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Age-related Macular Degeneration and Diabetic Macular Edema Highlights – American Academy of Ophthalmology 2024

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The **American Academy of Ophthalmology (AAO)** annual meeting was held in **Chicago** on **18–21 October** and included subspecialty days on 18–19 October. **Retina 2024** had twenty sections featuring a wide range of retinal diseases and treatments, including age-related macular degeneration (AMD) and diabetic macular edema (DME).

Age-related macular degeneration

Update on the treatment of AMD

Dr Daniel Martin presented an update on treatment advances for AMD. Faricimab and aflibercept 8 mg are the latest anti-vascular endothelial growth factor (anti-VEGF) agents; however, their true durability has yet to be assessed, and a head-to-head comparison has not been undertaken. For geographic atrophy (GA), pegcetacoplan and avacincaptad pegol are approved and show a modest reduction in GA growth. However, notable adverse events are the conversion to neovascular AMD (nAMD) and severe occlusive retinal vasculitis, which have contributed to limited acceptance of these drugs among physicians. Several ongoing Phase III randomized clinical trials (RCTs) for AMD are investigating tyrosine kinase inhibitors (TKIs), anti-VEGF C/D, gene therapy and the port delivery system.[1]

Impact of disease activity criteria on dosing interval in patients with neovascular AMD

Dr Marco Zarbin discussed how the definition of active disease in clinical trials affects estimates of drug durability in RCTs. Disease activity criteria – change in vision, central macular thickness (CMT), fluid on OCT, and/or other anatomic criteria – can significantly impact dosing interval adjustments and durability outcomes in patients with neurovascular AMD. The TENAYA and LUCERNE trials, which defined active disease in a manner closer to that used in clinical practice, indicated that 78% of patients achieved a dosing interval of ≥Q12W by Week 20/24. In contrast, a post hoc analysis based on disease activity criteria derived from the PULSAR trial suggested that 96% of patients would have achieved a dosing interval ≥Q12W by Week 20. Similar findings have been reported for faricimab. RCT disease activity criteria that closely align with real-world clinical practice may more accurately reflect actual reductions in treatment burden.[2]

EYP-1901 for the treatment of neovascular AMD: Phase 2 DAVIO 2 EOT 12-month results

Dr Carl Regillo presented results of the DAVIO 2 trial evaluating the safety and efficacy of EYP-1901 for previously treated wet age-related macular degeneration (wAMD). EYP-1901 is a bioerodible intravitreal insert that delivers a sustained dose of the TKI vorolanib over an extended duration. A single dose of EYP-1901 demonstrated statistical noninferiority to aflibercept Q8W in eyes with wAMD, with stable BCVA, strong anatomical control, reduced treatment burden (≥80% over 12 months vs pre-trial treatment) and a favorable safety profile. Pivotal Phase III global trials of EYP-1901 in wAMD commenced in the second half of 2024.[3]

Subretinal delivery of investigational ABBV-RGX-314 as a gene therapy for nAMD: First-time results of a fellow eye bilateral dosing study

Dr Arshad Khanani presented 9-month results of investigational ABBV-RGX-314 gene therapy in nAMD, marking the first time a fellow eye was dosed with gene therapy for this condition. Key considerations included the potential effect of pre-existing antibodies to the AAV vector. Second eyes treated with ABBV-RGX-314 achieved similar safety and efficacy outcomes compared to first eyes. The treatment was well tolerated, with sustained vision and anatomy, and similar protein production. This led to a meaningful reduction in anti-VEGF injections, with 78% of patients remaining injection-free and a 97% reduction in anti-VEGF treatment burden. The treatment of the second eye for a common disease using gene therapy represents a milestone.[4]

Restoret (EYE103) for the treatment of DME and nAMD: First-time extended results from the AMARONE Phase 1b/2a clinical trial

Dr Charles Wykhoff presented six-month safety extension results from the Phase IB/IIA AMARONE clinical trial. Restoret is a Norrin mimetic that acts as a Wnt pathway agonist and is well tolerated, showing no safety signals after 123 injections. Monotherapy in patients with DME through Week 12 resulted in a mean +11.2 letters and –143 µm reduction of CST on OCT. Combination therapy with aflibercept 2 mg in patients with nAMD demonstrated encouraging safety and efficacy. Wnt agonists may represent a potentially effective treatment independent of anti-VEGF.[5]

