Clinical Applications of Biologics in Eye Care
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Walter O. Whitley, OD, MBA, FAAO
Director of Optometric Services
Virginia Eye Consultants
Residency Program Supervisor
PCO at Salus University

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Biologics: What Are They?
- FDA defines biological products as "a wide range of products such as vaccines, blood and blood components, allergens, somatic cells, gene therapy, tissues, and recombinant therapeutic proteins...composed of sugars, proteins, or nucleic acids or complex combinations of these substances, or may be living entities such as cells or tissues...isolated from a variety of natural sources – human, animal, or microorganism"
- Any biologics considered for human use are approved via the Center for Biologics Evaluation and Research (CBER)
  - Safe
  - Effective
  - Available

Biologics: Great So What Do They Do?
- Used to diagnose, prevent, treat, and cure numerous diseases and medical conditions
  - Therapeutic proteins (filgrastim)
  - Monoclonal antibodies (adalimumab)
  - Vaccines (tetanus)
  - Many more....
- Most advance therapies available
  - 1st vs 2nd vs 3rd line treatments??
  - Fail first on other meds??

Biologics versus chemical drugs
- Biologically synthesized versus precise chemical process
- Size
- Parenteral delivery
- Sensitive to extreme physical conditions
- Complex activity
  - Engineered to target precise receptors/structures
- Cost – biologics often more expensive to produce and subsequently administer

Biologics versus Biosimilars
- Biosimilars
  - Highly similar to approved "reference" product, with difference in manufacturing process
  - Cheaper
- Interchangeable product
  - A biosimilar that meets additional requirement outlined by the Biologics Price Competition and Innovation act.
    - Expected to produce same clinical result
## Common Biologics You Already Know

- Adalimumab (Humira)
- Trastuzumab (Herceptin)
- Bevacizumab (Avastin)
- Insulin glargine (Lantus)
- Onabotulinumtoxin A (Botox)

## Applications in Eye Care

- **Inflammatory Disease**
  - Uveitis
  - Scleritis/Episcleritis
- **Dry Eye Disease**
- **Oculoplastics**
- **Cosmetic**
- **Functional**
- **Retina**
  - Age related macular degeneration
  - Diabetic retinopathy

## “The Common Eyeritis”

- 32YOWM, Red, Painful Eye OD, Photophobic, No discharge
- No previous episodes
- Ocular/Medical Hx: Unremarkable
- No other associated symptoms
- SLE: 2+ injection / 2+ cells

## Uveitis

**Classic Symptoms**

- Acute onset
- Decreased vision
- Redness
- Photophobia
- Pain
- Excessive tearing

**Signs**

- VA
- Conjunctiva
- Cornea
- Anterior chamber
- Iris
- Pupil
- IOP
- Lens
- Vitreous
- Disc edema
- Macular edema
- Periphlebitis

## Anterior Uveitis

- Causes
  - Idiopathic
  - Traumatic
  - HLA-B27
  - Herpetic
- Can be recurrent, recalcitrant, granulomatous, or non-granulomatous

## Intermediate Uveitis

- 8-15% of all uveitis
- Involves pars plana, peripheral retina, vitreous
- Anterior vitreous cells
  - Scleral depression
  - B scan
- Associated conditions
  - MS
  - Sarcoid
  - Syphilis
Posterior Uveitis

- Common findings
  - Active inflammation
  - Scarring
  - Vasculitis
  - Consider infectious causes

Panuveitis

- Defined as inflammation of the entire uvea
  - Anterior, intermediate, and posterior
  - Most serious of all uveitis cases

When Should Lab Tests Be Ordered?

