Can we improve the nAMD patient experience without compromising outcomes?

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Thinking beyond the VEGF pathway in nAMD

Mr Robin Hamilton
Moorfields Eye Hospital NHS Foundation Trust and UCL Institute of Ophthalmology, London, UK

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Anti-VEGF therapy is the standard of care in nAMD

Impact of anti-VEGF therapy as demonstrated in the ANCHOR and MARINA RCTs.[1,2]

Visual gains

At 24 months, 26–41% of patients gained ≥15 letters from baseline with anti-VEGF vs 4–6% with PDT or sham injection.[1,2]

Vision loss

At 24 months, 89–92% of patients avoided losing 15 letters with anti-VEGF vs 53–66% with PDT or sham injection.[1,2]

Safety

The incidence of AEs was similar between treatment groups.[1,2]

Neovascularization

At 24 months, patients treated with anti-VEGF had reduced growth of and leakage from choroidal neovascularization vs PDT or sham injection.[1,2]

AE, adverse event; PDT, photodynamic therapy; RCT, randomized controlled trial; VEGF, vascular endothelial growth factor

1. Brown DM, et al. *Ophthalmology*. 2009;116(1):57-65.e5; 2. Rosenfeld PJ, et al. *N Engl J Med.* 2006;355(14):1419-31.

Disconnection between real-world outcomes and clinical trial results

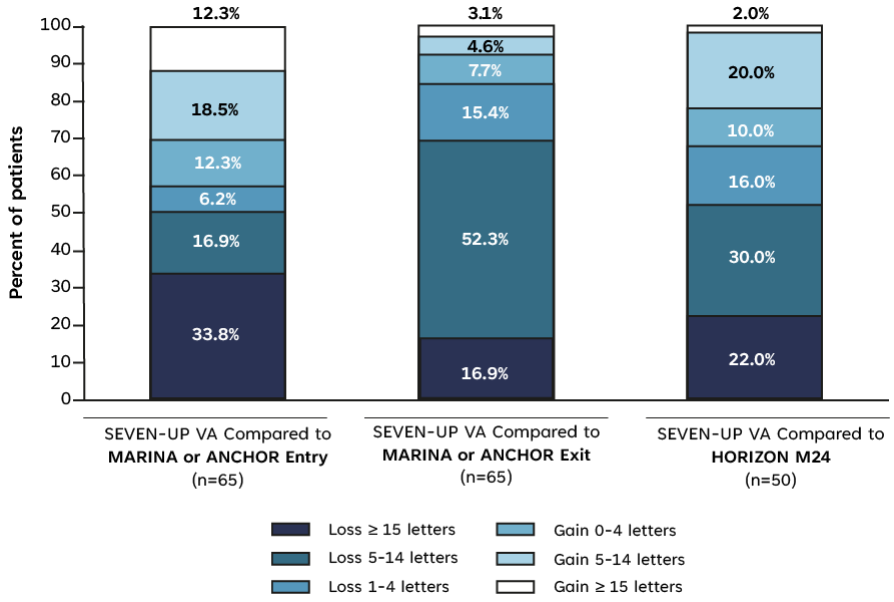
In the real-world **CATT** and **SEVEN-UP** studies, patients frequently demonstrated decreases from baseline in visual acuity from year 2 of anti-VEGF treatment.[1,2]

Several studies have demonstrated that visual outcomes differ by country and are related to the number of clinical visits and injections.[3–6]

VEGF, vascular endothelial growth factor.

1. CATT Research Group, et al. *Ophthalmology*. 2016;123(8):1751-1761; 2. Rofagha S, et al. *Ophthalmology*. 2013;120(11):2292-9; 3. Holz FG, et al. *Br J Ophthalmol.* 2015;99(2):220-6; 4. Holz FG, et al. *Retina*. 2020;40(9):1673-1685; 5. Ciulla TA, et al. *Ophthalmol Retina.* 2020;4(1):19-30; 6. Gillies M, et al. *Am J Ophthalmol.* 2020;210:116-124.

