES IN DEVELOPMENT

EYP-1901 (Duravyu, Eyepoint Pharmaceuticals) is a bioerodible sustained delivery platform that delivers vorolanib, a TKI that inhibits VEGFR-1, -2, and -3 and platelet-derived growth factor receptor. In the phase 2 DAVIO trial, patients receiving EYP-1901 achieved noninferior changes in BCVA compared with 2 mg aflibercept Q8W, with almost two-thirds of patients not requiring supplemental anti-VEGF injections at 6 months and an over 80% reduction in the annualized anti-VEGF injection rate.[5] The global phase 3 LUGANO (NCT06668064) and LUCIA (NCT06683742) clinical trials are underway.

OTX-TKI (Axpaxli, Ocular Therapeutix) incorporates axitinib, a TKI targeting VEGFR-1, -2 and -3, into a hydrogel implant that bioresorbs in approximately 9 months. In a phase 1 trial, OTX-TKI achieved BCVA gains similar to 2 mg aflibercept Q8W at 12 months, resulting in an 89% reduction in anti-VEGF injections.[6] Two phase 3 trials, SOL-1 (NCT06223958) and SOL-R (NCT06495918), are active.

CLS-AX (Clearside Biomedical) delivers an axitinib suspension using a proprietary suprachoroidal microinjector. Topline data from the phase 2 ODYSSEY trial showed an 84% reduction in treatment burden over 6 months, with 67% of treated patients not requiring supplemental treatment up to 6 months.[7] The company is planning two phase 3 trials.[8]

AR-14034 (Alcon) contains axitinib in a bioerodible polymer implant that can be injected intravitreally.[9] AR-14034 is being evaluated in the phase 1/2 NOVA-1 study as a supplement to an initial dose of 2 mg aflibercept.

KHK4951 (Kyowa Kirin) packages tivozanib, a TKI targeting VEGFR-1, -2 and -3, in nanocrystals as an eye drop that allows penetration into the posterior segment.[10] While not a sustained-release therapy, KHK4951 could potentially be an at-home therapy. A phase 2 trial (NCT06116890) is underway to evaluate its safety and efficacy.

MEETING AN UNMET NEED

Current durable anti-VEGF therapies for wet AMD include faricimab, 8 mg aflibercept, and the PDS. While faricimab and 8 mg aflibercept offer some extension of the treatment interval in most patients, many do not reach the extended intervals seen in clinical trials.[9,10] The PDS is a promising approach for treatment intervals of 6 months or more, but

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Several gene therapies are under investigation for the treatment of wet AMD, including the following:

- ABBV-RGX-314 (Regenxbio/Abbvie)
- Ixo-vec (ixoberogene soroparvovec, Adverum Biotechnologies)
- 4D-150 (4D Molecular Therapeutics)
- KH631 (Chengdu Origen Biotechnology)
- FT-003 (Frontera Therapeutics)
- HG202 (HuidaGene Therapeutics)
- EXG102-031/EXG202 (Exegenesis Bio)

To learn more about these therapies, check out *Gene Therapy for AMD: What You Need to Know*, on page 26.

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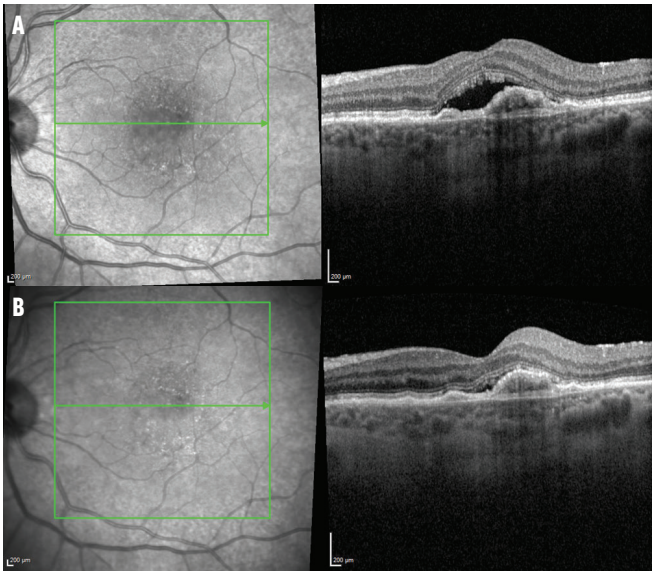

Figure 2. This patient with wet AMD being treated with 2 mg aflibercept had less than ideal fluid control (A). After three montly doses of faricimab, the patient's OCT imaging showed significant improvement (B).

it carries associated surgical risks that require careful patient counseling. Many alternative strategies for sustained VEGF suppression are currently under development.

All these approaches show promise in early clinical trials but must stand up to scrutiny against the high bar of current anti-VEGF therapies. ■

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