<table>
<thead>
<tr>
<th>Condition</th>
<th>Clinical Features</th>
<th>Test Indicated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ankylosing spondylitis</td>
<td>Young male, low back pain, chest pain</td>
<td>HLA-B27, sacroiliac X-ray</td>
</tr>
<tr>
<td>Reiter’s syndrome</td>
<td>Young male, arthritis, urethritis, conjunctivitis</td>
<td>ESR, CRP</td>
</tr>
<tr>
<td>Juvenile idiopathic arthritis</td>
<td>Slight male predilection, sacroiliitis common</td>
<td>ANA, RF, X-ray radiograph</td>
</tr>
<tr>
<td>Inflammatory bowel disease</td>
<td>Ulcerative colitis, diarrhea, abdominal cramps</td>
<td>HLA-B27, sigmoidal X-ray</td>
</tr>
<tr>
<td>Tuberculosis</td>
<td>African Americans, females, vasculitis, arthritis</td>
<td>PPD, chest X-ray or CT scan</td>
</tr>
<tr>
<td>Syphilis</td>
<td>Hx of sexual contact with infected person, rash, fever, malaise, headache, joint pain</td>
<td>FTA-ABS, VDRL, RPR</td>
</tr>
<tr>
<td>Toxoplasmosis</td>
<td>Immunocompromised status, exposure to cat, of eating raw meat, punctured-out retinal lesions</td>
<td>Toxoplasma IgG or IgM for acute acquired cases</td>
</tr>
<tr>
<td>Lyme disease</td>
<td>Recent tick bite</td>
<td>Lyme Western Blot</td>
</tr>
</tbody>
</table>

Treatments for Uveitis

- Steroids
  - Topical
  - Local
  - Systemic
- NSAIDs
- Cycloplegics
- Analgesics
- Immunosuppressants
- Calcineurin inhibitors
- Biological blockers
- Glaucoma medications

Systemic Therapy for Inflammatory Disease

- Acute inflammatory episodes typically necessitate steroid treatment (topical, periocular, intraocular, systemic)
- Steroids exhibit great efficacy (especially in anterior uveitis), but come with significant side effects, limiting chronic use
  - Cataract, glaucoma, herpetic reactivation, increased infection
  - Gastric ulcer, reactivation of latent disease, hyperglycemia, osteoporosis, Cushing syndrome
- MUST Study
  - Local and implant steroids effective for uveitis treatment
  - High incidence of local ocular SE and systemic complications
### Considerations for Steroid Sparing Options

- Steroid
- Relapse or recurrence
- Severity of local/Systemic Complications

### Disease Modifying Anti-rheumatic Drugs (DMARDs)

- Traditional – restrict immune system broadly
  - Antimetabolites – methotrexate, mycophenolate mofetil
  - T-Cell Inhibitors – cyclosporine, tacrolimus
  - Alkylating agents – cyclophosphamide, chlorambucil
- Targeted – block precise pathways in immune cells
  - PDE4 Inhibitor – Apremilast
  - Janus Kinase Inhibitor – Tofacitinib
- Biologics are the next “step” approach to treating ocular inflammation

### Antimetabolites

- **Methotrexate**
  - **Indications**
    - Acute lymphoblastic leukemia
    - Trophoblastic neoplasms
    - Lung cancer
    - Panniculitis
  - **MOA** - Inhibits DNA synthesis, repair and cellular replication
  - **Dosage**
    - Usually 2.5 to 7.5 mg/week orally
  - **Onset** – 2-12 weeks
  - **Side effects**
    - Gastrointestinal disturbance, hepatotoxicity, oral ulcers, alopecia, bone marrow suppression, pneumonia, fetal loss, and infections
  - Comanaged with rheumatology

### Traditional DMARDs - T-Cell Inhibitors

- **Cyclosporine**
  - **Indications**
    - Organ transplant
    - RA
    - Pernicious
  - **MOA** - Inhibits T-cell activation
  - **Dosage** - 2.5-10 mg/kg/day PO twice daily
  - **Onset** – 2-6 weeks
  - **Side effects**
    - Nephrotoxicity, hypertension, hirsutism, gingival hyperplasia, and infections
  - Comanaged with rheumatology or nephrologist

### Alkylating Agents

- **Cyclophosphamide**
  - **Indication**
    - Lymphoma
    - Myeloma
    - Leukemia
  - **MOA** – nonspecific alkylating agent that alters the composition of DNA bases
  - **Dosage** - 1-3 mg/kg/day PO
  - **Onset** – 2-8 weeks
  - **Side effects**
    - Bone marrow suppression, infections, hemorrhagic cystitis, increased risk of malignancy, sterility, and alopecia
  - Comanaged with rheumatologist + reproductive medicine specialist

### Biologics Therapies

- **Indications**
  - 1st line (following steroid pulse) to control active inflammation
  - When conventional immunosuppressants fail to control uveitis
  - More targeted approach
  - Safety profile
Biologic Therapies in Noninfectious Uveitis

- Suppress inflammation with oral steroid while starting biologic
  - Taper PO steroids 4-6 weeks
  - Needs 4-6 weeks onset of action
- Rule Out systemic conditions
  - Infections (TB and Hepatitis)
  - Multiple sclerosis
  - Risk of heart failure development
  - Coordinate care with specialist