Differential response to anti-VEGF therapy



- Patients demonstrate a differential response to anti-VEGF therapy.
- After 7 years of treatment, more than 50% of patients have lost vision.[1]
- Over 10 years of treatment, 27–49% of patients have lost ten or more letters from baseline vs 19–34% who have gained ten letters.[2]

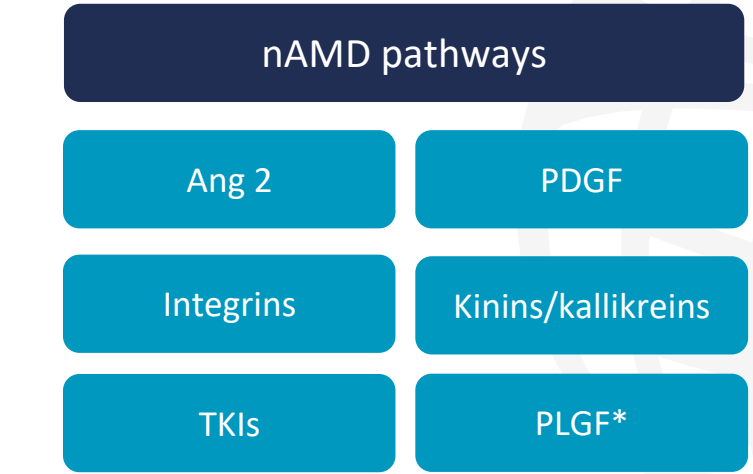
Patients participated in MARINA/ANCHOR for 2 years, HORIZON for 2 years and SEVEN-UP for 3 years.
VEGF, vascular endothelial growth factor

1. Rofagha S, et al. *Ophthalmology*. 2013;120(11):2292-9; 2. Gillies M, et al. *Am J Ophthalmol.* 2020;210:116-124.

Molecular pathways beyond VEGF in nAMD

A range of molecular pathways and potential therapeutic targets have been implicated in the pathogenesis of nAMD.[1,2]

Initial results with PDGF inhibitors in combination with anti-VEGF therapy have not resulted in long-term visual gains over anti-VEGF alone.[3]

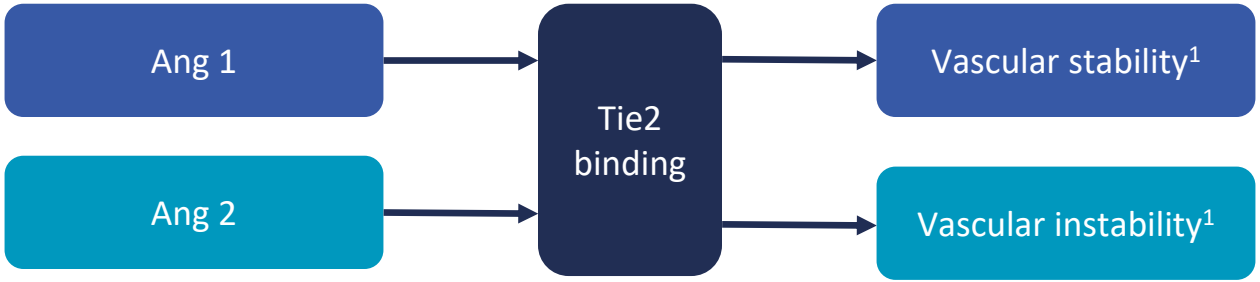


*Part of the VEGF pathway.

Ang, angiopoietin; BFGF; basic fibroblast growth factor; nAMD, neovascular age-related macular degeneration; PDGF, platelet-derived growth factor; PLGF, placental growth factor; TKI, tyrosine kinase inhibitor; VEGF, vascular endothelial growth factor.

1. Daruich A, et al. *Prog Retin Eye Res*. 2018;63:20-68; 2. Nakahara T, et al. *Biol Pharm Bull.* 2017;40(12):2045-2049; 3. Ricci F, et al. *Int J Mol Sci.* 2020;21(21):8242.

The Ang 2 pathway



- Ang 2 levels are elevated in patients with nAMD.[1]
- Increased Ang 2 levels lead to inflammation, vascular leakage and neovascularization.[1,2]

Ang, angiopoietin; nAMD, neovascular age-related macular degeneration; Tie, tyrosine kinase with immunoglobulin-like domains-2

1. Saharinen P, et al. *Nat Rev Drug Discov.* 2017;16(9):635-661; 2. Campochiaro PA. *Prog Retin Eye Res.* 2015;49:67–81.

