UPDATE ON CLINICAL TRIALS FOR AMD

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Agenda

Brief History of Current Rx

Recently Completed/New CTs: Wet AMD

Recently Completed/New CTs: Dry AMD

Current Treatment/Wet AMD

Anti-VEGF Drugs

Ranibizumab (Lucentis)

Aflibercept (Eylea)

Bevacizumab (Avastin)

History of Current Treatment

Judah Folkman, M.D.

1971: proposed that solid tumor growth required the formation of new capillary blood vessel growth (Angiogenesis)

Identified multiple factors that promote and inhibit angiogenesis

History of Current Treatment

Napoleone Ferrara, M.D., Ph.D.

VEGF gene identified and cloned in 1989 at Genentech

History of Current Treatment

Characterized VEGF as a major regulator of angiogenesis, including tumor angiogenesis.

Development of a humanized anti-VEGF antibody, bevacizumab (Avastin)

FDA approved in 2004 for the treatment, in combination with 5-FU-based chemotherapy, of first-line metastatic colorectal cancer

Subsequently approved for a variety of solid tumors

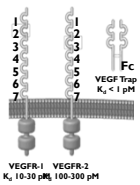
History of Current Treatment

Studies on the role of VEGF in intraocular neovascularization led to the clinical development of an anti-VEGF antibody fragment, Lucentis® (ranibizumab).

FDA approved in 2006, for the treatment of neovascular (wet) age-related macular degeneration (AMD).

History of Current Treatment

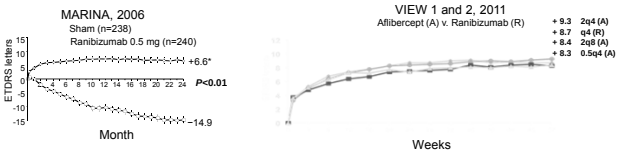
Aflibercept (Eylea, Regeneron)



Fusion protein of key domains from human VEGF receptors 1 and 2 with human IgGFc

FDA approved in 2011 for wet AMD

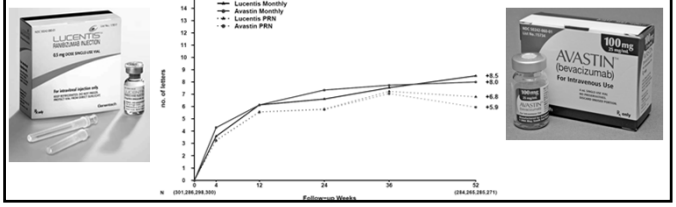
Previous Clinical Trials



Previous Clinical Trials

CATT, 2011

Ranibizumab vs Bevacizumab



Current Treatment/Wet AMD

Anti-VEGF Drugs Have Revolutionized Treatment, but…..

Only 1/3 of eyes gain 3 lines of vision

OCT "dry" in only 2/3 of eyes

…..Ongoing search for treatments with incremental efficacy

New Treatments/Wet AMD

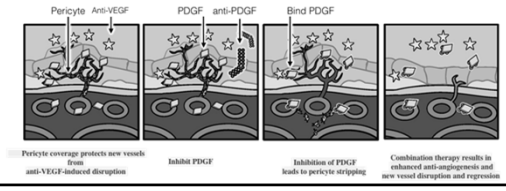
Focus on other growth factors

PDGF

Angiopoietins

[redacted]

PDGF



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PDGF

2 clinical trials

Capella (Regeneron)

Rinucumab, an anti-platelet-derived growth factor receptor (anti-PDGFR) antibody

Fovista (Ophthotech)

Pegpleranib-Aptamer (Peptide molecule) against PDGF

[redacted]

2016: The year of the anti-PDGF "Flame-Out"

[redacted]

Regeneron "Capella" Study

Phase 2 Study evaluated aflibercept co-formulated with rinucumab,

The combination therapy did not demonstrate an improvement in best corrected visual acuity (BCVA) compared to intravitreal aflibercept injection monotherapy at 12 weeks

Additionally, adding rinucumab to aflibercept showed no benefit on anatomic endpoints including reduction in retinal thickness or in resolution of subretinal hyper-reflective material

[redacted]

Ophthotech "Fovista" Trials

Compare combination anti-PDGF (Fovista) /Anti-VEGF vs Anti-VEGF monotherapy

Phase 2: 24 weeks. Combination therapy/anti-VEGF. 10.6 vs 6.5 letters gained/62% benefit

Phase 3 completed: Ophthotech Corporation announced that the pre-specified Primary endpoint of mean change in visual acuity at 12 months was not achieved. The addition of Fovista to a monthly Lucentis regimen did not result in benefit

1248 patients: Ranibizumab alone gained 10.01 letters; Ranibizumab + Pegpleranib 10.24 letters

[redacted]

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

New Clinical Trials/Wet AMD

Anti-angiopoietin

Avenue (Genentech)

Onyx (Regeneron)

New Clinical Trials/Wet AMD

Avenue Trial

RO6867461 is a humanized bispecific immunoglobulin G monoclonal antibody that selectively binds VEGF-A and Ang-2.