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Diabetic macular edema

Update on the treatment of DME

Dr Jennifer Sun provided an update on the latest advances in treating DME. Current evidence-based care is guided by multiple RCTs, allowing for treatment to be tailored to baseline visual acuity (VA). Recent pivotal trials RHONE X and PHOTON have demonstrated that faricimab and aflibercept 8 mg may allow for extended dosing while producing similar VA gains when compared to aflibercept 2 mg. Additionally, many biosimilars are now approved for the reference biologics, ranibizumab and aflibercept. In the past two years, sixteen clinical trials have been completed, with 87 currently active, focusing on alternative mechanisms to anti-VEGF, delivery routes, and durability.[6]

Treatment response and safety of faricimab in underrepresented patients with DME: Year 1 results from the ELEVATUM trial

Dr Jeremiah Brown presented results of the first industry-sponsored Phase IV trial in retinal research focused exclusively on underrepresented patients. Results were consistent with those of YOSEMITE and RHINE, demonstrating robust gains in VA and improved central subfield thickness (CST) for African American and Hispanic Latino patients. Faricimab was also well tolerated. Hispanic Latino patients had worse disease at baseline yet showed the greatest improvements in best corrected visual acuity (BCVA), central subfield thickness (CST) and diabetic retinopathy (DR) disease severity. Looking ahead, segmentation and AI tools will be used to assess biomarkers, while the impact of Ang-2 inhibition on disease progression and extended durability will be assessed in a long-term extension study.[7]

Aflibercept 8 mg in DME: Key results from the PHOTON extension study

Dr Diana Do presented key results from Week 156 of the PHOTON extension study showing that patients in the 8q12/8q16 group maintained the visual and anatomic improvements achieved in the first two years, with the majority on extended dosing intervals. In the 2q8→8 mg group, the visual and anatomic improvements achieved with fixed 2q8 dosing were maintained with aflibercept 8 mg. No new safety signals through Week 156 were reported.[8]

Phase IIA results of RZ402: A novel oral plasma kallikrein inhibitor shows promise for DME treatment

Dr Joel Pearlman presented Phase IIA results of RZ402, the first plasma kallikrein inhibitor and oral therapy of any class to demonstrate CST improvement in patients with DME. In diabetes, plasma kallikrein may form part of a secondary pathway to macular edema independent of VEGF. RZ402 may augment the effects of anti-VEGF, allow for systemic treatment, and provide an opportunity for early intervention. RZ402 led to a clinically significant reduction in CST at all dose levels in study eyes, with a lesser effect observed in fellow eyes. With a three-month study duration, no improvements in VA were expected. RZ402 was well tolerated and demonstrated systemic safety. The results support advancement into a longer phase IIB/III trial.[9]

Management of DME in an era of faricimab, aflibercept 8 mg, and biosimilars

Dr Neil Bressler reviewed the role of biosimilar ranibizumab which reduces treatment costs with non-inferior VA outcomes; however, it has not yet demonstrated the same safety duration as reference products. Additionally, there is no definitive evidence that switching to newer agents yields long-term VA benefits.[10]

Randomized trial of MYL-1701P (proposed aflibercept biosimilar) vs. aflibercept through 76 weeks in DME, including switch from aflibercept

Dr Susan Bressler presented results from an open-label extension study of MYL-1701P (aflibercept-jbvf, an FDA-approved biosimilar), which included a subgroup of Indian patients switched from reference aflibercept to MYL-1701P. The primary endpoint was treatment-emergent adverse events. Similar safety, efficacy, and immunogenicity profiles were observed between patients who continued on MYL-1701P and those who switched from reference aflibercept. Furthermore, no new safety signals were identified, and the immunogenicity potential of MYL-1701P remained low across both the pivotal efficacy study and the extension study, including the subset of participants assigned to switch from originator to biosimilar. Sustained improvements in efficacy, even after switching to MYL-1701P, suggest that biosimilars, as a less expensive alternative to originator biologic products, could potentially improve patient access and treatment compliance.[11]

Clinical trials testing anti-angiogenic agents change our thinking about the pathogenesis of disease

Dr Mary Elizabeth Hartnett emphasized the need to refine existing hypotheses and develop new ones regarding the mechanism of action by critically reviewing human clinical trial data from basic scientists, as animal models can be unrepresentative of human disease. There is a heightened need for collaboration between basic scientists and clinicians to enhance understanding of angiogenesis and improve patient management. Dr Hartnett proposed that inflammatory pathways and signalling systems such as plasma kallikrein, the Tie2 receptor, chemokines, and the Wnt pathway

play significant roles in DME, in addition to the anti-permeability effects of anti-VEGF. In ROP, anti-VEGF can, paradoxically, facilitate developmental angiogenesis by regulating VEGFR2 pathways and pathological signalling at the VEGF receptor level in endothelial cells, without affecting physiological growth. Infants treated with anti-VEGFs rather than laser therapy showed greater extension of vascularization compared to natural history at two months post treatment. Dr Hartnett also cautioned that blocking the VEGF excessively can lead to neuronal damage and dysfunction.[12]

