Ocular Biologics, Biosimilars, and Drugs for the Eye

Greg A. Caldwell, OD, FAAO
Tracy Offerdahl, PharmD, FAAO
Heart of America
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Disclosures - Greg Caldwell, OD, FAAO
- The content of this activity was prepared independently by me - Dr. Caldwell
- Lectured for: Alcon, Allergan, Aerie, BioTissue, Kala, Menologix, Optovue, RVL, Heru
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- Evolveth: PA Medical Director, Credential Committee
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Biologic Drugs
- Biologic therapies include wide range of medical products
  - First-generation biologic therapies
  - Vaccines
  - Blood products
  - Stem cell injections
- Today, when people talk about “biologics” they usually mean the second-generation biologic therapy drugs
  - Humira, Remicade, Enbrel
- Biologic therapies
  - Can not be made using a simple chemical reaction
  - Mixing ingredients together in a laboratory, the way conventional drugs are made
  - Are made using living organisms

Small Molecule Drugs versus Biologics
- Small molecule drugs are made by adding and mixing together known chemicals and reagents using a series of controlled and predictable chemical reactions (i.e. organic chemistry)
- Small biologics are made by harvesting the substances produced and secreted by constructed cells (i.e. genetic engineering)

Size and Complexity of Biologic Drugs
- Small molecule drugs can be taken orally
  - Tend to work in the body within cells
  - Biologics are significantly larger in size
  - Typically targeted and interact within the body in the bloodstream or on the surfaces of cells, rather than within the cells
- Small molecule drugs
  - Both in aqueous
  - Composed of only 30 to 100 atoms
- Small biologics
  - Both in aqueous
  - Composed of 200 to 3000 atoms
- Large biologics
  - Both in aqueous
  - Composed of 5000 to 50,000 atoms
Biologic Drugs versus Small Molecule Drugs

**Biologic Drugs**
- Larger, complex, dynamic structures
- Diverse populations of molecules
- Not easily documented
- Complicated manufacturing
- Example: Teprotumumab (Tepezza)

**Small Molecule Drugs**
- Synthesis
- Manufactured using a defined chemical process
- Smaller and simpler
- Example: Aspirin

Size and Complexity of Biologic Drugs

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Making Biologics

A piece of DNA is inserted into a living cell—yeast, bacterial, viral, or mammalian cell

- Cell then produces a large amount of a specific molecule (e.g. protein)
- Desired molecular isolation (living cells/material removed - only the desired molecules are left)
- The isolated molecules become the active ingredient in a biologic drug

What is a Biologic versus Biosimilar?

**Biologic**
- Isolated from natural sources: human, animal, or microorganism
- "High-tech" treatments; AKA "biotechnology"
- Difference between "regular/chemical drugs" and "biologics"...
  - "Regular/Chemical drug"—usually synthesized with known chemical structures
  - "Biologic"—very complex mixtures that are NOT easy to identify

**Biosimilar**
- "Highly similar" to the "reference product" (i.e. the biologic/reference or innovator product)
- FDA’s approach: The biosimilar company’s research is to PROVE "biosimilarity" between the proposed biosimilar product and the reference product…NOT to independently establish the safety and effectiveness of the proposed product

- There are no clinically meaningful differences in terms of:
  - Safety
  - Efficacy
  - Bioavailability

- Why is there no such thing as a GENERIC biologic medication?
  - Biologics come from LIVING "things", so it is not likely to be EXACTLY the same as the reference product (USUALLY differs in terms of inactive ingredients)
  - Generic medications are chemically synthesized so that the active ingredient is IDENTICAL to the brand name medication
Biologic versus Biosimilar

Biologics are Immunomodulating/Immunosuppressive medications
- HIGH immunogenicity potential because they "tinker" with the immune system & come from nature
- Small molecule drugs have LOW immunogenicity because they are synthetic
- Many of the systemic agents for autoimmune disease can cause significant morbidity and mortality!
- Most place PPD before initiating = if PPD+, then initiation of a biologic may convert latent TB to ACTIVE tuberculosis
- Once a biologic is initiated, watch for any signs or symptoms of infection
  - If the patient has a "cold", "flu", or is taking antibiotics
  - The biologic dose must be HELD until the patient is healthy
  - FULL work-up for signs/symptoms of infection!
  - Ask your patients about meds!
  - We will look at the diversity of the side effects with these newer biologics