The disconnection between RCTs and the real-world in nAMD outcomes

Dr Roberto Gallego-Pinazo
Unit of Macula and Clinical Trials, Oftalvist Clinic, Valencia, Spain

touch OPHTHALMOLOGY®

Long-term outcomes in nAMD

Type 1 neovascularization

- Ingrowth of vessels initially from the choriocapillaris into and within the sub-RPE space.[1]
- Improvement in visual acuity over 12 months of anti-VEGF therapy.[2]

Type 2 neovascularization

- Originates from the choroid and then proliferates in the subretinal space.[1]
- Improvement in visual acuity over 12 months of anti-VEGF therapy.[2]

Type 3 neovascularization

- Originates from the retinal circulation and grows toward the outer retina.[1]
- Initial improvements in visual acuity with anti-VEGF treatment diminished after 12 months.[3]
- Poorer outcomes in patients with geographic atrophy or fibrotic scars.[3]

Overall, initial visual gains made in the first 2 years of anti-VEGF therapy are not maintained at 5 years.[4]

nAMD, neovascular age-related macular degeneration; RPE, retinal pigment epithelium; VEGF, vascular endothelial growth factor.

1. Spaide RF, et al. *Ophthalmology*. 2020 127(5):616-636; 2. Kim JM, et al. *Semin Ophthalmol*. 2019;34(3):168-176. 3. Kim J, et al. *Clin Med*. 2020 9(4):1145; 4. CATT Research Group, et al. *Ophthalmology*. 2016;123(8):1751-1761.

Anti-VEGF dosing schedules

- Real-world evidence suggests that visual outcomes correlate with the number of anti-VEGF injections patients receive.[1]

- Anti-VEGF treatments require frequent dosing.

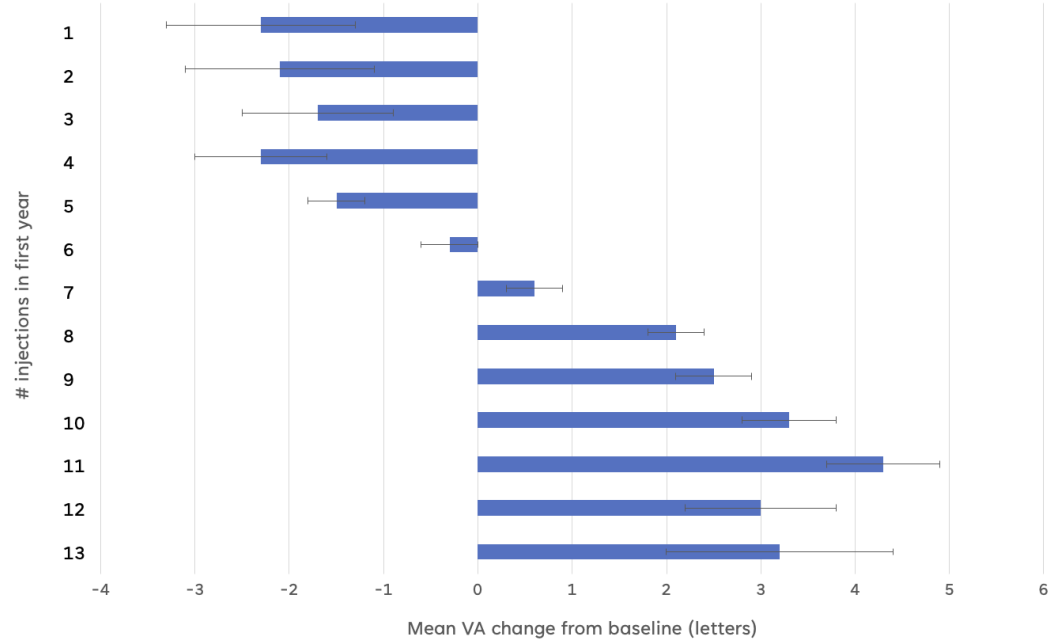
- Evidence suggests 32–95% of patients are non-adherent to treatment or monitoring appointments.[2]

VEGF, vascular endothelial growth factor.

