Update on Clinical Trials for Retinal Diseases

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Agenda
- Wet AMD I
- Diabetic Retinopathy
- Wet AMD II
- Dry AMD
- Inherited Retinal Diseases

Current Treatment-Wet AMD

Anti-VEGF Drugs
- Ranibizumab
- Aflibercept
- Bevacizumab (Not FDA approved)

Recent/Ongoing New Treatments-Wet AMD

Focus on other growth factors
- PDGF
- Angiopoietins

Long-acting delivery

Sprouting choroidal vessels in neovascular AMD cause PDGF-mediated pericyte recruitment that stabilizes pathologic vasculature

Cheung, I.B. Lobov, G. Yancopoulos and S. Wiegand.
In preclinical studies, REGN2176 (anti-PDGF mab) removed pericytes from pathologic vessels which may increase sensitivity to anti-angiogenic agents.

**Update on Clinical Trials**

**Angiopoietin**

Angiopoietin molecules and their tyrosine protein kinase receptor Tie-2 have been shown to play a crucial role in angiogenesis, have been identified in surgically excised CNVMs, and also provide a link between angiogenic and inflammatory pathways. Anti-angiopoietin molecules are being studied in various cancers as well as other angiogenic diseases such as AMD.

**Update on Clinical Trials**

2016: The year of the anti-PDGF “Flame-Out”

2 clinical trials failed

Future of anti-PDGF therapy in question

**Angiopoietin/Tie2 Signaling Pathway**

- **Tie2** is an endothelial cell-specific tyrosine kinase receptor to which two ligands bind:
  - Ang1 – Expressed in normal adult tissue to help maintain vascular integrity
  - Ang2 – Only expressed under pathological conditions. Modifies Tie-2 signaling in a context-dependent way

**Effect of IVT Administration of Nesvacumab, Alone OR in Combination with Aflibercept in a Retinal Vascular Development Model**

Area of the superficial retinal plexus

Total length of vessels of superficial retinal plexus

P0 (postnatal day 0), P1 (postnatal day 1)
Update on Clinical Trials

Recent/Ongoing Clinical Trials-Wet AMD
2 Anti-VEGF/Anti-angiopoietin formulations under study (Both also studied in DME)
Co-formulation of anti-Ang2 and anti-VEGF: phase 2 trial failed primary endpoint and program terminated
Bispecific monoclonal antibody: 2 trials completed recruitment, at or near final analysis; should hear results soon

LADDER Trial
A Phase II, Multicenter, Randomized, Active Treatment-Controlled Study of the Efficacy and Safety of the Ranibizumab Port Delivery System (RPDS) for Sustained Delivery of Ranibizumab in Patients With Subfoveal Neovascular AMD
Phase II/200 patients/60 sites
4 arms: Monthly ranibizumab IVI and 3 fill doses of the RPDS
Patients evaluated monthly
RPDS refilled per protocol-defined refill criteria
9 month study
Fully enrolled as of July, 2017; awaiting results

Current Treatment-Diabetic Retinopathy
Ranibizumab FDA approved for both DME and Diabetic Retinopathy (DR)
Aflibercept FDA approved for DME
Bevacizumab (Not FDA approved)
Dexamethasone Intravitreal Implant (FDA+ DME)
Fluocinolone Acetonide Intravitreal Implant (FDA+ DME)

Two Ongoing Studies-Aflibercept

PANORAMA
- Phase 1 (single intravitreal, no dilution, patients with non-proliferative DR and severe NPDR)
- 3 cycles of aflibercept
- Week 24 (primary endpoint: proportion of patients improving ≥2 steps on DRSS)
- Week 52 (primary endpoint: proportion of patients improving ≥2 steps on DRSS)
- Week 100 (secondary endpoint)

PROTOCOL W
- Aflibercept IVI for the treatment of diabetic macular edema
- Primary outcome: % eyes with ≥2 step improvement in ETDRS visual acuity over 2 years
- Study expected to finish in 2019
Update on Clinical Trials

Recent/Ongoing Clinical Trials - Diabetes (DME)

- Anti-VEGF therapy has improved diabetes-related vision loss
- Angiopoietin-2 is an angiogenic factor and a potential regulator of inflammatory pathways
- Is there potential to further improve visual outcomes with combination therapy?

