

Anti-VEGF for Neovascular AMD: An Insight Into The Future

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Where do we stand

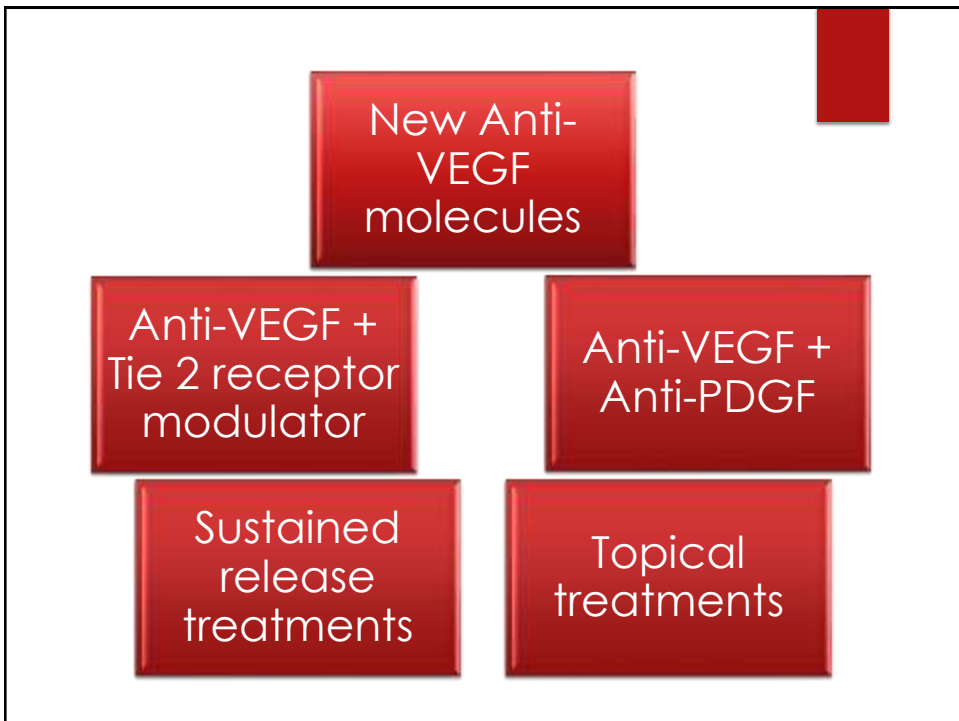
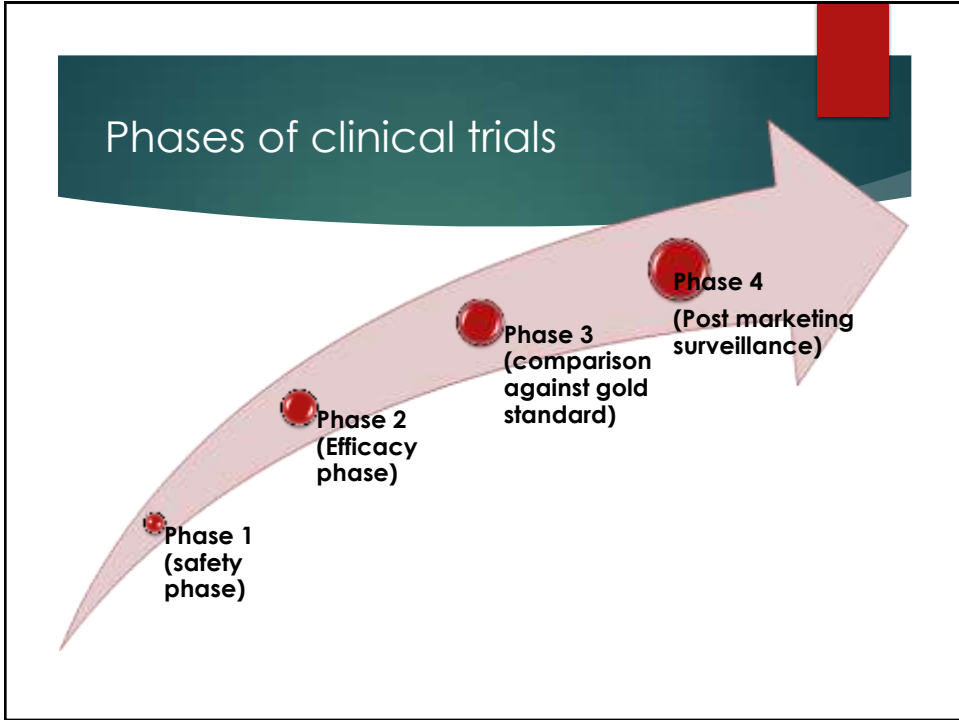
- ▶ Anti-VEGF intravitreal injection is the current gold standard for neovascular AMD treatment
- ▶ Even with regular injection, 20% lose vision, 60% do not gain 3 or more letters on ETDRS chart
- ▶ Anti-VEGF stops permeability but doesn't stop the progression of the disease. 50% of patients develop submacular scar even with regular injection
- ▶ Real world patients are under treated