Ocular Biologics

Disorders of the blood vessels in the retina are responsible for some of the most common causes of blindness in the world
- Retinopathy of prematurity
  - Important cause of blindness in children in middle-income countries
- Diabetic retinopathy
  - Common cause of blindness in the working-age population of industrialized countries
- Age-related macular degeneration
  - A common cause of blindness in the world
- These conditions are caused partly by over-production of a protein called vascular endothelial growth factor (VEGF)
- VEGF was discovered in the 1980s and is important in the growth and development of blood vessel in tumor growth
- 1994 it was proven that retinal hypoxia produces VEGF

Treatments for Choroidal Neovascularization (CNV)

Current Anti-VEGF treatments
- Pegaptanib (Macugen)
  - First FDA Approved December 2004
  - RNA aptamer
  - AMD
- Bevacizumab (Avastin)
  - Humanized full length monoclonal antibody
  - 2005 AMD
- Ranibizumab (Lucentis)
  - Humanized monoclonal antibody fragment
  - 2006 AMD, DME, DR, RVO
- Aflibercept (Eylea)
  - Fusion protein
  - 2011 AMD, DME, D
- Brolucizumab (Beovu)
  - Humanized single chain antibody fragment
  - 2019 Up to 3 months dosing intervals, most are 4-6 weeks

Greg-grubod@gmail.com  814-931-2030
Tracy-drofferdahl@gmail.com  267-241-9146
Oxervate™ (cenegermin-bkj)
- Approved 2018 (August 28, 2018)
- Dompe farmaceutici SpA
- Ophthalmic solution indicated for the treatment of neurotrophic keratitis
- Dosing: Insert 1 drop in affected eye 6 times per day (at 2-hour intervals) for 8 weeks
  - Use as eye drop
  - Take before or after meals
- Contraindications
  - None

Storage issues: In the freezer at the pharmacy
- Patient keeps the individual vials in the fridge
- Once “actively ready” for use, then it is only stable for 20 hours

Escherichia Coli

Corneal Homeostasis

Pathophysiology of NK

- The loss of corneal sensory innervation via damage to the trigeminal nerve induces release of neurotransmitters that provide both functional support to the ocular surface tissues, maintain wound healing and maintain ocular homeostasis
- Impairment of corneal sensitivity also affects tear production and blink rate due to the reduction of trigeminal nerve stimulation
- Impairment of trigeminal innervation leads to diminished corneal epithelial renewal and healing rate, and ultimately the development of NK

Etiologies Associated with NK

- Necrotizing limbal or corneal ulcers
- Other infections (e.g., acanthamoeba, HSV, CMV, EBV, VZV, Coxsackievirus)
- Progressive corneal neurotrophic keratitis
- Drug toxicity
- Central nervous system disorders
- Degenerative CNS disorders
- Post-neuromuscular conditions
- For acute cornea
- For subacute cornea
- For corneal scar
- Familial corneal hypoaesthesia

Central nervous system
- Multiple sclerosis
- Amyotrophic lateral sclerosis
- Neurogenic facial palsy
- Post-traumatic

Scarring
- Traumatic
- Chemical or physical burn
- Other infections
- Surgical or laser treatment

- Neurotrophic keratitis
- Impairment of trigeminal innervation

Central nervous system
- Multiple sclerosis
- Amyotrophic lateral sclerosis
- Neurogenic facial palsy
- Post-traumatic

Genetic
- Sjogren-Syndrome Parabiosis
- Goldenhar-Gorlin syndrome
- Multiple congenital
- Familial corneal hypoaesthesia

Corneal nerve damage leading to NK
Ocular Biologics, Biosimilars, and Drugs for the Eye

NK classification

- Stage 1: Substantia propria only
- Stage 2: Substantia propria, with overlying defect
- Stage 3: Complete epithelial defect

Assessment of Corneal Sensitivity is Essential to Confirm NK diagnosis

- Ocular symptoms
- History
- Clinical examination and tests
- Corneal sensitivity tests
  - Qualitative (touching cornea with cotton thread)
  - Quantitative (corneal aesthesiometer)
  - Severity of NK-related to severity of corneal sensory impairment

Corneal Sensitivity

- Normal
- Mild
- Further tests required

Endogenous NGF maintains corneal integrity by three mechanisms

- CORNEAL INNERVATION
- CELL PROLIFERATION AND DIFFERENTIATION
- TEAR SECRETION

OXERVATE™ (cenegermin-bkbj) ophthalmic solution 0.002% Weekly Device Kit

- OXERVATE is supplied in a weekly carton containing 7 multiple-dose vials
- A separate weekly Delivery System Kit contains the supplies needed to administer treatment