Update on Clinical Trials

Recent/Ongoing Clinical Trials - Diabetes (DME)

- 2 Anti-VEGF/Anti-angiopoietin formulations under study (both also studied in wet AMD)
- Co-formulation of anti-Ang2 and anti-VEGF: phase 2 trial failed primary endpoint and program terminated Late 2017
- Bispecific monoclonal antibody: Phase 2 completed recruitment, at or near final analysis; results 2018

Update on Clinical Trials

Wet AMD

Brolucizumab

- Designed Ankryen Repeat Proteins (DARPin)
- Gene Therapy

Update on Clinical Trials

Wet AMD

Brolucizumab

- Designed to have longer durability to reduce injection frequency and number of visits
- Pivotal phase 3 data available

Molecular Sizes of Anti-VEGF Agents

<table>
<thead>
<tr>
<th>Name</th>
<th>Unbound</th>
<th>Fc-Trimmed</th>
<th>Full-length Fusion Proteins</th>
<th>Single-chain Antibody</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-VEGF 1</td>
<td>1,125 kDa</td>
<td>75 kDa</td>
<td>480 kDa</td>
<td>60 kDa</td>
</tr>
<tr>
<td>Anti-VEGF 2</td>
<td>1,250 kDa</td>
<td>70 kDa</td>
<td>450 kDa</td>
<td>60 kDa</td>
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</tbody>
</table>

* Molecular weight represented as a range to reflect phase I/IIa data
Complementarity-determining regions (CDRs) are part of the variable chains in antibodies where these molecules bind to their specific antigen.

**Potential Clinical Implications of Molecular Characteristics of Brolucizumab**

- Unique in design, as any antibody can have CDRs duplicated and grafted onto the single-chain antibody fragment
- Allows for a greater dosing because it includes the greatest molar amount that can be dosed into the target at this time
- Potentially a greater drug effect more rapidly
- Hypothetically a greater durability than with previous anti-VEGF treatments

**BCVA Change From Baseline Over Time**

**Central Subfield Thickness**

**Proportion of Patients Maintaining Every 12 Week Dosing of Brolucizumab at 48 Weeks**

**Relevance of Clinical Trial Results**

- Brolucizumab showed better anatomic results in comparison with aflibercept
  - Improved disease control
- A majority of patients could be extended to 12-week dosing while maintaining a superior anatomic result vs aflibercept
  - Lower sustainable treatment regimen
Designed Ankyrin Repeat Protein (DARPin®): Abicipar Pegol

- DARPin® is a drug class of genetically engineered binding proteins derived from natural ankyrin repeat proteins
  - Mimics antibodies, with greater stability and at least equal affinity with immunoglobulins
  - Small molecules with high potency, stability, and solubility
- Abicipar pegol is a DARPin® in development for nAMD
  - Recombinant protein of the designed ankyrin repeat protein family
  - Inhibits VEGF-A

Gene Therapy in nAMD

- Genetic material is incorporated into cells
  - To compensate for abnormal genes
  - To produce beneficial proteins
- Use of a viral vector
  - Integrating vectors (e.g., lentiviral vectors) insert themselves into the recipient’s genome
  - Nonintegrating vectors (e.g., adenovirus) usually form episomes in the transduced cell

Abicipar Pegol: REACH Phase 2 Clinical Study Visual Acuity Results

- Patients received abicipar pegol 2 mg (n = 23), 1 mg (n = 25), or ranibizumab (n = 16) and were followed for 20 weeks
- Intravitreal injections of day 1, weeks 4 and 8 (abicipar or ranibizumab), and also weeks 12 and 16 (ranibizumab only)