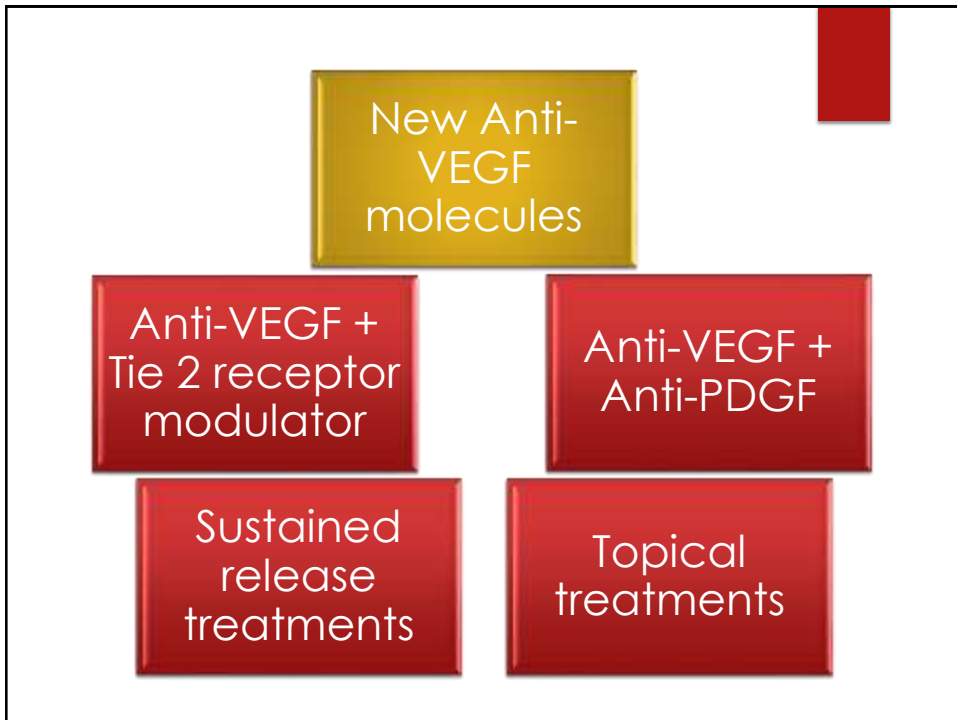
How to Improve

- ▶ Increase Efficacy
- ▶ Decrease Injection Frequency

Current anti-VEGF agents

Agent	Mechanism	FDA Approval
Macugen (Pegaptanib)	Synthetic RNA based oligonucleotide targeting VEGF ₁₆₅	December 2004
Avastin (Bevacizumab)	Humanized monoclonal IgG1 antibody against VEGF	February 2004 for metastatic colorectal cancer Used off-label for nAMD
Lucentis (Ranibizumab)	Humanized monoclonal IgG1 antibody fragment against VEGF	June 2006
Eylea (Aflibercept)	VEGF-trab, recombinant protein formed by fusing second domain of VEGF receptor 1 with third domain of VEGF receptor 2 to the Fc portion of human IgG1	November 2011





Brolucizumab (Novartis)