Common Systemic Biologics in Inflammatory Disease

- Tumor Necrosis Factor (TNF-alpha) Inhibitors
  - Humira (adalimumab)
  - Remicade (infliximab)
  - Enbrel (etanercept)
  - Lymphocyte Inhibitors
    - Rituxan (rituximab)
    - Ocrevus (abatacept)
  - Interferons
  - Anti-Interleukin antibodies
    - Actemra (tocilizumab)

Tumor Necrosis Factor

- TNF found in two forms in the body
  - Transmembrane – maintain innate immune response and tolerance to autoantigens
    - Inhibition results in increased sensitivity to infection, exacerbation of demyelinating conditions
  - Soluble – drives inflammatory response
    - Inhibition leads to anti-inflammatory effect
- Current TNFalpha inhibitors act on both forms

TNF-Alpha Inhibitors

- First-generation agents
  - Infliximab
  - Etanercept
  - Adalimumab
- Second-generation agents
  - Certolizumab
  - Golimumab
  - Not yet in general use for the management of uveitis

TNF-Alpha Inhibitors

- Adalimumab (Humira)**
  - Only FDA approved biologic for treatment of intermediate, posterior, or panuveitis
  - Subcutaneous injection
- Infliximab (Remicade)**
  - IV infusion
  - Etanercept (Enbrel)
  - Not shown to benefit ocular disease

TNF-Alpha Inhibitors

- Infliximab particularly effective in Behcet’s
  - 86% remission rate in as little as two weeks with infliximab alone
  - Also effective in JIA and birdshot chororetinopathy
  - Chief application is for those who have failed adalimumab
- Adalimumab very effective in uveitis control
  - VISUAL 1 and 2 – reduction in treatment failure and relapse rate
  - SYCAMORE – trial halted before conclusion, clear benefit of adalimumab plus methotrexate versus methotrexate alone in JIA
TNF-Alpha Inhibitors

- Biosimilars
  - Inflectra – infliximab
    - Demonstrated highly similar structure/function to Remicade
    - Identical dosing
  - ABP501 – adalimumab
    - Pipeline, not yet available

- Adverse Effects with TNF-a Inhibitors
  - Activation of latent TB or hepatitis
  - Demyelinating disease
    - These first two tied with action on tmTNF
    - Must rule out MS with MRI in patients with pars planitis
  - Hepatotoxicity
  - Secondary malignancies
  - Drug-induced disease
  - Tachyphylaxis – due to antibody development
  - MULTISPECIALTY APPROACH TO MANAGEMENT IS CRITICAL

Lymphocyte Inhibitors

- Rituximab (Rituxan)
  - Binds CD20 receptor on B cells, leading to their replacement
  - Approved for forms of lymphoma/leukemia
  - Off-label use for SLE and JIA-related uveitis
  - Rarely leads to progressive multifocal leukoencephalopathy
- Abatacept (Orencia)
  - Binds CD80 and CD86 receptors on antigen-presenting cells to suppress inflammation
  - Use in uveitis limited to case reports

Interferons

- Naturally occurring cytokines which aid in regulation of immune system
- Anti-proliferation of T cells
- IFN-alpha2a
  - Effective in Behcet’s
  - Small cohort of intermediate uveitis or MS related uveitis showed significant reduction in macular edema with improved VA
- Side effects
  - Flu-like symptoms
  - Depression

Anti-Interleukins

- Interleukins 1, 6, 12, 17, and 23 all linked to inflammatory process and have antagonist drugs in study
  - Secukinumab (Cosentyx)
    - Monoclonal antibody against IL-17A
    - Failed three phase III trials for Behcet and other uveitides
  - Tocilizumab (Actemra)

Anti-IL-6R

First New Treatment for GCA in 50 Years

FDA Approval
September 23, 2017

ACTEMRA®
tocilizumab

First FDA Approval for Giant Cell Arteritis
Anti-Interleukins

- Tocilizumab (Actemra)
  - IL-6 antagonist, used in moderate to severe RA, GCA, PJIA, SJIA
  - Subcutaneous or IV infusion
  - STOP-Uveitis study – reduction of vitreous haze and CME at either 4 or 8 mg/kg of IV infusion
  - Recently approved for treatment of GCA
    - Subcutaneous injection weekly or every other week with concurrent steroid taper
    - 53-56% remission versus 14% placebo
    - Dosed at one subcutaneous injection weekly