<table>
<thead>
<tr>
<th>Week 16 (primary endpoint)</th>
<th>Abicipar 2 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>BCVA Letter Gain</td>
<td>8.2</td>
</tr>
<tr>
<td>Abicipar 1 mg</td>
<td>6.5</td>
</tr>
<tr>
<td>Ranibizumab</td>
<td>5.5</td>
</tr>
</tbody>
</table>

Phase 3 trials are ongoing

Squalamine Eyedrops

- Squalamine lactate inhibits downstream signaling of angiogenic factors
- Delivered in eye drops in combination with anti-VEGF agents

**INPUT Study:** a phase 2 evaluation of squalamine eyedrops plus ranibizumab vs ranibizumab monotherapy showed an additional benefit with the combination:

![Graph showing visual acuity results]

<table>
<thead>
<tr>
<th>Treatment Arm</th>
<th>Mean Visual Acuity Letter Gain @ 9 Months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ranibizumab + squalamine</td>
<td>67</td>
</tr>
<tr>
<td>Ranibizumab</td>
<td>5</td>
</tr>
</tbody>
</table>

Phase 3 trials are ongoing

Update on Clinical Trials

Dry AMD (GA)

Focused on Complement Cascade

Update on Clinical Trials

Dry AMD (GA)

The complement cascade is primarily involved in the detection and removal of foreign pathogens such as bacteria. Involving more than 30 known cell-associated and systemically circulating proteins, activation of the complement cascade can lead to inflammation, opsonization, phagocytosis, and cell death through the formation of the membrane attack complex (MAC).
Update on Clinical Trials

Dry AMD (GA)

The case for complement cascade dysfunction in AMD is supported by three key lines of evidence:

Landmark genome-wide association studies (GWAS) identified AMD-associated variants in complement factor genes, particularly those such as CFH that promote alternative complement pathway termination on host cells.

Patients with GA exhibit alterations in complement cascade components both systemically and locally within the eye. Preclinical research in vitro and in mice, which have demonstrated that complement dysfunction is associated with GA-like pathology.

Cumulative damage to the retina by aging, environmental stress, and other factors triggers inflammation via multiple pathways, including the complement cascade. When regulatory components in these pathways are compromised, as with several GA-linked genetic risk factors in the complement cascade, chronic inflammation can ultimately lead to the retinal cell death characteristic of GA. Complement inhibition has been identified as a key candidate for therapeutic intervention, and drugs targeting the complement pathway are currently in clinical trials.

Update on Clinical Trials

Dry AMD (GA)

Targets

- Factor D mAb
- C3 Peptide
- C5 + Properdin Antibodies
- C5 Aptamer
- MAC Gene therapy

- Anti-Factor D (Lampalizumab)
  - Factor D is required for alternative complement pathway activation
  - Phase 2 (1124 patients) appeared to show positive response
  - Phase 3 (~2000 patients) failed to meet primary and secondary endpoints
  - Program dead

- Anti-C3 Peptide
  - Central inhibition of complement
  - Phase 2 trial (~240 patients) met primary endpoint
  - Phase 3 trial to start 2H 2018
Update on Clinical Trials

Dry AMD (GA)

Anti-C5 Antibody

Complement component 5 is cleaved into C5a and C5b. C5a plays an important role in chemotaxis. C5b forms the first part of the complement membrane attack complex.

Phase 2 trial (~158 patients) as monotherapy failed primary endpoint. Currently being studied in combination with an anti-properdin antibody in a phase 2 trial.

Properdin: positive regulator of complement activation. Promotes the association of C3b with factor B.

Update on Clinical Trials

Dry AMD (GA)

Anti-C5 Aptamer

Aptamers: oligonucleotide or peptide molecules that bind to a specific target molecule.

Phase 1b/2a study (47 patients) showed no safety signals. Phase 2b (200 patients) currently underway.

Update on Clinical Trials

Dry AMD (GA)

Membrane Attack Complex (MAC) inhibition via Gene Therapy

MAC is the final step of the complement cascade and forms a pore in the target cell membranes causing cellular damage.

MAC levels are elevated in certain eyes with dry AMD.