► **What's new?**

In Maintenance phase injection is every 3 months

► **Mechanism:**

Humanized single chain antibody fragment for VEGF-A

► **Results:**

Phase 3 study ongoing

HAWK and HARRIER trials

Brolucizumab 6mg is non inferior to aflibercept 2mg at 1 year according to press release in June 2017

Abicipar pegol (Allergan)

▶ **What's new?**

In Maintenance phase injection is every 3 months

▶ **Mechanism:**

synthetic protein that block all isoforms of VEGF-A

▶ **Results:**

phase 3 study ongoing

Phase 3 will compare Abicipar at 2 month interval , Abicipar at 3 month interval and ranibizumab at monthly interval

OPT-302 (Opthea)

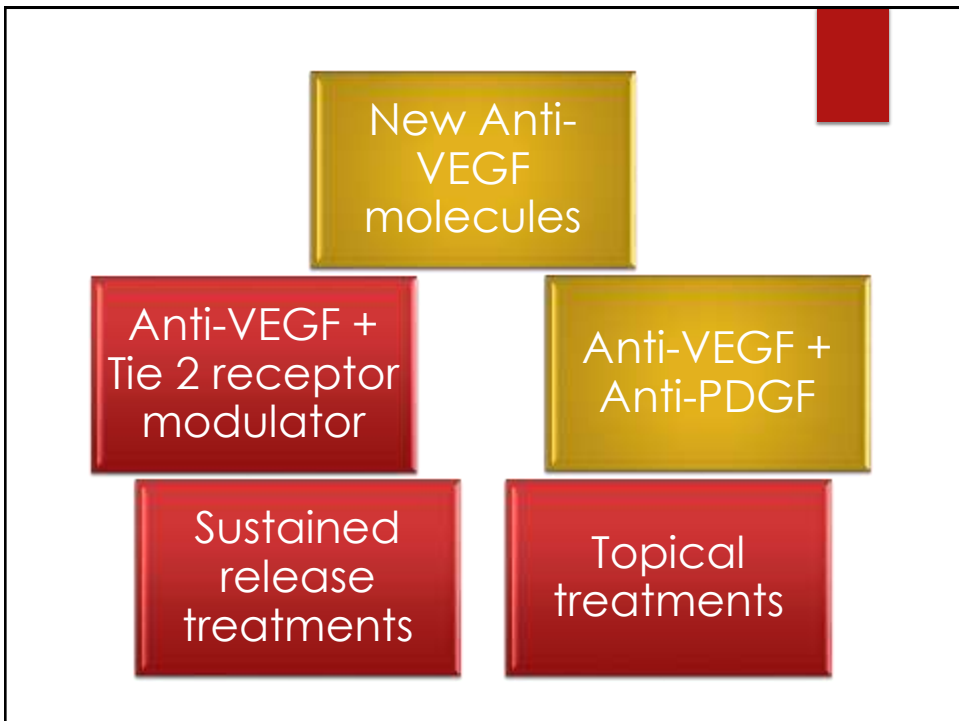
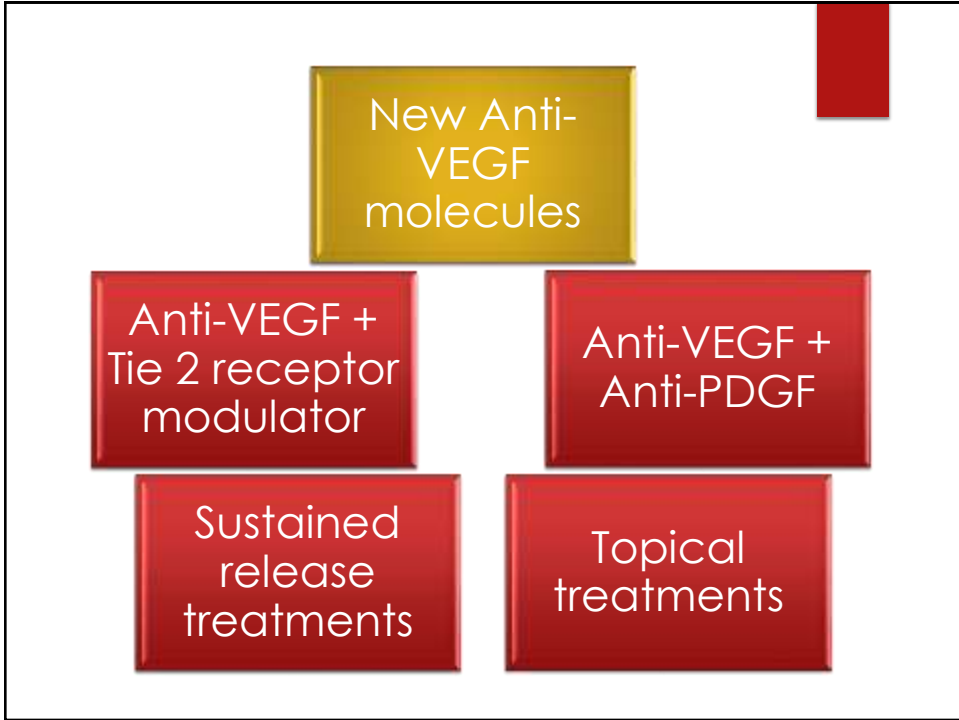
▶ **What's new?**