The Delivery System Kit Contains:

- 7 vial adapters
- 42 pipettes
- 42 sterile dispensing tips
- 1 dose recording card
- 1 extra adapter, 3 extra pipettes, 3 extra tips are included as spares

Active ingredient structurally identical to human nerve growth factor produced in ocular tissues

- Naturally occurring neurotphin is responsible for differentiation, growth, and maintenance of nerve
- The regenerative potential of nerve growth factor (NGF) was discovered by Nobel prize winning scientist, in the early 1990s
- Cenegermin-bkbj, a novel recombinant human nerve growth factor, is STRUCTUARILY IDENTICAL to the NGF protein

Greg-grubod@gmail.com 814-931-2030
Tracy-drofferdahl@gmail.com 267-241-9146
Cenegermin Mimics the Structure of Endogenous NGF in the Ocular Tissues

Cenegermin-bkbj, the active ingredient in the FDA-approved OXERVATE™ (cenegermin-bkbj ophthalmic solution) 0.002% (20 mcg/mL), is structurally identical to the human NGF protein found in ocular tissues.

OXERVATE™ (cenegermin-bkbj) ophthalmic solution 0.002%

Dosing and Administration

2 6 8

Every 2 hours Apply 6 times daily Continue for 8 weeks

Let’s Hear From a Patient

April 7, 2020 - After 1 week
April 21, 2020 - After 3 weeks
May 12, 2020 - After 6 weeks

Study Conclusions

After 8 weeks of treatment, 6 times daily

Of patient who healed after one 8-week course of treatment...

80% Remained healed for one year*

*Based on REPARO, the study with longer follow-up

Safety:
The most common adverse reaction was eye pain following instillation which was reported in approximately 16% of patients. Other adverse reactions occurring in 1-10% OXERVATE™ patients and more frequently than in the vehicle-treated patients included:

- Corneal deposits
- Foreign body sensation
- Ocular hyperemia
- Ocular inflammation
- Tear increase

Contact lenses (therapeutic or corrective) should be removed before applying cenegermin. Presence of a contact lens may limit the distribution of cenegermin-bkbj onto the corneal lesion. Lenses may be reinserted 15 minutes after administration.

Thyroid Disease and Thyroid Eye Disease
What is the most common cause of thyroid dysfunction?
A. Cancer
B. Surgically induced
C. Medication toxicity or side effect
D. Pregnancy
E. Autoimmune disease

In autoimmune disease the body typically produces _______ that attacks itself, this can be systemic or organ specific.
- Antibodies, immunoglobulins

Antibodies of Thyroid Dysfunction

**TSH Receptor Antibodies**
- Stimulation TSH receptor antibody
- Thyroid Stimulating Immunoglobulin (TSI)
- Thyroid blocking antibody (TBAb)
- TPO is found in thyroid follicle cells where it converts the thyroid hormone T4 to T3
- TBAb contributes to thyroid cellular destruction

**Thyroid Peroxidase Antibodies (TPOAb)**
- TPO is found in thyroid follicle cells where it converts the thyroid hormone T4 to T3
- TPOAb contributes to thyroid cellular destruction

Most autoimmune thyroid dysfunctions have a combination of thyroid antibodies, however depending on which AB is more abundant results in the outcome of the disease

**Thyrotoxicosis**
- Graves Disease
- Basedow or von Basedow

**Hypothyroidism**
- Chronic Autoimmune Thyroiditis
- Hashimoto’s thyroiditis
- Autoimmune atrophic thyroiditis
- Primary myxedema
- Opposite of Graves disease
- Postpartum thyroiditis

**Thyroid eye disease**

**Thyroid eye disease has 2 phases**
- A phase secondary to abnormal thyroid hormone levels
  - Increased or decreased T3 and T4 levels
- Once these levels are normalized, ocular symptoms will resolve
- Congenital Autoimmune form of Thyroid eye disease
- Active phase/occurs in the early stage or treatment
- Protein phase/resolves activity
- Resolution phase/symptoms regress and eyes return to normal
Congestive Autoimmune form of Thyroid Eye Disease
(Active phase, Plateau phase, Resolution phase)

