touchEXPERT BRIEFING

Addressing unmet needs in DME

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The multifactorial nature of DME

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The multifactorial nature of DME

Several processes contribute to the alterations in the blood-retinal barrier leading to fluid accumulation.[1–2]

Cell hypoxia

- Chronic hyperglycemia activates several pathways that lead to hypoxia, further triggering downstream pathways.[1,2]

Inflammation

- Hyperglycemia leads to inflammation, the promotion of leukocyte migration and the secretion of factors, which contribute to blood-retinal barrier breakdown.[1,2]

Cytokines/chemokines

- Multiple cytokines and chemokines are involved in the pathogenesis of DME.[2]
- Patients with DME have elevated levels of VEGF, ICAM-1, IL-6, and MCP-1 compared with nondiabetic patients.[3]

DME, diabetic macular edema; ICAM-1, intercellular adhesion molecule-1 activation ; IL-6, interleukin-6; MCP-1, monocyte chemoattractant protein-1; VEGF, vascular endothelial growth factor.

1. Urias EA, et al. *Vision Res.* 2017;139:221-227; 2. Das A, et al. *Ophthalmology*. 2015;122(7):1375-1394; 3. Browning DJ, et al. *Indian J Ophthalmol*. 2018;66(12):1736-1750.

Anti-VEGF therapy: Unmet needs

- The introduction and adoption of intravitreal anti-VEGF treatment facilitated meaningful visual recovery for people with blinding eye conditions including DME.[1]

- A proportion of eyes with DME demonstrate a poor or incomplete response to anti-VEGF treatment,[2–4] with up to 40% of eyes demonstrating a minimal response (<5 letter gain) in BCVA after 3 months of anti-VEGF treatment.[4]

- Edema may persist despite monthly injections; limited improvement in disease outcomes with multiple anti-VEGF treatments highlights the potential contribution of other pathological mediators to DME.[5]

BCVA, best-corrected visual acuity; DME, diabetic macular edema; nAMD, neovascular age-related macular degeneration; VEGF, vascular endothelial growth factor.

1. Adamis AP, et al. *Eye (Lond).* 2020;34(11):1966-1972; 2. Dugel PU, et al. *Retina*. 2019;39(1):88-97; 3. Bressler NM, et al. *JAMA Ophthalmol*. 2018;136(3):257-269; 4. Gonzalez VH, et al. *Am J Ophthalmol*. 2016;172:72-79; 5. Urias EA, et al. *Vision Res.* 2017;139:221-222.

Key mediators in the pathology of DME

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

VEGF

Ang-2

IL-6

Integrins

Kallikrein-kinin

VAP-1

Ang-2, angiopoietin-2; DME, diabetic macular edema; IL-6, interleukin-6; PDGF, platelet-derived growth factor; VAP-1, vascular adhesion protein; VEGF, vascular endothelial growth factor.

1. Urias EA, et al. *Vision Res*. 2017;139:221-227; 2. Das A, et al. *Ophthalmology*. 2015;122(7):1375-1394.

Angiopoietins in retinal vascular diseases

Ang-TIE pathway

- Tie2 is an endothelial cell-specific tyrosine kinase receptor for Ang-1 and Ang-2.[1]
- The Ang-TIE pathway regulates vascular homeostasis, and controls vessel permeability, inflammation and angiogenic responses.[1]

