MODULE 9.10
Future Therapies and Imaging Techniques

Diabetic macular edema (DME) is currently an area of intense research and development. Several new agents for the treatment of DME are on the horizon (see Table 1).

Conbercept is a recombinant fusion protein composed of the second immunoglobulin (Ig) domain of vascular endothelial growth factor–receptor 1 (VEGFR1) and the third and fourth Ig domain of VEGFR2 to the constant region (Fc) of human immunoglobulin G1 (IgG1).[1,2] The inhibitory effects of conbercept on VEGF have been evaluated in vitro and vivo (NCT02194634), indicating that it has potent antiangiogenic and antitumor effects.

Abicipar pegol (previously called AGN-150998 or MP0112) is a long-acting potent VEGF antagonist.[3] A phase 2 study in patients with wet age-related macular degeneration (AMD), showed that abicipar pegol, comapred with ranibizumab, provided equal or potentially higher gains in vision.

PF-655 is a synthetic small interfering RNA (siRNA) that targets the gene RTP801, which is overexpressed in patients with wet AMD and diabetic retinopathy (DR).[4] The agent is under investigation in the DEGAS (NCT00701181) and MATISSE (NCT01555710) studies.

Squalamine is an antiangiogenic small molecule, which counteracts multiple growth factors and pathways implicated in the angiogenic process, including vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF), and basic fibroblast growth factor (bFGF).[5] The IMPACT study showed squalamine eye drops administered in combination with ranibizumab PRN improved visual outcomes and reduced the treatment frequency of ranibizumab in patients with treatment- naïve wet AMD.

AKB-9778 appears to activate the Tie-2 pathway, a key control axis for retinal vascular stability.[4] Tie-2 activation, through VEGF suppression may also block development of choroidal neovascularization (CNV) and promote regression of new CNV, particularly when the agent is used in combination with anti-VEGF agents.

ALG-1001 is a synthetic anti-integrin oligopeptide that inhibits integrin receptors in vitro.[6] The compound arrests aberrant blood vessel growth in vivo meditated by αvβ3, αvβ5, as well as α2β1 and α5β1 - integrin sites that are expressed in neovascular ocular tissue from patients with wet AMD and DR. In a small study by Boyer and colleagues,[6] 8 of 15 patients reported a 3-line or more increase in best-correct visual acuity (BCVA) after receiving 3 injections with up to a corresponding 83% reduction in central macular thickness on optical coherence tomography (OCT).

Systemic therapies for DME target the key modifiable risk factors, such as metabolic and blood pressure control.[7] Improved glycemic and blood pressure control remain the most effective ways of reducing morbidity from DME. There may also be a role for modulation of the renin-angiotensin system and for lipid lowering agents. For example, the lipid lowering agent fenofibrate has beneficial effects in terms of the requirement for first laser and the development of DME, but the mechanisms for this are unclear.

New technologies for retinal imaging are providing insights into the progression of DR and DME. Swept-source OCT (SS-OCT; DRI-OCT; Topcon; Japan) has recently been introduced.[8] This instrument utilizes a longer wavelength to overcome scattering by the retinal pigment epithelium, which previously did not allow for visualization of deeper retinal structures. Using a longer wavelength of light also helps to overcome cataractous lens opacities and allows visualization of the macula. This capability may enhance the retinal specialist's ability to identify patients who require treatment beyond simple cataract surgery.

Table 1: New Therapeutic Agents Under Development for the Treatment of DME.

From Simo et al, 20142

Drug	Target	Phase	Indication	Notes
Conbercept (KH902) (Human recombinant VEGF-Fc fusion protein)	Decoy receptor protein constructed by fusing VEGF receptor 1 and VEGF receptor 2 extracellular domains with the Fc region of human immunoglobulin	Approved (China only)	Neovascular Age-related Macular Degeneration (Approved only in China), P3 for Diabetic Macular Edema, Myopic CNV	Blocks all VEGF-A isoforms, as well as VEGF-B, VEGF-C, and PlGF and has the longest half-life of any anti-VEGF agent. In phase 2 trial, After the initial 3 injections, only 2 or 3 injections were needed until month 12 by patients in the prn treatment group.
Abicipar Pegol (AGN-150998) (anti-VEGF DARPin)	anti-VEGF DARPin	II	Neovascular Age Related Macular Degeneration	Will initiate Phase 3 studies in the second quarter of 2015.
PF-655 (REDD14NP, RTP801i) (Synthetic siRNA inhibitor of HIF-1 responsive gene)	CCR2/5 receptor antagonist	II	Diabetic Macular Edema	In combination with Ranibizumab
Squalamine lactate eye drops (small molecule targets VEGF, PDGF, bFGF)	VEGF, PDGF, bFGF	II	Neovascular Age Related Macular Degeneration, Diabetic Macular Edema, proliferative diabetic retinopathy	Planned interim analysis: There were no significant differences in the frequency of Lucentis PRN injections, which was the primary endpoint of the exploratory Phase II study, but visual outcomes were promising.
AKB-9778 (Tie2 activator)	Tie2 activator	II	Diabetic Macular Edema	Works by inhibiting the human protein tyrosine phosphatase β (HPTPβ) enzyme, which acts as a negative regulator of the Tie2 receptor. The TIME-2 study (Phase 2), initiated to confirm the efficacy of AKB-9778 alone and in combination with ranibizumab in patients with DME, is currently ongoing. "AKB-9778, reduces abnormal blood vessel growth and leakage in mouse models of ophthalmic diseases, such as diabetic macular edema (DME) and age-related macular degeneration"
ALG-1001 (Oligopeptide targeting α5β1, αvβ3, αvβ5 and α2β1 integrins)	Oligopeptide targeting α5β1, αvβ3, αvβ5 and α2β1 integrins	I / II	Neovascular Age-Related Macular Degeneration, Diabetic Macular Edema	ALG-1001 is an integrin antagonist that blocks all the integrin α-β combinations. In the ALG-1001 phase Ib/IIa monotherapy trials for wet AMD — which were primarily designed to test safety — investigators also saw very good efficacy, even in patients who had already had multiple previous anti-VEGF injections.

References

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