NEW DRUG UPDATE 2019: A FORMULARY APPROACH *AND* EXCITING DRUGS IN THE PIPELINE

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Disclosure

- Dr. May does not have (nor does any immediate family member have) actual or potential conflict of interest, within the last twelve months, a vested interest in or affiliation with any corporate organization offering *financial support or grant monies* for this continuing education activity, or any affiliation with an organization whose philosophy could potentially bias this presentation.

Learning Objectives

After attending the lecture and discussion, the attendee should be able to:

- Compare and contrast newly approved drugs with older agents regarding their pharmacology, pharmacokinetics, efficacy, safety, dosage and cost.
- Apply the “formulary approach” to evaluating new drugs.
- Analyze potential utility of drugs in the pipeline for possible release in the next two years.

Drugs Currently Under Consideration for the "Formulary Approach" at AU

Meropenem/Vaborbactam (Vabomere®) by Medicines Co.
Plazomicin (Zemdri ®) by Achaogen
Omadacycline (Nuzyra®) by Paratek
Angiotensin II (Giapreza®) by La Jolla Pharmaceuticals
L-Glutamine (Endari ®) by Emmaus
Lofexidine (Lucemyra ®) by US WorldMeds/Salix
Erenumab (Aimovig ®) by Amgen/Novartis
Sarilumab (Kevzara ®) by Sanofi
Baloxavir (Xofluza®) by Shionogi
Dupilumab (Dupixent®) by Regeneron
Esketamine (Spravato®) by Janssen
Revefenacin (Yupelri®) by Theravance Biopharma

Formulary Approach

- A finite list of therapeutic agents
- Established value in light of current medical opinion
- Sufficiently broad to meet the usual clinical problems
- Avoids duplication of clinical effect
- Subject to continuing revision based on new therapeutic knowledge

Formulary Criteria

For a drug to be recommended for addition to our Formulary, it must meet at least one of the following:

- New Pharmacological Class
- More Efficacious
- Safer
- Pharmacokinetic Advantage (clinically relevant)
- More Cost Effective

Plazomicin (Zemdri®)

- Pharmacology
  - An aminoglycoside
  - Broad coverage against gram-negative aerobic organisms (like other aminoglycosides)
  - *Some* gram-positive coverage (*S. aureus*)
  - May cover multi-drug-resistant *Enterobacteriaceae*, including strains resistant to other aminoglycosides
  - Indication: Complicated UTIs in adults

Plazomicin (Zemdri®)

- Pharmacokinetics
  - Half-life 3 to 4 hours (normal renal function)
  - Eliminated via kidneys (97.5% unchanged)
    - Adjust dose with impaired renal function

Plazomicin (Zemdri®)

- Efficacy
  - Double-blind, randomized trial versus meropenem in cUTIs in adults (n=609) EPIC
    - Day 5 rates of symptomatic resolution, or improvement and microbiologic eradication
      - Plazomicin 88% Meropenem 91.4% (n.s.)
    - Days 15-19 composite cure
      - Plazomicin 81.7% Meropenem 70.1% ($p<0.05$)
    - Subgroup - 48 patients with bacteremia, day 15-19 composite cure
      - Plazomicin 72% Meropenem 56.5% (stats not reported)
    - Subgroup – 105 patients with aminoglycoside resistant *Enterobateriaceae*
      - Plazomicin 78.8% Meropenem 68.6%

Cloutier D et al. Unpublished study available at www.achaogen.com (accessed 12/21/18)

Plazomicin (Zemdri®)

- Safety
  - Impaired renal function ~3.6%
    - Most reversible
  - Reversible hearing loss – 1 patient in EPIC trial
  - Irreversible ototoxicity (hearing loss, tinnitus, or vertigo) – class effect?
  - Others similar to aminoglycoside class

Plazomicin (Zemdri®)

- Dosage
  - 15 mg/kg IV q24hr (total body weight)
    - If TBW ≥25% above IBW: use adjusted body weight (IBW+0.4X[TBW-IBW])
    - CrCl 30-59: 10 mg/kg q24hr
    - CrCl 15-29: 10 mg/kg q48hr
    - CrCl <15: no information available
  - Cost:
    - Plazomicin average daily cost = $945
    - Other aminoglycosides = < $25

Plazomicin (Zemdri®)