Ang-1 and Ang-2

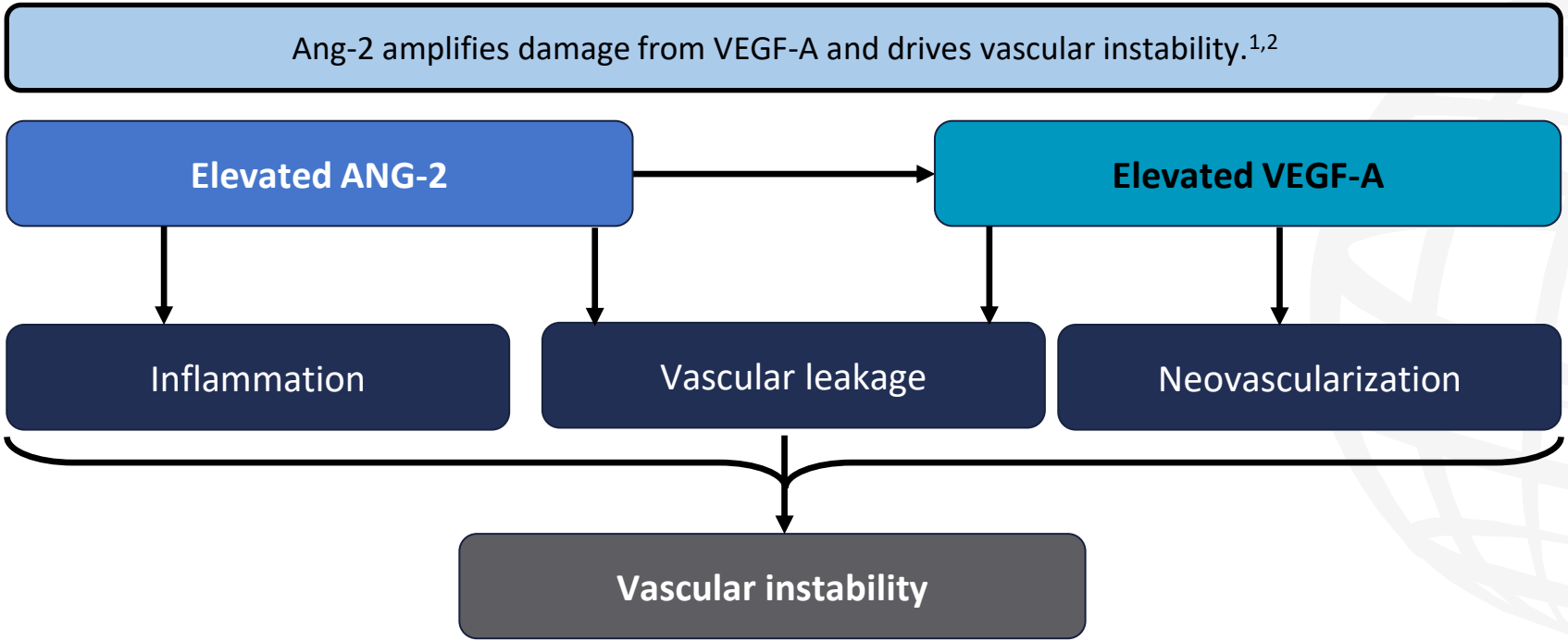
- Ang-1 binding to the Tie2 receptor promotes vascular stability.[1,2]
- Ang-2 promotes vascular instability in disease by competing with Ang-1 binding to Tie2.[1,2]
- In patients with DME, an elevated Ang-2/Ang-1 ratio leads to increased vascular instability.[1]

The Ang-TIE pathway plays a critical role destabilizing the vasculature, and driving subclinical inflammation, vascular leakage and/or neovascularization.[2]

Ang-1, angiopoietin-1; Ang-2, angiopoietin-2; Tie2, tyrosine kinase with immunoglobulin-like domains-2.

1. Saharinen P, et al. *Nat Rev Drug Discov*. 2017;16:635-661; 2. Heier JS, et al. *Retina*. 2021;41:1-19;

Overexpression of Ang-2 can lead to vascular instability



Ang-2, angiopoietin-2; VEGF, vascular endothelial growth factor.

1. Heier JS, et al. *Retina.* 2021;41:1-19; 2. Saharinen P, et al. *Nat Rev Drug Discov*. 2017;16:635-661.

Real-world limitations of standard of care for DME

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Current standard of care for center-involved DME

Treatment guidelines

- Intravitreal anti-VEGF therapy is standard of care for patients with visual impairment due to CI-DME.[1,2]
- Laser photocoagulation is no longer recommended for CI-DME. [1,2]
- Intraocular corticosteroids are generally used as second-line agents, especially for phakic patients.[1,2]

Clinical findings

- In clinical trials, intravitreal VEGF inhibitors reduce edema, and improve and maintain VA compared with photocoagulation or sham injection.[2–5]
- Anti-VEGF therapy is generally well tolerated.[3–5]
- Intravitreal injections can be associated with a risk of rare serious complications such as endophthalmitis.[6]

Robust visual gains in clinical trials

- In pivotal trials, anti-VEGF therapy was associated with mean BCVA gains of 10.7–12.5 ETDRS letters at 1 year.[3,4]
- Across clinical studies, ~30–40% of patients receiving anti-VEGF therapy experienced an improvement of 3 or more lines of BCVA (≥15 letters) a 1 year.[3,4]

BCVA, best-corrected visual acuity; CI-DME, center-involved diabetic macular edema; ETDRS, Early Treatment Diabetic Retinopathy Study; VA, visual acuity; VEGF, vascular endothelial growth factor.