CD59 is a natural protein bound to host cell membranes that blocks C9 and protects them from complement damage.

Update on Clinical Trials

Dry AMD (GA)

Membrane Attack Complex (MAC) inhibition via Gene Therapy

Soluble CD59 (sCD59) blocks MAC formation at the terminal step of the complement cascade.

sCD59 is a solubilized form of CD59 delivered to the retina via a sustained release gene therapy.

Single intravitreal injection may allow for long-term protein expression in the posterior segment.

Phase 1b completely enrolled, showing no ocular or systemic safety issues.

Update on Clinical Trials

Dry AMD (GA)

Complement inhibition questions

- Is inhibition at the top of the cascade (factor D) efficient enough to block complement overactivity at the bottom of the cascade?
- Is local therapy sufficient to block C3 and C5, though these components are found at high levels systemically?
- Is chronic suppression necessary?
- Does inhibiting specific factors in the cascade result in unwanted side effects?
  - Local (e.g., endophthalmitis)
  - Systemic (increased risk of infection)

Update on Clinical Trials

Inherited Retinal Diseases

Voretigene neparvovec is a gene therapy vector recently FDA approved for the treatment of patients with vision loss due to confirmed bi-allelic \textit{RPE65} mutation-associated retinal dystrophy.
**Inherited Retinal Diseases**

**Update on Clinical Trials**

**Inherited Retinal Diseases**
IRDs are clinically heterogeneous and vary widely in their pathogenesis, progression, and mutation inheritance. Many different clinical diagnoses have been associated with IRDs based on time of onset, severity, and presenting phenotype. However, distinctions in clinical diagnoses are poorly defined, and may have overlapping features, leading to inaccurate or inconsistent diagnoses.

**Update on Clinical Trials**

**Inherited Retinal Diseases**
Visual impairment can result from mutations in more than 250 different genes. For RPE65 alone, approximately 125 discrete gene mutations have been identified to date. Prior to both the identification of the specific gene(s) associated with the disease and to genetic testing, precise diagnosis was challenging.

**Update on Clinical Trials**

**Inherited Retinal Diseases**
*RPE65* mutation-associated retinal dystrophy is one of many different types of IRDs. Orphan disease, with an estimated 1,000-3,000 patients affected by this disease in the US. For patients with *RPE65* mutation-associated retinal dystrophy, common clinical diagnoses include Leber congenital amaurosis (LCA), retinitis pigmentosa (RP), and severe early childhood onset retinal dystrophy (SECORD).

**Update on Clinical Trials**

**Inherited Retinal Diseases (IRDs)**

For patients with *RPE65* mutation-associated retinal dystrophy, voretigene neparvovec supplies a functional copy of the *RPE65* gene within the retinal pigment epithelium cells, allowing for restoration of the visual cycle.

**Update on Clinical Trials**

**Inherited Retinal Diseases (IRDs)**

Voretigene neparvovec
Confirmed *RPE65* mutation associated IRD
Phase 1 trial-12 patients, No major safety signals
Phase 2 trial-21 treated patients, 10 control (controls received treatment at 1 year follow-up)
Update on Clinical Trials

Inherited Retinal Diseases
Voretigene neparvovec

Primary outcome- Change in performance on the Multi-Luminance Mobility Test (MLMT)
Secondary outcomes- Full-light Sensitivity Testing, Monocular MLMT, Visual Acuity

A change of one light level in passing the MLMT was considered clinically significant. Improvements in the ability to navigate more quickly and more accurately at lower light levels than previously possible increases an individual's safety and independence.

The lighting levels selected and utilized for MLMT testing span a range that is routinely encountered in everyday situations: walking to class or through an office building, crossing streets at dusk, playing outside, or locating objects in dimly lit conditions.

The ability to safely navigate in dimmer conditions than previously possible opens up a wider range of potential opportunities for a patient and expands the environments in which they can safely and efficiently function independently, including college students who are now able to take night classes, children who are able to play outside longer when it gets dark, and adults who can independently commute to their job, go shopping at night, draw in dimly lit restaurants, or get a glass of water during the night.