- Caused by both stimulating and blocking TSH receptor antibodies (TRAbs) and also immune system chemicals known as cytokines
- Secondary targets appear to be TSH receptor antigens (epitopes) located on orbital fibroblasts as well as dermal fibroblasts
- Active "inflammatory" phase of TED varies
  - Symptoms resolve quickly on average the active phase lasts about 12-18 months
  - If TRAbs levels are high, patients are smokers, nutrient deficiencies are present, or the patient continues to be exposed to environmental triggers such as excess dietary iodine, the active phase can last as long as 5 years
  - Avoid any lid, muscle or orbital surgery
- Plateau phase and Resolution "Passive" phase
  - An idiosyncratic mix of epithelial changes such as eye protrusion, eyelid retraction, and in some cases, double vision
  - There are corrective procedures that can be performed to address these problems

Symptoms:

- Lid Retraction: von Graefe’s Sign
  - Immobility or lagging of upper eyelid on downward gaze
  - Fibrosis of the inferior rectus muscle may induce lower lid retraction

- Conjunctiva
  - Conjunctival and epithelial injection
    - Especially near the horizontal eye lesions
  - Chemosis
    - Swelling of the conjunctiva and cornea
  - Infection (bacterial or viral)
  - 60-70% correlation between TED and systemic thyroid disease
  - Rheumatoid arthritis
  - Sjögren’s syndrome

Normal Lid Position:

- Upper lid intersects cornea at 2 and 10 o'clock positions
- ~2 mm below the limbus
- Lower lid coincident or 1-2 mm below the limbus

Normal Values:

- Thyroglobulin: 20 IU/ml
- Perioxidase: <35 IU/ml
- TSI: 1.75 IU/ml

It does work!
**Periorbital Edema**

- Inflammation of the subcutaneous connective tissue
- May be first sign of thyroid eye disease
- Greatest in the morning

**Infiltrative Orbitopathy (Exophthalmos/Proptosis)**

- Thyroid Eye Disease is most common cause of unilateral and bilateral exophthalmos
- The term exophthalmos is reserved for prominence of the eye secondary to thyroid disease
- May need MRI to determine or obvious exophthalmos may be present
- It is permanent in 70% of cases
- Caused by increased volume of the extra ocular muscles
  - Lymphocytic infiltration
  - Proliferation of fibroblasts
  - Edema within the interstitial tissue of the muscle

**Infiltrative Orbitopathy (Exophthalmos/Proptosis)**

**Treatment of Thyroid Eye Disease**

- **Palliative (hormone imbalance, active, passive)**
  - Lubricants
  - Topical anti-inflammatory (Lotemax/Restasis)
  - Prisms
- **Steroids (active phase)**
  - Oral
  - Periocular injections
  - IV with oral steroid taper
- **Orbital radiotherapy (active phase)**
- **Orbital Decompression (passive phase)**
  - Large orbits
  - Bone removal orbital decompression (BROD)
  - Endoscopic
  - Both BROD and FROD

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Greg-grubod@gmail.com  814-931-2030  
Tracy-drofferdahl@gmail.com  267-241-9146
Lid Retraction, Eyelid Lag, Lagophthalmos

- Must treat underlying thyroid dysfunction
- Abnormal hormone level and Active phase
- Treat the exposure keratitis with lubricants
- Tape eyelids shut at night
- Moist chamber at night
- Antibiotic ointments

Passive Phase
- Surgical management
- Inferior rectus recession
- Mullerotomy
- Recession of lower lid retractors

Lid Retractor Surgery

Conjunctiva, Periorbital edema

- Topical lubricants
  - Artifical tears
  - Ointment
  - Eyelash gloves
  - Bandage
- Tape eyelids closed at night or use mask
- Elevate head at night to decrease lid edema
- Oral diuretics: acetazolamide
- Oral steroids
  - 60-80mg/day for 3 months
  - IV steroids
- Periorbital steroids
  - Kenalog
- Topical steroids
- Restasis

- Tape eyelids closed at night or use mask
- Elevate head at night to decrease lid edema
- Oral diuretics: acetazolamide
- Oral steroids
  - 60-80mg/day for 3 months
- IV steroids
- Periorbital steroids
- Kenalog

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Restrictive Myopathy

- Non-surgical (while waiting for stability)
  - Teach patient head position to alleviate diplopia
  - Place in spectacle corrections (below or ground it)
  - Oral steroids
  - Botulinum toxin injection
- Surgical Consult
  - Decompression of the rectus muscle involved
  - Dilation of primary gaze, reading gaze or both
  - At least one of these for at least 6 months
  - No evidence of active disease
  - Binocular vision in at least primary and reading positions