1. Schmidt-Erfurth U, et al. *Ophthalmologica*. 2017;237(4):185-222; 2. Flaxel CJ, et al. *Ophthalmology*. 2020;127(1):P66-P145; 3. Nguyen QD, et al. *Ophthalmology*. 2012;119(4):789-801; 4. Korobelnik JF, et al. *Ophthalmology*. 2014;121(11):2247-2254; 5. Virgili G, et al. *Cochrane Database Syst Rev.* 2017;6(6):CD007419; 6. McCannel CA. *Retina*. 2011:31:654-661.

Suboptimal visual outcomes in DME in real world practice

- Patients with DME treated in routine clinical practice receive fewer injections and achieve lower vision gains compared with those in anti-VEGF randomized clinical trials.[1,2]

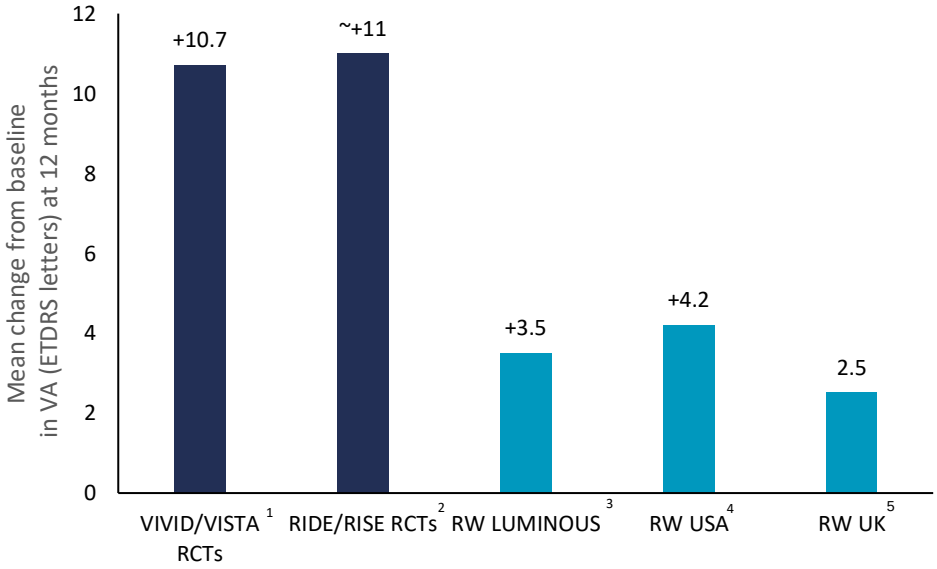
- Worse real-world visual outcomes are often attributed to undertreatment, marked by inconsistent or variable adherence to recommended treatment regimens.[1–4]

- Long-term data reveal that treatment intensity is lower, and vision and anatomic outcomes are poorer, than those observed in early efficacy trials, highlighting patient heterogeneity and variable treatment patterns in the real world.[3,4]

DME, diabetic macular edema; VEGF, vascular endothelial growth factor.

1. Ciulla TA, et al. *Br J Ophthalmol*. 2021;105(2):216-221; 2. Sivaprasad S, et al. *Eye (Lond)*. 2022;36(1):64-71; 3. Van Aken E, et al. *Clin Ophthalmol*. 2020;14:4173-4185; 4. Massin P, et al. *Ophthalmic Res*. 2021;64(4):577-586.

Vision gains with anti-VEGF in clinical practice vs trials in patients with DME



Mean no. of injections	8.4–8.7	12	4.5	6.4	6.4

The discrepancy between RCT and real-world outcomes[1–5] suggests that there is scope for improvement of visual outcomes in response to anti-VEGF therapy in clinical practice.

DME, diabetic macular edema; ETDRS, Early Treatment Diabetic Retinopathy Study; RCTs, randomized clinical trials; RW, real world; VA, visual acuity; VEGF, vascular endothelial growth factor.

1. Korobelnik JF, et al. *Ophthalmology*. 2014;121(11):2247-2254; 2. Nguyen QD, et al. *Ophthalmology*. 2012;119(4):789-801; 3. Mitchell P, et al. *PLoS ONE*. 2020;15(6):e0233595; 4. Ciulla TA, et al. *Br J Ophthalmol.* 2021;105(2):216-221; 5. Sivaprasad S, et al. *Eye (Lond).* 2022;36(1):64-71.