Acthar Gel (repository corticotropin injection)

- Indicated for severe acute and chronic allergic and inflammatory processes involving the eye and its adnexa such as: keratitis, iritis, iridocyclitis, diffuse posterior uveitis and choroiditis, optic neuritis, chorioretinitis, anterior segment inflammation
- Complex formulation containing ACTH, a melanocortin peptide that binds to the 5 identified melanocortin receptors (MCRs) on tissues and cells throughout the body
- MOA unknown however in addition to stimulation of the body’s endogenous cortisol release, Acthar is believed to impact steroid-independent immunomodulatory and anti-inflammatory pathways
- Currently no clinical trial data available for uveitis

Biologics: Side Effects

- Increased risk of infection
- Reactivate Hepatitis B
- Allergic reaction
- Symptoms
  - I/V infusions – Shortness of breathe, chills, redness, itchiness, itchy eyes, itchy lips
  - Injections – redness, itchiness, warm/tender to touch, full body rash
- Less common
  - CNS disorders
  - Cardiac issues
  - Lupus-like syndrome

Current Uses for Topical Biologics for OSD

- Persistent epithelial defects
- Neurotrophic keratopathy
- Exposure keratopathy
- Recalcitrant dry eye
- Filamentary keratitis
- Corneal ulcers
- Herpetic keratitis
- Steven-Johnson’s Syndrom
- Keratoneuralgia
- Recurrent corneal erosion
- Limbal stem cell deficiency

Autologous Serum

- Blood drawn via 18 gauge needle – 40 mL blood collected into blood tubes
- Blood set aside to clot at room temperature for two hours, then centrifuged at 5600 rpm for 10 minutes
- Serum filtered to remove fibrin strands before mixing with saline
- Typically start with 20% AS up to 50%
- Unopened bottles stored in freezer up to 3 months; open bottles in refrigerator for 48 hours
- Potential for safe refrigerator storage for up to 1 month

Healing factors in Autologous Serum

- Vitamin A
- Lysozyme
- Transforming Growth Factor-beta
- Fibronectin
- Substance P
- Insulin-like growth factor-1
- Nerve growth factor
Benefits and Pitfalls of Autologous Serum

**Benefits**
- Preservative free and innately allergy free
- Adverse events rare
- Improvement in symptomology
- Demonstrated improvement in staining (Tsubota – SS pts)

**Complications**
- Cost – no insurance coverage
- Frequent blood draw
- Availability of labs to make ASED
- Strict handling

Amniotic Membrane

- Amnion is innermost layer of placenta and contains components that produce factors in proliferation/differentiation, help decrease infection, and increase membrane integrity
  - Collagen
  - Fibronectin
  - Laminin
  - Fibroblasts
  - Growth factors – Nerve Growth Factor
- Suppress TGF-β, myofibroblasts to limit scarring/haze while promoting epithelial healing and tissue reconstruction
- Sequesters inflammatory cells

Amniotic Membranes

- Cryopreserved
- Dehydrated

Pros and cons of Amniotic Membrane Modalities

**Cryopreserved**
- Self-retaining on cornea
- Higher levels of regenerative complex HC-HA/PTX3
- Shorter storage life – requires refrigeration
- Potential discomfort from symblepharon ring
- Avoid with filtering procedures

**Dehydrated**
- Longer storage life – room temperature
- No ring = better comfort
- Frequent slippage
- Requires bandage lens to maintain position

***For all amniotic membranes, RCTs limited***

Clinical Study

**Corneal Nerve Regeneration after Self-Retained Cryopreserved Amniotic Membrane in Dry Eye Disease**

Thomas John,1,2,3 Sunnithi Thippa,1,2,3 Homam Shehata,1,2,3 Pedram Hashemi,1,2,3 Zeina M. Salama,1,2
Amy M. L. Cheng,1,2 Ming L. Wang,1,2,3 and Nathan D. Rock1,2

1Department of Ophthalmology, Case Western Reserve University, Cleveland, OH, USA
2Johns Hopkins University School of Medicine, Baltimore, MD, USA
3Johns Hopkins University School of Medicine, Baltimore, MD, USA
**Neurotrophic Keratitis: Etiology**