Anti-VEGF C and D

▶ **Results:**

phase 2 study ongoing

In Phase 1 study, higher efficacy when combined with ranibizumab than ranibizumab monotherapy.



Anti platelet derived growth factor (Anti-PDGF)

- ▶ PDGF promotes recruitment, maturation and survival of pericytes.
- ▶ Pericytes cover the endothelial cells of capillaries and can secrete VEGF-A by paracrine signalling, thereby providing anatomical and physiological barriers to anti-VEGF A.
- ▶ combination of Anti-VEGF and Anti-PDGF can enhance efficacy of Anti-VEGF A.

DE-120 (Santen Pharma)

- ▶ **What's new?**

Single molecule with anti-VEGF A and anti-PDGF activity

- ▶ **Results:**

Phase 2 ongoing

Compare DE-120 monotherapy to combination therapy with aflibercept

X-82 (Tyrogenex)

► **What's new?**

Oral anti-PDGF and anti-VEGF A

► **Results:**

phase 2 ongoing

compare X-82 with as needed aflibercept to aflibercept fixed dose.

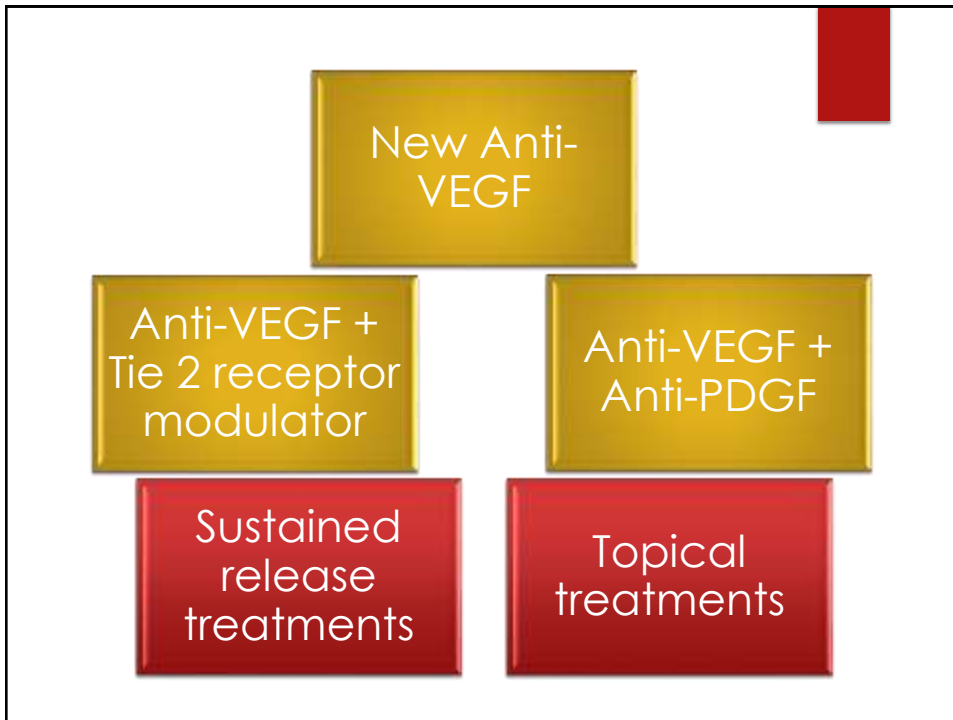
New Anti-VEGF

Anti-VEGF +
Tie 2 receptor
modulator

Anti-VEGF +
Anti-PDGF

Sustained
release
treatments

Topical
treatments



Tie 2 receptor modulator

- ▶ Tie 2 receptors are expressed on endothelial cells. Their activation results in stabilization of vasculature and limiting permeability.
- ▶ Angiopoietin-1 (Ang-1) is a ligand that activates the receptor. Angiopoietin -2 (Ang-2) is a competitive antagonist to Ang-1.
- ▶ The enzyme vascular endothelial protein tyrosine phosphatase (VE-PTP) inactivates the receptor.

Nesvacumab (Regeneron)

▶ **What's new?**

Ang-2 inhibitor

▶ **Results:**

phase 2 ongoing

Compare combination between aflibercept and nesvacumab to aflibercept monotherapy

RG7716 (Roche)

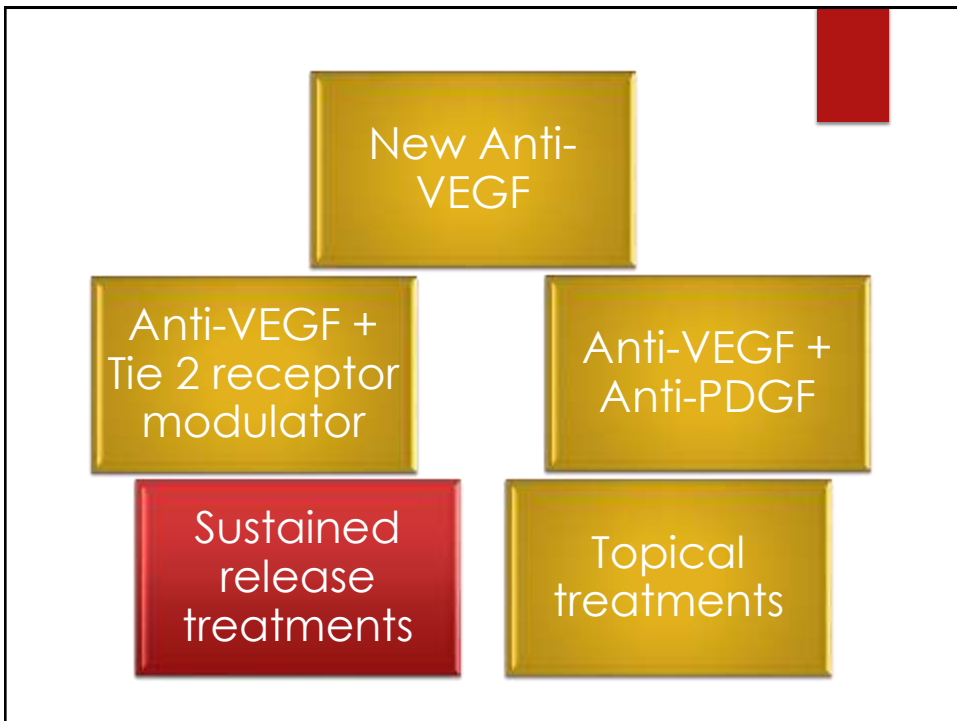
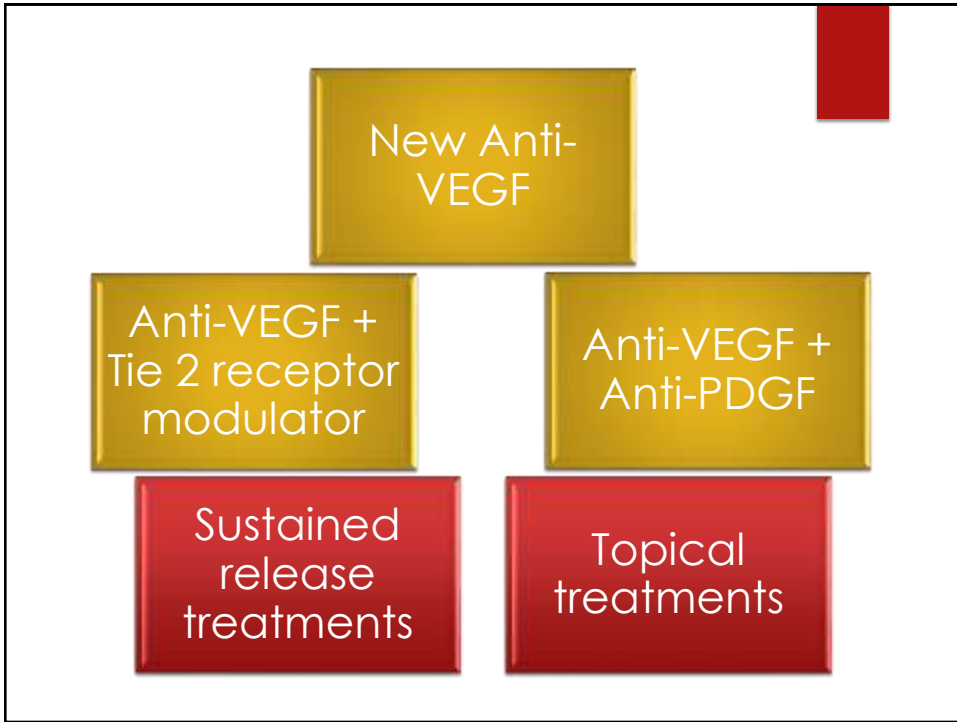
▶ **What's new?**