Impact of anti-VEGF treatment regimen on patient adherence

Retention of patients with DME is challenging in most clinical settings

Visit adherence

- Compliance and therapy adherence are key for good VA outcomes with continued anti-VEGF therapy in patients with DME.[1]
- Evidence shows suboptimal compliance:
  - Attendance rates vary: **35–85%.**[2]
  - Missed or delayed attendance: **14–51%.**[2]
  - Lost to follow-up:
    - **25%** over 12 months.[2]
    - **29%** over 3 years.[3]

Reasons for poor adherence

- Absenteeism for working patients.[4]
- Need for caregiver support for clinic visits and injection appointments.[4]
- Lack of transportation.[5]
- Comorbidities.[6]
- Anxiety and discomfort.[4,5]
- Lack of belief in treatment efficacy.[5]

DME, diabetic macula edema; VA, visual acuity; VEGF, vascular endothelial growth factor.

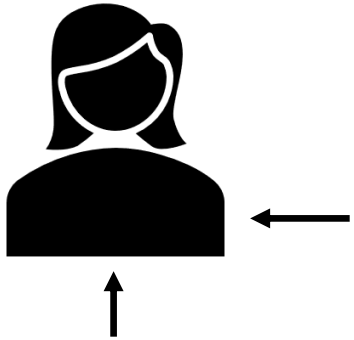
1. Ramakrishnan MS, et al. *Graefes Arch Clin Exp Ophthalmol.* 2021;259(6):1419-1425; 2. Rose MA, et al. *Clin Exp Ophthalmol.* 2020;48(9):1286-1298; 3. Talks SJ, et al. *Eye (Lond).* 2022;36(1):72-77; 4. Sivaprasad S, Oyetunde S. *Clin Ophthalmol.* 2016;10:939-46; 5. Ehlken C, et al. *Graefe's Arch Clin Exp Ophthalmol.* 2020;258:2077-2090; 6. Weiss M, et al. *Retina.* 2018;38(12):2293-2300.

Strategies to improve treatment adherence

Strategies are needed to reduce treatment burden and improve long-term outcomes

Explain goals and expectations

Patients should understand the goal of treatment and have realistic expectations for clinical benefits and required clinical visits.[1,2]



Maintain patient education

Provide support and maintain regular and recurrent patient education to ensure disease, treatment and complication details are retained.[1]

Clear communication

Direct communication between the patient and HCPs is required.[2]

DME, diabetic macular edema; HCP, healthcare practitioner; VA, visual acuity.

1. Ehlken C, et al. *Graefe's Arch Clin Exp Ophthalmol*. 2020;258:2077–2090; 2. Gale R, et al. *Eye (Lond).* 2017;31(S1):S1-S20.

The burden of current DME treatment

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Patient experience: treatment burden and heterogenous response

- Initial **loading phase of monthly intravitreal anti-VEGF injections**, followed by a flexible treatment regimen based on patient need (typically 8–9 injections in the first year).[1*]

- Both **as needed (PRN)** and **T&E** (guided by OCT and vision criteria) regimens are effective approaches compared with fixed dosing after an initial loading phase of monthly injections.[2,3*]

- Most patients respond well to anti-VEGF agents; however, approximately 30–40% of patients experience moderate or even poor responses requiring **continued intensive retreatment** (q4 or q8) **or alternative treatment**.[4–9]

*Treatment of patients in clinical practice settings may differ from the recommended posology for anti-VEGF agents in the treatment of DME. Please consult local guidance for relevant licensed regimens.

DME, diabetic macular edema; OCT; optical coherence tomography; PRN, pro re nata; T&E, treat-and-extend; VEGF, vascular endothelial growth factor.

1. Schmidt-Erfurth U, et al. *Ophthalmologica*. 2017;237(4):185-222; 2. Freund KB, et al. *Retina*. 2015;35(8):1489-506; 3. Payne JF, et al. *Am J Ophthalmol*. 2019;202:91-99; 4. Hirano T, et al. *Sci Rep*. 2021;11(1):4488; 5. Dugel PU, et al. *Retina*. 2019;39(1):88-97; 6. Bressler NM, et al. *JAMA Ophthalmol*. 2018;136(3):257-269; 7. Gonzalez VH, et al. *Am J Ophthalmol*. 2016;172:72-79; 8. Schmidt-Erfurth U, et al. *Ophthalmologica*. 2017;237(4):185-222; 9. Flaxel CJ, et al. *Ophthalmology*. 2020;127(1):P66-P145.

Bilateral treatment for fellow-eye involvement

- Bilateral treatment with intravitreal anti-VEGF injections for patients with DME is common.[1]

- Patients with DME are more likely to be treated bilaterally with anti-VEGF injections compared with patients with nAMD.[2]

- Same-day bilateral injection decreases the resource burden on the healthcare system and treatment burden experienced by patients.[2]

Lack of bilateral treatment a risk factor for noncompliance

- Being from an ethnic minority, lack for bilateral treatment, and poorer glycemic control have been identified as risk factors for noncompliance.[3]

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

1. Ness S, et al. *Graefes Arch Clin Exp Ophthalmol.* 2021;259(8):2203-2212; 2. Giocanti-Auregan A, et al. *BMC Ophthalmol.* 2016;16:142; 3. Agarwal D, et al. *Ophthalmic Surg Lasers Imaging Retina.* 2021;52(4):200-206.