Blocks VEGF-A and Ang-2 function simultaneously.

New Clinical Trials/Wet AMD

Avenue Trial

STUDY DESIGN OVERVIEW

Phase II study/271-343 patients

5 arms comparing monotherapy ranibizumab to various doses of RO6867461

9 month duration

New Clinical Trials/Wet AMD

Stairway Trial-Successor to Avenue

STUDY DESIGN OVERVIEW

Phase II study/75 patients

Evaluate extended durability of treatment with RO6867461

3 arms comparing monotherapy ranibizumab given monthly to RO6867461given q1month x 4 followed by treatment either every 12 weeks or 16 weeks

56 week duration

New Clinical Trials/Wet AMD

Onyx Trial

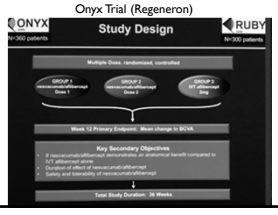
Phase II, 360 patients

The Angiopoietin-2 antibody nesvacumab, co-formulated with aflibercept

Compare monotherapy Aflibercept with 2 doses of co-formulated drug

New Clinical Trials/Wet AMD

Onyx Trial (Regeneron)



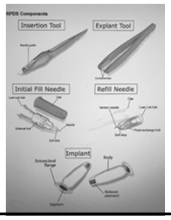
New Clinical Trials/Wet AMD

Current anti-VEGF treatment protocols can be burdensome for patients and families

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

New Clinical Trials/Wet AMD-



New Clinical Trials/Wet AMD

LADDER Trial

Phase II/120 patients/30 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

Clinical Trials/Dry AMD (G A)

S.E.A.T.T.L.E. (Acucela)

Mahalo (Genentech)

Spectri/Chroma (Genentech)

Clinical Trials/Dry AMD (GA)

S.E.A.T.T.L.E.

Light-mediated oxidative stress and excessive accumulation of vitamin A-based toxins have been implicated in pathogenesis of GA in dry AMD

Emixustat Hydrochloride: Orally administered, non-retinoid small molecule

Hypothesized to Inhibit activity of RPE65 to reduce rate of vitamin A processing in the visual cycle; modulate visual cycle activity to reduce vitamin A toxins; reduce metabolic rate of photoreceptors; protect retina from light damage

Clinical Trials/Dry AMD (GA)

S.E.A.T.T.L.E.

Phase 2b/III Study/ 508 patients/ 2 years

Placebo + 3 doses of investigational drug

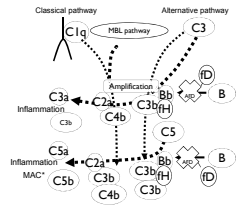
Clinical Trials/Dry AMD (GA)

S.E.A.T.T.L.E: 2016 Flame-out

No significant different in growth of GA

No difference in change in BCVA

Clinical Trials/Dry AMD (G A)- Mahalo (Phase 1b/II trial)- Genentech



Lampalizumab-(Anti-factor D)
–Fab of a humanized monoclonal antibody

SCIENTIFIC RATIONALE
–Complement-mediated damage and inflammation may promote AMD, including GA, an advanced form of AMD

TARGET: Complement factor D (alternative pathway)
–Factor D is a rate-limiting enzyme that lies upstream of both amplification loops of the alternative complement pathway (ACP)
–Anti-factor D is selective for the ACP preserving the classical and MBL pathways

Clinical Trials/Dry AMD (GA)

Mahalo (lampalizumab)

For all patients enrolled, lampalizumab given monthly showed a 20.4% reduction in growth of GA at month 18, compared to sham; difference detectable at month 6

Clinical Trials/Dry AMD (GA)

Mahalo (lampalizumab)

Patients were assayed for exploratory biomarkers, including complement factor I (CFI)

57% were positive

In the group of patients treated monthly and positive for CFI, disease progression was 44% lower than sham

Clinical Trials/Dry AMD (GA)

Chroma/Spectri

Identical, parallel phase III trials/936 patients/study/Bio-marker + and –

300 sites/24 countries

Injection of Lampalizumab every 4 or 6 weeks

Primary end-point: Progression of GA

Ongoing- Will run for 2 years after last patient enrolled

Other Clinical Trials

Stem Cells-few studies in dry AMD/GA and Stargardt's Disease

Gene Therapy using Adenovirus Vectors for Lebers Congenital Amaurosis and for Stargardt's Diesease

[redacted]

Summary

Brief History of Current Rx

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Recently Completed/New CTs: Dry AMD

[redacted]