

Advances in retinal disease therapy: What's new and what's coming.

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Current treatment options

1. Anti-VEGF Therapies

Anti-VEGF (vascular endothelial growth factor) therapies are the cornerstone for treating retinal diseases such as Wet AMD, DME, and MEfRVO. VEGF is a signaling protein that promotes blood vessel formation (angiogenesis) and increases vascular permeability, leading to fluid leakage and retinal swelling.

Key Anti-VEGF Agents

1. Avastin (Bevacizumab)

- Mechanism: Monoclonal antibody that binds VEGF-A, neutralizing its activity and preventing interaction with VEGF receptors (VEGFR-1 and VEGFR-2) on endothelial cells.
- Outcome: Inhibition of abnormal blood vessel growth and reduction in vascular permeability.

2. Lucentis (Ranibizumab)

- Mechanism: A smaller monoclonal antibody fragment (Fab) specifically designed for

intraocular use, binding VEGF-A with high affinity.

- Advantage: Small size allows for better retinal penetration compared to full-length antibodies like Avastin.
- Outcome: Reduction in leakage and stabilization or improvement of vision.

3. Eylea (Aflibercept)

- Mechanism: A fusion protein that acts as a VEGF trap. It binds both VEGF-A and placental growth factor (PlGF), blocking their interaction with VEGFR-1 and VEGFR-2.
- Advantage: High binding affinity and broader inhibition compared to other anti-VEGF drugs.
- Outcome: Prolonged suppression of vascular leakage and neovascularization.

4. Beovu (Brolucizumab)

- Mechanism: A single-chain antibody fragment with high binding capacity for VEGF-A, leading to sustained VEGF inhibition.
- Unique Feature: Smaller molecular size allows higher drug concentration per injection, enabling longer dosing intervals.
- Limitation: Rare but significant risk of retinal inflammation and vascular occlusion.

5. Vabysmo (Faricimab)

- Mechanism: Dual inhibition of VEGF-A and Angiopoietin-2 (Ang2).
 - VEGF-A: Promotes angiogenesis and vascular leakage.
 - Ang2: Destabilizes blood vessels by disrupting the interaction between Tie-2 receptors and Ang1, making vessels more vulnerable to VEGF-induced leakage.
- Outcome: Stabilization of blood vessels, reduced leakage, and improved durability of treatment.

6. Eylea HD (Aflibercept 8mg)

- Mechanism: Similar to standard Eylea but with a higher drug concentration for longer VEGF suppression.

2. Corticosteroid Therapies

Corticosteroids reduce inflammation, vascular permeability, and edema by inhibiting multiple inflammatory pathways.

Key Agents

1. Triamcinolone (Kenalog, Triescence)

- Mechanism: Binds glucocorticoid receptors, suppressing pro-inflammatory cytokines like interleukin-1 (IL-1), tumor necrosis factor-alpha (TNF- α), and VEGF.
- Outcome: Decreased vascular permeability and resolution of macular edema.

2. Ozurdex Implant (Dexamethasone)

- Mechanism: Gradual release of dexamethasone, a potent corticosteroid, into the vitreous cavity.
- Effects: Long-term suppression of inflammation and edema with fewer injections.

3. Iluvien Implant (Fluocinolone Acetonide)

- Mechanism: Continuous low-dose release of a corticosteroid targeting chronic inflammation in DME.
- Outcome: Prolonged reduction of edema and improvement in vision over years.

4. Yutiq Implant

- Mechanism: Fluocinolone implant specifically designed for chronic non-infectious uveitis, releasing corticosteroids for up to 36 months.

3. Complement Inhibitors for Geographic Atrophy (GA)

In GA, excessive activation of the complement cascade contributes to chronic inflammation and progressive retinal degeneration.

Key Agents

1. Syfovre (Pegcetacoplan)

- Mechanism: Inhibits complement component 3 (C3), a central protein in the complement cascade.
- Rationale: Reducing C3 activation prevents downstream formation of pro-inflammatory proteins (C3a, C5a) and membrane attack complexes (MAC), which damage retinal cells.
- Outcome: Slows progression of GA and protects retinal tissue.

2. Izervay (Avacincaptad Pegol)

- Mechanism: Targets complement C5, preventing the formation of the MAC.
- Outcome: Reduces retinal cell death and preserves vision.

4. Gene Therapy for Retinal Diseases

Gene therapies aim to address the root cause of inherited or chronic retinal diseases by delivering functional genes to the retina.

Key Agents

1. Luxturna (Voretigene Neparvovec-rzyl)

- Mechanism: Delivers a functional RPE65 gene to retinal pigment epithelial cells via an adeno-associated virus (AAV) vector.
- Indication: Treats biallelic RPE65 mutation-associated retinal dystrophy.
- Outcome: Restores the ability of retinal cells to regenerate 11-cis-retinal, a key molecule in the visual cycle.

2. ABBV-RGX-314

- Mechanism: AAV vector delivers a gene encoding an anti-VEGF protein, enabling continuous VEGF suppression.
- Routes: Administered via subretinal or suprachoroidal injection.

3. Ixo-Vec (Ixoberogene Soroparvovec)

- Mechanism: AAV-based gene therapy designed for intravitreal administration, producing anti-VEGF molecules directly in retinal cells.
- Potential: Long-term reduction in treatment burden for Wet AMD.

5. Stem Cell Therapies

Stem cell-based approaches focus on replacing damaged retinal cells and restoring retinal function.

1. Stem Cell Patches for GA and Stargardt Disease

- Mechanism: Implantation of retinal pigment epithelium (RPE) cells derived from stem cells onto the damaged retina.
- Rationale: Replace dysfunctional RPE cells responsible for maintaining photoreceptor health.
- Outcome: Potential restoration of visual function and slowing of disease progression.

6. Dual-Targeting Therapies

Dual-targeting therapies like Vabysmo are emerging as advanced solutions that address multiple pathways contributing to retinal diseases:

- **VEGF-A Inhibition:** Reduces angiogenesis and vascular permeability.
- **Ang2 Inhibition:** Stabilizes blood vessels, reducing inflammation and leakage.

7. Emerging Drug Delivery Systems

1. PDS-Susvimo (Ranibizumab Implant)

- Mechanism: Refillable ocular implant that continuously delivers ranibizumab to the retina.

- Advantage: Reduces treatment burden by replacing frequent injections with refills every 6 months.

2. Iluvien and Ozurdex Implants:

- Mechanism: Sustained-release corticosteroid implants gradually release drugs over months to years, targeting chronic inflammation