Impact of reduced treatment burden

- Longer injection free-intervals remains as an unmet need not covered by current anti-VEGFs intravitreal therapies.[1]
- Providing sustained efficacy with decreased dosing frequency may help preserve visual gains in a clinical practice setting.[2]

- Extended flexible dosing may provide a more acceptable management regimen with decreased treatment exposure, reducing the clinic appointment and monitoring burden.[3]
- Reduced burden on patients and caregivers is expected to improve treatment compliance and ultimately result in better visual outcomes.[4]

- Quarterly or longer intravitreal dosing regimens are simpler to schedule and implement than more intensive treatment protocols.[5]
- Decreased treatment burden has the potential to help release resources and clinic capacity for expanded service and care provision.

1. Adamis AP, et al. *Eye (Lond).* 2020;34:1966-1972; 2. Sahni J, et al. *Ophthalmology*. 2019;126(8):1155-1170; 3. Wykoff CC, et al. *Lancet*. 2022;399(10326):741-755; 4. Ramakrishnan MS, et al. *Graefes Arch Clin Exp Ophthalmol.* 2021;259(6):1419-1425; 5. Freund KB, et al. *Retina*. 2015;35(8):1489-506;

General health of patients with DME

Engaging collaborative multidisciplinary teams early may help to improve patient outcomes.[1]

Complex, highly comorbid profiles

- Patients with DR and DME often have complex comorbidity profiles associated with diabetes-related complications.[1,2]
- Real-world patients with diabetes generally suffer from more comorbidities, have poorer glycemic control and health literacy, and varied socioeconomic or cultural backgrounds compared with clinical trial patients.[3]

Systemic control demands collaborative engagement

- Patients with DME frequently have CV risk factors that are poorly controlled,[4] highlighting the opportunity for improving care by multidisciplinary interaction for detection and treatment of these conditions.[1]
- Appropriate consideration needs to be given to systemic comorbidities, with specific attention to control of blood sugar (HbA1c), blood pressure, serum lipids, body weight, renal disease, coronary artery disease, and neuropathy.[2,5]

CV, cardiovascular; DME, diabetic macular edema, DR, diabetic retinopathy; HbA1c, hemoglobin A1c.

1. Strain WD, et al. *Diabetes Res Clin Pract*. 2017;126:1-9; 2. Schmidt-Erfurth U, et al. *Ophthalmologica*. 2017;237(4):185-222; 3. Okada M. *Eye (Lond)*. 2022;36(1):1-2; 4. Busch C, et al. *PLoS One*. 2021;16(6):e0252321; 5. Flaxel CJ, et al. *Ophthalmology*. 2020;127(1):P66-P145.

Conclusions: Addressing unmet needs in DME

Innovative strategies are needed to improve visual and anatomic outcomes, while reducing treatment burden.[1,2]

- DME is a multifactorial disease, driven by a range of molecular pathways beyond VEGF.[3,4]
- Limited improvement in disease outcomes with multiple anti-VEGF treatments highlights the need for further innovation in DME.[1-3]
- Visual and anatomic outcomes are difficult to maintain long term with current therapies due to high frequency of injections.[5-8]
- There is a need for more durable therapies and technologies that extend time between treatments without compromising efficacy.[1,2,9,10]

VEGF, vascular endothelial growth factor.

1. Adamis AP, et al. *Eye (Lond).* 2020;34(11):1966-1972; 2. Heier JS, et al. *Retina*. 2021;41:1-19. 3. Urias EA, et al. *Vision Res.* 2017;139:221-227;
4. Das A, et al. *Ophthalmology*. 2015;122(7):1375-1394; 5. Ciulla TA, et al. *Br J Ophthalmol*. 2021;105(2):216-221; 6. Sivaprasad S, et al. *Eye (Lond).* 2022;36(1):64-71;
7. Van Aken E, et al. *Clin Ophthalmol.* 2020;14:4173-4185; 8. Massin P, et al. *Ophthalmic Res.* 2021;64(4):577-586; 9. Wykoff CC, et al. *Lancet*. 2022;399(10326):741-755;
10. Tan GS, et al. *Lancet Diabetes Endocrinol*. 2017;5(2):143-155.

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