Optic Neuropathy

- Systemic steroids
  - If rapidly progressive and painful in the early stage of the disease
  - Only if no contraindications
  - Prednisolone 80-100mg, expect results within 48hrs. Taper dose and dc within 3 mo
- IV Methylprednisolone
- Radiotherapy: if contraindication to steroid
- Orbital decompression

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Greg grubod@gmail.com  814-931-2030
Tracy drofferdahl@gmail.com  267-241-9146
Orbital Decompression

- Not effective if no medical treatment
- Two-wall decompression
  - 3-6 mm retroplacement of the globe
- Three-wall decompression
  - 6-10 mm retroplacement
- Four-wall decompression
  - 10-16 mm retroplacement

February 25, 2019
“Nothing Else Can Be Done”

Oral and Topical Steroids

February 25, 2019
“Nothing Else Can Be Done”

Oral and Topical Steroids

March 1, 2019 (4 days later)

March 1, 2019 (4 days later)

March 25, 2019
Teprotumumab-trbw (Tepezza)

- Horizon Therapeutics – HQ Dublin, Ireland and US based Chicago
- Biologic pharmaceutical
  - Ocular human IgG1
  - Infuse 3 total monthly
- Thyroid eye disease
  - U.S. Food and Drug Administration approved for treatment
  - IgG1 receptor inhibitor monoclonal antibody
  - Inhibits IGF-1 receptor
  - Inhibits downstream inflammatory cytokines, hyaluronidase, and chemokines
- Phase 2 and published in New England Journal of Medicine
- Phase 3 completed
- PDUFA - March 2020; was approved early in 2020

https://www.tepezza.com/hcp/tepezza-moa/
Teprotumumab-trbw (Tepezza)

- **Optics and Optic-X Studies**
  - 6 infusions, every 3 weeks: 24 weeks
  - Optic: acute, less than 6 months of disease
  - Optic-X: chronic, 12-16 months disease

- **Clinical Activity Score**
  - Spontaneous pain, gaze evoked pain, eyelid erythema, chemosis, inflammation
  - Scale of 7, needed 4 to be in the study

- **Proptosis**
  - Improvement of 2 mm or better
  - Scale of 0, 1, 2, or 3
  - Grave’s Optic Neuropathy - Quality of Life Score
  - Scale 0-100

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  - Spontaneous pain, gaze evoked pain, eyelid erythema, chemosis, inflammation
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  - Grave’s Optic Neuropathy - Quality of Life Score
  - Scale 0-100

- **Adverse Reactions**
  - Very well tolerated
  - The most common adverse reactions (incidence ≥5% and greater than placebo) are muscle spasm, nausea, alopecia, diarrhea, fatigue, hyperglycemia, hearing impairment, dysgeusia, headache, and dry skin.

- **Infusion Reactions (mild/moderate):** approximately 4% of patients
  - Transient increase in blood pressure, feeling hot, tachycardia, dyspnea, headache, and muscular pain
  - Consideration should be given to premedicating with an antihistamine, antipyretic, or corticosteroid and/or administering at a slower infusion rate.

- **Hyperglycemia:** Increased blood glucose or hyperglycemia
  - In clinical trials, 10% of patients experienced hyperglycemia
  - Monitor patients for elevated blood glucose and symptoms of hyperglycemia while on treatment with teprotumumab
  - Patients with preexisting diabetes should be euglycemic before beginning treatment

- **Humira™ (adalimumab)**

  - **Company:** AbbVie
  - **Approved July 2016**
  - **Indications:** uveitis
    - Specifically indicated for the treatment of non-infectious intermediate, posterior and panuveitis
  - **Dosage:** subcutaneous injection
    - Recommended dose is 80 mg initial dose
    - Followed by 40 mg every other week starting one week after initial dose
  - The significance of this FDA approval is important! Many insurance companies (ex. Medicare) will not pay for “off-label” uses.

Greg-grubod@gmail.com  814-931-2030
Tracy-drofferdahl@gmail.com  267-241-9146
Non-infectious intermediate, posterior and panuveitis

Reason for reduced acuity?

Monitoring parameters:
- Must place PPD before initiating = if PPD+, then initiation of Humira may convert latent TB to active tuberculosis.
- Once Humira is initiated, watch for any signs or symptoms of infection...if the patient has a "cold", "flu", or is taking antibiotics, then Humira dose must be HELD until the patient is healthy.