Bispecific antibody against Ang-2 and VEGF-A

▶ **Results:**

phase 2 ongoing

Phase 2 compares ranibizumab monotherapy, RG7716 monotherapy and combination between them



PAN-90806 (PanOptica)

▶ **What's new?**

VEGF-A inhibitor eye drop

▶ **Results:**

finished phase 1

In phase 1, monotherapy was tried in 50 ttt naïve patients and results were comparable to those of currently available anti-VEGF therapies

LHA510 (Alcon)

▶ **What's new?**

eye drops, anti-VEGF A

▶ **Results:**

phase 2 ongoing

Phase 2 will investigate whether addition of LHA510 to ranibizumab injection would decrease the injection frequency

Squalamine Lactate (Ohr Pharmaceutical)

► **What's new?**

eye drops, prevent signaling of receptors VEGF-1, VEGF-2, PDGF, b-FGF

► **Results:**

phase 3 ongoing

In phase 2 : combination with ranibizumab showed VA benefit for lesion size <10mm²

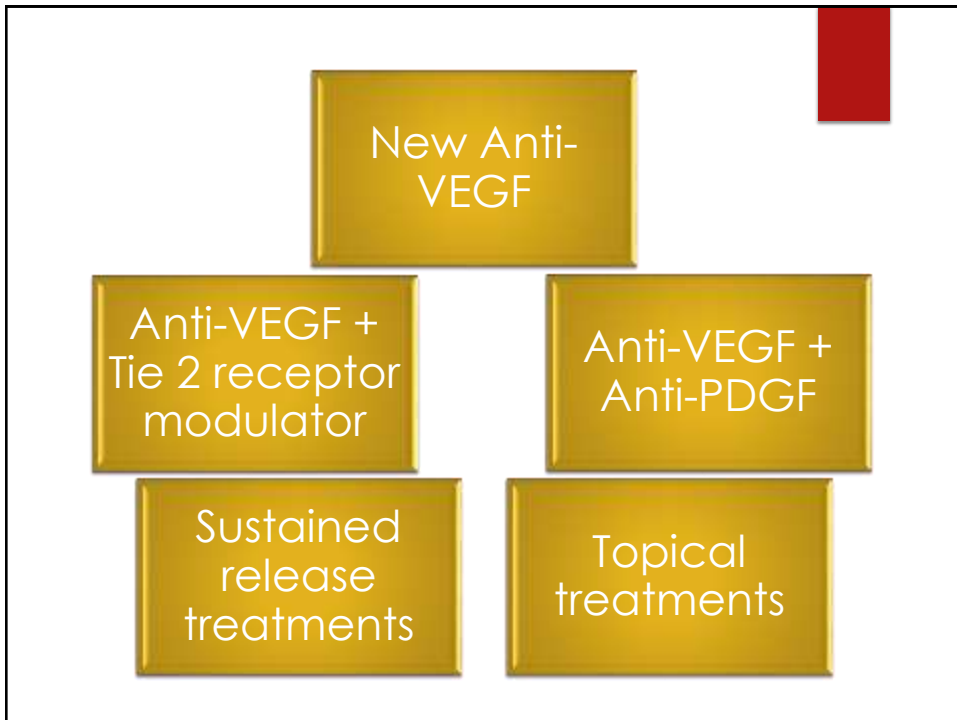
New Anti-
VEGF

Anti-VEGF +
Tie 2 receptor
modulator

Anti-VEGF +
Anti-PDGF

Sustained
release
treatments

Topical
treatments



Ranibizumab port delivery system (Genetech)

► **What's new?**

Nonbiodegradable port fixed to the sclera with a reservoir filled in the office

► **Results:**

phase 2 ongoing

Phase 1 results showed that it improved VA to a greater degree than monthly ranibizumab at 12 mth follow up

Endophthalmitis and vitreous hemorrhage are side effects

Intravitreal depot injections

Agent	Mechanism	Phase
Hydrogel anti-VEGF depot (Ocular Therapeutix)	biodegradable hydrogel contain anti-VEGF A particles	Pre-clinical
ENV1305 (Envisia Therapeutics)	nanoparticles containing VEGF-A inhibitors	Pre-clinical
Durasert (pSvidia corp)	bioerodable implant contain TKI that inhibits VEGF-A and PDGF	Pre-clinical