1. Infectious: HSV, VZV, leprosy
2. CN V palsy
   - Surgery for trigeminal neuralgia, neoplasia (acoustic neuroma), aneurysm, facial trauma, congenital, familial dysautonomia (Riley-Day syndrome), Goldenhar-Gorlin syndrome, Möbius syndrome, familial corneal hypesthesia
3. Topical medications: anesthetic abuse
4. Iatrogenic: LASIK/PRK, corneal incisions (RK, AK), contact lens wear, scleral bands, vitrectomy and photoacoagulation to treat diabetic retinopathy
5. Chemical and physical burns
7. Increasing age, chronic DED

**Neurotrophic Keratitis: Classification**

Mackie classification

- Stage I is characterized by hyperplasia and/or irregularity of the epithelium, evolving to punctate keratopathy, corneal edema, neovascularization, stromal scarring.
- Stage II is defined by a recurrent or persistent epithelial defects or a PED without stromal thinning.
- Stage III: stromal involvement leads to corneal ulcer, melting and perforation

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**Improvements in Clinical Signs and Symptoms**

- Corneal Staining Grading
- Pain Scoring
- SPEED Questionnaire Scoring

**Improvements in Corneal Nerve Density & Sensitivity**

- Baseline
- 1 Month
- 3 Months

**Cryopreserved Self-retaining AMT**

- Pre-Prokera
- s/p Prokera (placed for 5 days)

**Amniotic Cytokine Extract Drop**

- Genesis - Amniotic cytokine extract (ACE) for the treatment of ocular surface disease.
- Cryopreserved amniotic eye drops contain more than 120 cytokines, growth factors and anti-inflammatory molecules to modulate and restore balance to the tear film
- Regener-Eyes
- Sterile, acellular biologic made from 771 anti-inflammatory cytokines, and growth factors

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Endogenous Nerve Growth Factor (NGF) and its Role in NK:

- Neuregulin/neuregulin (NE) is a crucial factor in ocular neuronal development and maintenance.
- Endogenous NGF maintains corneal integrity by three mechanisms:
  - Lacrimation and blink reflex
  - Epithelial cell vitality, metabolism, mitosis
  - Corneal Trophism and repair
- Cenegermin-bbkj, a novel recombinant human nerve growth factor (rhNGF), is structurally identical to the NGF protein.

Active Ingredient Structurally Identical to Human Nerve Growth Factor Produced in Ocular Tissues

- Naturally occurring neurotrophin is responsible for differentiation, growth, and maintenance of neurons.
- The regenerative potential of nerve growth factor (NGF) was discovered by Nobel-prize winning scientists in the early 1950s.
- Cenegermin-bbkj, a novel recombinant human nerve growth factor (rhNGF), is structurally identical to the NGF protein.

OXERVATE™ (cenegermin-bbkj 20 mcg/ml) was approved by FDA in August 2018

- Approved for the treatment of neurotrophic keratitis in adults and children age 2 and older.
- Available for ordering since January 2019.
- Developed by Dompé pharmaceuticals, available through specialty pharmacy.

OXERVATE™ (cenegermin-bbkj) 0.002%

- Pivotal Trials Study Design: All subjects with Stage 2 or 3 NK
- Efficacy Established as Early as Week 4

OXERVATE™ (cenegermin-bbkj) ophthalmic solution 0.002% Dosing and Administration

- Every 2 hours, instill 1 drop of OXERVATE™ (cenegermin-bbkj ophthalmic solution 0.002%)
- Apply 6 times daily
- Continue for 8 weeks

Efficacy Established as Early as Week 4

- Up to 72% of patients who received OXERVATE™ (cenegermin-bbkj ophthalmic solution 0.002%) were completely healed at week 8.
Up to 72% of patients achieved complete corneal healing; 80% of healed patients were recurrence free after 1 year*

Dry Eye Disease

- **Anakinra (Kineret)**
  - Recombinant version of human IL-1Ra currently approved for RA
  - Inhibits the interaction of IL-1 alpha and IL-1 beta
  - IL-1 directly correlated to corneal fluorescein staining, nociception
  - Anakinra 2.5% topical
    - Significantly more effective than vehicle (Refresh Lipigel) in improving signs and symptoms of dry eye
    - 4x reduction in corneal staining
    - 6x reduction in symptoms
    - Termination of use at week 12 led to increased symptoms at 3 month