Biosimilars
- Hadlima (Adalimumab-bwwd)
- Biologic agent SIMILAR to Humira

What is a "biosimilar" agent?
- Remember what the FDA say about "biosimilars"

Let's qualify this statement

**Actemra** (tocilizumab)

**Actemra** (tocilizumab)

Actemra™ (tocilizumab)

- First innovative therapy for GCA in more than 50 years
- Design to speed the development for treatments of serious diseases such as GCA and certain cancers

Patients were randomized to receive tocilizumab 162 mg weekly injections plus a 6-month and 12-month prednisone taper compared to controls receiving placebo plus similar steroid taper.

The preliminary results indicate that patients receiving high dose tocilizumab had superior disease remission at 1 year compared to the steroid-only taper.

Further investigation from this study will attempt to identify the lowest therapeutic dose of prednisone that can be used in patients also using tocilizumab, the amount of tocilizumab needed to induce remission, and how long patients stay in remission on this therapy.

Sustained Glucocorticoid-free Remission at Week 52

Cumulative Prednisone Dosage
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Greg - grubod@gmail.com  814-931-2030
Tracy - drofferdahl@gmail.com  267-241-9146

Actemra™ (tocilizumab)

- Tocilizumab does not directly treat GCA
  - Reduces steroid load after disease has been adequately treated by steroids and enhances disease remission
- Steroids are main therapy
- Studies are ongoing to see:
  - What is the lowest steroid tapering dose that can be used with tocilizumab
  - Future studies may show tocilizumab as steroid replacement

Tocilizumab (Actemra)

- WARNING: RISK OF SERIOUS INFECTIONS
  - See full prescribing information for complete boxed warning.
  - Serious infections leading to hospitalization or death, including tuberculosis (TB), bacterial, invasive fungal, viral, and other opportunistic infections have occurred in patients receiving ACTEMRA. (5.1)
  - If a serious infection develops, interrupt ACTEMRA until the infection is controlled. (5.1)
  - Perform test for latent TB if positive, start treatment for TB prior to starting ACTEMRA. (5.1)
  - Monitor all patients for active TB during treatment, even if initial latent TB test is negative. (5.1)

Biologics

No ocular indication

Olumiant™ (baricitinib) and Rinvoq™ (upadacitinib)

- Janus Kinase inhibitors – approved 2018 and 2019
  - Indicated for the treatment of adult patients with moderate/severe active rheumatoid arthritis
  - Must have failed 1 or more TNF-α inhibitors (e.g. Remicade, Humira)
- THE HUB-BUB? It is orally administered, as opposed to MOST of the others that are injectables!
  - Known as “un-injections”

Family Medicine

- Aimovig™ (erenumab-aooe)
  - Approved 2018
  - Indicated for the PREVENTIVE treatment of migraine in adult patients
  - Galcanezumab gene related receptor antagonist
    - SQ injection
    - Once per month for either product
    - Once every three months for Ajovy™
  - ADRs: constipation, injection site reactions

Erenumab (Aimovig)

- Aims to prevent migraine in adults with or without aura
  - AOCO in the pre-marketing setting. There were seven cases of apparent hospitalizations, including cases where severe nausea managed. In a majority of these cases, the use of concomitant medication was critical for the treatment. AOCO is not recommended in patients with a history of severe or moderately severe complex migraine. Concomitant use of any two medications is recommended in patients with a history of severe or moderately severe complex migraine. Concomitant use of two medications is recommended in patients with a history of severe or moderately severe complex migraine. Concomitant use of two medications is recommended in patients with a history of severe or moderately severe complex migraine.

Emetron (Remicade)

- Approved 2018
- Indicated for the Treating of adult patients with moderate/severe active rheumatoid arthritis
- Must have failed 1 or more TNF-α inhibitors (e.g. Remicade, Humira)

Aimovig™ (erenumab-aooe)

- Approved 2018
- Indicated for the PREVENTIVE treatment of migraine in adult patients
- Galcanezumab gene related receptor antagonist
  - SQ injection
  - Once per month for either product
  - Once every three months for Ajovy™
- ADRs: constipation, injection site reactions
Galimedix Therapeutics is a Phase 2 neuropharmaceutical company developing novel first-in-class drugs with ground-breaking potential to slow or stop the progression of neurodegeneration and to improve function in glaucoma and dry AMD – leading causes of blindness – and also in Alzheimer’s disease.

https://www.galimedix.com/