Table 12: Light Levels for Multi-Luminance Mobility Test

<table>
<thead>
<tr>
<th>Light Levels</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 lux</td>
<td>Moonless summer night; indoor nightlight</td>
</tr>
<tr>
<td>4 lux</td>
<td>Cloudy night with half moon; Parking lot at night</td>
</tr>
<tr>
<td>10 lux</td>
<td>1 hour after sunset in city; Bus stop at night</td>
</tr>
<tr>
<td>50 lux</td>
<td>Outdoor train station at night; Inside of lighted alleyway</td>
</tr>
<tr>
<td>125 lux</td>
<td>30 minutes before sunrise; Interior of train / bus at night</td>
</tr>
<tr>
<td>250 lux</td>
<td>Interior of elevator or office hallway</td>
</tr>
<tr>
<td>400 lux</td>
<td>Office environment or food court</td>
</tr>
</tbody>
</table>

Table 13: MLMT Light Levels and Lux Scores

<table>
<thead>
<tr>
<th>Light Level</th>
<th>MLMT Lux Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 lux</td>
<td>6</td>
</tr>
<tr>
<td>4 lux</td>
<td>5</td>
</tr>
<tr>
<td>10 lux</td>
<td>4</td>
</tr>
<tr>
<td>50 lux</td>
<td>3</td>
</tr>
<tr>
<td>125 lux</td>
<td>2</td>
</tr>
<tr>
<td>250 lux</td>
<td>1</td>
</tr>
<tr>
<td>400 lux</td>
<td>0</td>
</tr>
</tbody>
</table>
Update on Clinical Trials

Inherited Retinal Diseases
Voretigene neparvovec - Safety

• The safety profile of voretigene neparvovec is consistent with vitrectomy and the subretinal injection procedure. The safety profile includes subjects followed for up to nine years.
• AEs tended to occur early and resolve over time. Most AEs were mild or moderate in severity. There were no deaths reported during the clinical development program, and no deleterious immune responses were observed.
• There were two ocular SAEs reported, and both led to loss of VA. One event was related to the administration procedure and one was a known adverse reaction to a concomitant medication.

Update on Clinical Trials

Inherited Retinal Diseases (IRDs)
Voretigene neparvovec - Efficacy

Voretigene neparvovec treatment resulted in clinically meaningful and statistically significant improvements in functional vision, light sensitivity, and visual function compared to control subjects, with observed improvement as early as 30 days after administration.

Findings from the Phase 3 Control subjects treated with voretigene neparvovec after the initial 1 year of observation replicated the overall benefit and improved functional vision and visual function observed in the original Intervention subjects.
• Improvement after voretigene neparvovec was maintained throughout the efficacy follow-up period, up to three years in Phase 3, with observation ongoing.

Overall, 72% of all treated subjects (21 of 29) achieved the maximum possible MLMT improvement one-year post-administration, demonstrating significant improvement in functional vision at lower light levels. The benefits observed at one year in the original intervention group continued through at least two years post-administration, with observation ongoing.

Outcomes-based rebate arrangement with both:

• A short-term efficacy (30-90 days) measure
• A longer-term durability (30 months) measure

Price: $425,000/eye*

*Outcomes-based rebate arrangement with both:
Inherited Retinal Diseases
Voretigene neparvovec

Availability-tightly controlled
Limited number of Centers of Excellence associated with an active ophthalmology practice that treats patients with IRDs including RPE65 mutation-associated retinal dystrophy.

Medical retina specialists, vitreoretinal surgery expertise, and pharmacies adequately equipped and trained to handle the product. All involved healthcare professionals will complete a training program. For surgical staff, this will include a surgical training program on subretinal delivery of the product (in-person workshop/wet lab hands-on training).

Detailed surgeon manual with illustrations describing the subretinal injection procedure.
In-person training program for pharmacists and other pharmacy personnel regarding the preparation of the product (Manual with step-by-step written instructions and illustrations).

Thank you