What's in the pipeline for diabetic retinopathy

Dr David Boyer provided an interesting look at the latest drugs in the pipeline for DR, where new treatments are needed as 40% of eyes have suboptimal responses. TKIs are being considered to reduce the treatment burden to one injection every six months. OPT-302 targets VEGF-C and -D as part of combination therapy and has improved DME outcomes compared to aflibercept 2 mg monotherapy. The Norrin mimetic/Wnt agonist, Restoret, has produced exceptional results thus far, targeting a different pathway. The topical treatment, OCS-0, a dexamethasone eye drop for DME, has recently met its primary endpoint. The ALTITUDE and SPECTRA gene therapy studies show results comparable to anti-VEGF therapy. Many drugs are using combinations or new mechanisms of action such as AG-73305 which has a bispecific antibody design. Senescent cells that accumulate in areas of disease activity and secrete inflammatory factors are also being targeted (UBV-1325). APX3330 is a Ref-1 inhibitor given as an oral medication to reduce visual loss. Finally, research is also focusing on endothelin-1 agonists to reduce retinal vascular ischemia.[13]

References

1. Daniel F Martin. Update on the Treatment of AMD. Speaker presented at: American Academy of Ophthalmology 2024; October 18, 2024; Chicago.
2. Marco A Zarbin. Impact of Disease Activity Criteria on Dosing Interval in Patients with Neovascular AMD. Speaker presented at: American Academy of Ophthalmology 2024; October 18, 2024; Chicago.
3. Carl D Regillo. EYP-1901 for the Treatment of Neovascular AMD: Phase 2 DAVIO 2 End-of-Trial 12-Month Results. Speaker presented at: American Academy of Ophthalmology 2024; October 18, 2024; Chicago.
4. Arshad M Khanani. Subretinal Delivery of Investigational ABBVRGX-314 as a Gene Therapy for nAMD: First-Time Results of a Fellow Eye Bilateral Dosing Study. Speaker presented at: American Academy of Ophthalmology 2024; October 19, 2024; Chicago.
5. Charles C Wykoff. Restoret (EYE103) for the Treatment of Diabetic Macular Edema and Neovascular AMD: First-time Extended Results From the AMARONE Phase 1b/2a Clinical Trial. Speaker presented at: American Academy of Ophthalmology 2024; October 18, 2024; Chicago.
6. Jennifer K Sun. Update on the Treatment of Diabetic Macular Edema. Speaker presented at: American Academy of Ophthalmology 2024; October 18, 2024; Chicago.
7. Jeremiah Brown. Treatment Response and Safety of Faricimab in Underrepresented Patients with DME: Year 1 Results from ELEVATUM in the US. Speaker presented at: American Academy of Ophthalmology 2024; October 18, 2024; Chicago.
8. Diana V Do. Aflibercept 8 mg in DME: Key Results from the PHOTON Extension Study. Speaker presented at: American Academy of Ophthalmology 2024; October 18, 2024; Chicago.
9. Joel A Pearlman. Results from a Phase 2a Study of a Novel Orally Administered RZ402 a Plasma Kallikrein Inhibitor in Patients With Diabetic Macular Edema. Speaker presented at: American Academy of Ophthalmology 2024; October 18, 2024; Chicago.
10. Neil M Bressler. Management of Diabetic Macular Edema in an Era of Faricimab, Aflibercept 8 mg, and Biosimilars. Speaker presented at: American Academy of Ophthalmology 2024; October 19, 2024; Chicago.
11. Susan B. Bressler. Randomized Trial of MYL-1701P (Proposed Aflibercept Biosimilar) vs. Aflibercept Through 76 Weeks in DME, Including Switch From Aflibercept. Scientific Poster presented at: American Academy of Ophthalmology 2024; October 19, 2024; Chicago.
12. Mary E Hartnett. Clinical Trials Testing Anti-angiogenic Agents Change Our Thinking About the Pathogenesis of Disease. Speaker presented at: American Academy of Ophthalmology 2024; October 19, 2024; Chicago.
13. David S Boyer. What's in the Pipeline for Diabetic Retinopathy. Speaker presented at: American Academy of Ophthalmology 2024; October 19, 2024; Chicago.