GB-102 (GrayBug Vision)	TKI against VEGF-A and PDGF. erodable nanoparticles that slowly degrade and remain away from visual axis	Pre-clinical

Gene therapy

- ▶ The eye is a good site for gene therapy due to accessibility, tight blood ocular barrier, immune privileged site.
- ▶ Non harmful viruses are used as conduits for genetic material.
- ▶ Current viruses used are adeno associated virus (AAV) and lentivirus

AVA-101 (Ocular Biofactory)

▶ **What's new?**

AAV injected subretinal after PPV produce anti-VEGF A continuously

▶ **Results:**

phase 2 finished

In phase 2 no significant difference in VA was obtained at 1 year when AVA-101 was added to PRN ranibizumab.

Difference in rescue injections was not large (2 vs. 4)

RGX-314 (Regenexbio)

▶ **What' new?**

AAV8 carrying genes for anti-VEGF expression. Delivered subretinal after PPV

▶ **Results:**

phase 1 started in 2017

Retinostat (Oxford Biomedica)

▶ **What's new?**

EIAV encoding endostatin and angiostatin delivered subretinal after PPV

▶ **Results:**

finished phase 1

21 patients with advanced nAMD poorly responsive to anti-VEGF A were treated with Retinostat. At 1 year, only 1 patient showed reduction of retinal fluid compared to baseline

References

- ▶ Hussain R. M., Ciulla T. A.: **Emerging vascular endothelial growth factor antagonists to treat neovascular age-related macular degeneration.** *Expert opinion on emerging drugs* 2017, **22**(3):235-246.
- ▶ Schlottmann P. G., Alezzandrini A. A., Zas M., Rodriguez F. J., Luna J. D., Wu L.: **New Treatment Modalities for Neovascular Age-Related Macular Degeneration.** *Asia-Pacific journal of ophthalmology (Philadelphia, Pa)* 2017, **6**(6):514-519.