1. Holekamp NM, et al. *Am J Ophthalmol*. 2014;157(4):825-833.e1; 2. Okada M, et al. *Ophthalmology*. 2021;128(2):234-247.

Impact of less frequent anti-VEGF dosing

Less frequent anti-VEGF dosing is associated with poorer visual acuity in many patients (Figure).[1–3]



1. Holz FG, et al. *Br J Ophthalmol*. 2015;99(2):220-6; 2. Rofagha S, et al. *Ophthalmology*. 2013;120(11):2292-9; 3. Ciulla TA, et al. *Ophthalmol Retina*. 2020;4(1):19-30.

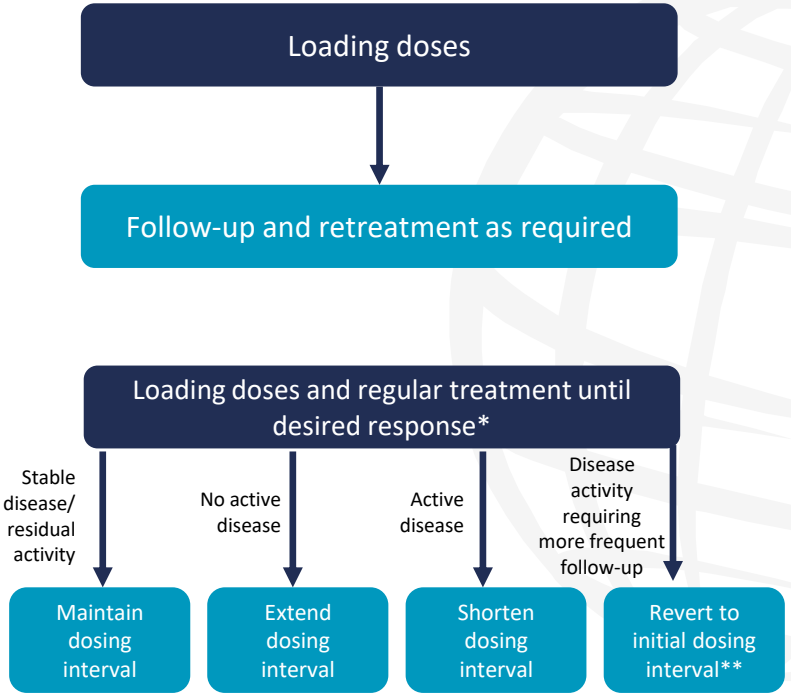
Strategies for extending time between anti-VEGF injections

PRN

- Initial monthly injections followed by further as-needed treatment guided by monthly OCT-assessment of visual acuity and subfoveal fluid (Figure).[1]
- PRN dosing is non-inferior to monthly dosing over 1–2 years but most patients do not retain early visual gains.[1–3]

T&E

- Fixed treatment dosing until the desired response is reached, followed by an extended dosing interval to 12 –16 weeks depending on specific treatment (Figure).[4,5]
- The T&E regimen non-inferior to monthly anti-VEGF dosing and PRN dosing.[4,6]



*Complete resolution of SRF and IRF without new retinal haemorrhage or no further reduction of SRF or IRD for ≥2 consecutive visits on OCT in the absence of a new retinal haemorrhage;
**4 or 8 week dosing.
IRF, intraretinal fluid; IVB,nAMD, neovascular age-related macular degeneration; OCT, optical coherence tomography; PRN, pro re nata; SRF, subretinal fluid; T&E, treat and extend; VEGF, vascular endothelial growth factor.

1. Fung AE, et al. *Am J Ophthalmol*. 2007;143(4):566-83; 2. Li E, et al. *Cochrane Database Syst Rev*. 2020;5(5):CD012208; 3. Lin T, et al. *Br J Ophthalmol*. 2020;104(1):58-63;
4. Freund KB, et al. *Retina*. 2015;35(8):1489-506; 5. Ross AH, et al. *Eye (Lond)*. 2020;34(10):1825-1834; 6. Oubraham H, et al. *Retina*. 2011;31(1):26-30.