Guidelines for use of Biological Medications in Sjogren’s Disease

- TNF-a inhibitors should not be used to treat sicca symptoms in patients with primary SD.
  - Strength of recommendation: strong
- Rituximab may be considered as a therapeutic option for KCS in patients with primary SD and for whom conventional therapies, including topical moisturizers, secretagogues, anti-inflammatories, immunomodulators, and punctual occlusion, have proven insufficient.
  - Strength of recommendation: weak

Botulinum Toxin

- Cosmetic uses
- Functional uses
  - Blepharospasm – 70-90% effective
  - Hemifacial spasm
  - Eyelid apraxia
  - Myokemia
  - Lid Retraction
  - Exposure keratopathy
  - Strabismus

“Beauty is in the Eye of the Beholder.”

- By treating the visual evidence of loose skin (by improving wrinkles and volume), a combination of both fillers and neurotoxin can reduce the evidence of aging
Botulinum Toxin

- Neurotoxin produced by *C. botulinum*
- Blocks release of acetylcholine from presynaptic neuron at neuromuscular junction causing paralysis
- Serotype A used commercially in two forms:
  - Botox (onabotulinumtoxinA)
  - Dysport (abobotulinumtoxinA)
  - Botox 3x more potent than Dysport

Botulinum Toxin

- Inhibits neurotransmission at neuro-muscular junction (acetylcholine, others)
- Leads to chemical denervation striated muscle
- Peaks at 2 weeks
- Neuronal sprouting heralds return of function @ 3 – 6 mos.

Botulinum Toxin

- On-label therapeutic uses in ophthalmology
  - Blepharospasm
  - Hemifacial spasms
  - Strabismus
- Off-label therapeutic uses in ophthalmology
  - Protective ptosis → induce upper lid ptosis and closure
    - Lag ophthalmos s/p acute Bell's Palsy, exposure keratopathy, poorly healing defect
  - Alternative to permanent tarsorrhaphy
  - Tx of filamentary keratitis with a blepharospasm component

ZYTAZE®

- ZYTAZE® provides nutritional support to enhance and prolong the effectiveness of botulinum toxin injections in the treatment of blepharospasm, hemifacial spasm or facial cosmetic procedures.
- ZYTAZE® is specially formulated with a unique patent-pending combination of organic zinc along with phytase (an enzyme that neutralizes phytates in the digestive tract aiding in the absorption of zinc) to enhance the effectiveness of botulinum toxin injections.
- Each Capsule Contains:
  - 25 mg Zinc Citrate
  - 500 mg Phytase

ZYTAZE® Study

In the completed formal study* consisting of 77 patients, ZYTAZE® again demonstrated a significant increase in the effect and duration of botulinum toxin injections. In fact, the duration of effect increased from 23.6% in the pilot study to 30% in the completed formal study.

The completed formal study has been published in the Journal of Drugs in Dermatology.

Teprotumumab (RV 001)

- An antibody directed against IGF-1, the growth factor pathway associated with the thyroid-hormone receptor
- Teprotumumab is the only medicine to date proven to reduce overall clinical severity and proptosis, and provide a sustained response.1
- Can halt progression of active disease and reverse any changes associated with TED, and the effects are long-lasting.1

Anti-VEGF

- Bevacizumab (Avastin)
  - Full length monoclonal antibody that non-specifically binds to VEGF at two sites.
  - Off-label use, must be compounded.
  - CHEAPER.
- Ranibizumab (Lucentis)
  - Fragment antigen binding monoclonal antibody derived from bevacizumab.
  - Specifically targets VEGF-A.
  - 0.3 and 0.5 mg injection.

Systemic Considerations in Anti-VEGF

- True prevalence of AE’s difficult as patients often have multiple co-morbidities.
- Systemic effects uncommon, but include the following:
  - Stroke.
  - Hypertension.
  - Myocardial infarction.
  - Hemorrhage.
  - Decreased pulmonary surfactant – pediatric consideration.

Future Treatments in Pipeline

**Newer Anti VEGF’s**
- Brolucizumab.
- Faricimab.
- Abicipar.
- Conbercept.

**Other Modalities**
- Sustained release devices.
- Gene therapy.
- Stem cells.

Conclusions

- Biologics are the next wave of pharmaceutical development, and are playing an increasing role in the management of ophthalmic conditions.
- Integration and management of these medications requires a multi-disciplinary approach.
- Staying up to date on the most active biologics allows us to find a role in this care team.