The burden of current nAMD treatment

Prof. Francesco Bandello

Department of Ophthalmology, University Vita-Salute, Ospedale San Raffaele, Milan, Italy

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Reasons for low anti-VEGF dosing frequency

Treatment durability

Currently available treatments require frequent dosing to ensure efficacy, necessitating regular clinical visits.[1]

HCP burden

The requirement for frequent anti-VEGF dosing places a significant logistical burden on clinics and their staff.[1,4]

Patient awareness

Low patient awareness of nAMD can lead to late diagnosis, decreasing vision and disease prognosis.[2,3]

Patient burden

Frequent clinical visits represent a time burden on the patient, and injections are associated with discomfort and uncertainty around visual gains.[1]

nAMD, neovascular age-related macular degeneration; VEGF, vascular endothelial growth factor.

1. Monés J, et al. *Ophthalmologica*. 2020;243(1):1-8. 2. Keane PA, et al. *Clin Ophthalmol.* 2015; 9:353-66; 3. Oliver-Fernandez A, et al. *Can J Ophthalmol.* 2005;40(3):313-9; 4. Prenner JL, et al. *Am J Ophthalmol.* 2015;160(4):725-31.e1.

Burden of anti-VEGF treatment

Appointment time

- Visit time is reported to be 12 h, including pre-appointment preparation, travel, waiting time, treatment time, and post-appointment recovery.[1]
- Appointments required caregivers to take time off work and personal activities to accompany patients.[1]

Travel

- Travel time to the clinic is reported as a factor for non-adherence,[2,3] with patients living >100 km from the clinic 2.5-fold more likely to drop anti-VEGF therapy than those within 100 km (50% vs 28% of patients dropped therapy, respectively).[3]

Anxiety

- Patients can be apprehensive at anticipated discomfort of having an injection, fear of losing their eyesight and fear of the unknown.[4]
- Anxiety is reported to the most common psychosocial impact of anti-VEGF therapy.[4]

VEGF, vascular endothelial growth factor.

1. Prenner JL, et al. *Am J Ophthalmol.* 2015;160(4):725-31.e1; 2. Boulanger-Scemama E, et al. *J Fr Ophtalmol.* 2015;38(7):620-7; 3. McGrath LA & Lee LR. *Asia Pac J Ophthalmol (Phila).* 2013;2(5):295-9; 4. Monés J, et al. *Ophthalmologica.* 2020;243(1):1-8.

Strategies for reducing the impact of treatment

Novel treatments and administration options

- Treatments with a longer dosing window are currently in development.[1,2]
- Alternative administration routes including eye implants providing continuous drug delivery offer the promise of fewer clinical visits and continuous anti-VEGF delivery.[3,4]

Less frequent administration

- T&E dosing can reduce the doing interval to 12–16 weeks depending on specific treatment,[5,6] resulting in less frequent clinical visits.

Administrative solutions

- Calling patients following a missed appointment and transportation schemes may facilitate clinic attendance.

VEGF, vascular endothelial growth factor.

1. Hussain RM, et al. *Drug Des Devel Ther*. 2021;15:2653-2665; 2. Dugel PU, et al. *Ophthalmology*. 2020;127(1):72-84; 3. Campochiaro PA, et al. *Ophthalmology*. 2019;126(8):1141-1154; 4. Wan CR, et al. *Transl Vis Sci Technol*. 2020;9(11):27; 5. Ross AH, et al. *Eye (Lond)*. 2020;34(10):1825-1834; 6. Oubraham H, et al. *Retina*. 2011;31(1):26-30.

Remote monitoring

- Currently under development, home OCT technology is intended to allow for nAMD monitoring remotely, minimising clinical visits.[1]
- Initial results suggest that >90% of patients with nAMD can self-operate the machine, with images of similar quality to a commercial OCT.[1]

nAMD, neovascular age-related macular degeneration; OCT, optical coherence tomography.

1. Nahen K, et al. *Klin Monbl Augenheilkd*. 2020;237(12):1410-1418;

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