Criteria

- New Pharmacological Class
- *More Efficacious?*
- Safer
- Pharmacokinetic Advantage (clinically relevant)
- More Cost Effective

Erenumab (Aimovig®)

- Pharmacology
  - Monoclonal antibody against calcitonin gene-related peptide (CGRP) receptor
    - First drug in class
    - Blocks receptor activation
    - CGRP is potent vasodilator and pain signaling neurotransmitter.
    - CGRP levels increase during migraine attacks
  - Indication: preventive treatment of migraine in adults

Erenumab (Aimovig®)

- Pharmacokinetics
  - After SC injection:
    - Mean peak serum concentration: 6 days
    - Bioavailability: 82%
    - Elimination: Saturable binding to CGRP receptor then non-specific, non-saturable proteolytic pathway
  - No dosage adjustment for renal or liver impairment ***expected***
    - Only studied in mild to moderate renal impairment

Erenumab (Aimovig®)

- Efficacy
  - 3 randomized, double-blind, placebo-controlled trials (n = 955, 577, 677)

	Change in MMD	>50% reduction in MMD
• Episodic 1	-3.2 vs -1.8	43.3% vs 26.6%
• Episodic 2	-2.9 vs -1.8	39.7% vs 29.5%
• Chronic	-6.6 vs -4.2	39.9% vs 23.5%

Goadsby PJ et al. N Engl J Med 2017;377:2123
Dodick DW et al. Cephalagia 2018;38:1026
Tepper S et al. Lancet Neurol 2017;16:425

Erenumab (Aimovig®)

- Safety
  - Incidence and severity of ADRs
    - Most similar to placebo
      - Injection site reactions 5 – 6%
      - Constipation 1 – 3%
  - Anti-erenumab antibodies: 6.2%
  - No studies in pregnancy

Erenumab (Aimovig®)

- Dosage
  - 70 mg SC once monthly
    - Self injected in abdomen or thigh or
    - Caregiver injected in upper arm
  - Some patients need 140 mg (2 X 70 mg)
  - Note: auto injector contains dry natural rubber
    - May be a problem in patients with latex allergy
- Cost: $575 per month

Erenumab (Aimovig®)

Criteria

- New Pharmacological Class
- More Efficacious
- Safer
- Pharmacokinetic Advantage (clinically relevant)
- More Cost Effective

Baloxavir (Xofluza®)

- Pharmacology
  - Inhibits Cap-dependent endonuclease
    - Necessary for viral messenger RNA transcription
    - Blocks viral replication
  - First drug with new mechanism in 20 years
  - Active against influenza A and B
  - Indicated for acute uncomplicated influenza in patients ≥ 12 years

Baloxavir (Xofluza®)

- Pharmacokinetics
  - Tmax = 4 hours
  - Metabolized
    - UGT1A3 (major) CYP3A4 (minor)
  - Elimination: feces (80%) urine (15%)
  - Half-life: 79 hours

Baloxavir (Xofluza®)

- Efficacy
  - CAPSTONE – 1 (n = 1064)
    - 12- 64 years, uncomplicated influenza, symptomatic ≤48 hours
    - Baloxavir 40 mg once vs placebo vs oseltamivir 75 mg X 5 days

    Both drugs: reduced symptom time by 26 hours

    Viral shedding cessation: baloxavir 24 hours, oseltamivir 72 hours
  - CAPSTONE – 2 (n = 1163) NOTE: not published
    - Baloxavir may shorten symptom alleviation time > oseltamivir in patients with influenza B

Hayden FG et al. New Engl J Med 2018;379:913

Hayden FG et al. Med 2018;379:913

Baloxavir (Xofluza®)

- Safety
  - Well tolerated in trials
  - *May* have less N & V than oseltamivir
  - Avoid co-administration with antacids or other agents containing:
    - Calcium, aluminum, iron, magnesium, selenium, or zinc
  - Reduced susceptibility has been reported after a single dose

Baloxavir (Xofluza®)

- Dosage
  - 40 kg to <80 kg: 40 mg (2 X 20 mg) once
  - ≥ 80 kg: 80 mg (2 X 40 mg) once
  - Must start within 48 hours of symptom onset
- Cost
  - Baloxavir $150
  - Oseltamivir $93 (generic) - $152 (brand)

Baloxavir (Xofluza®)

Criteria

- New Pharmacological Class
- More Efficacious
- Safer
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Other Approvals of Interest

- Tezacaftor/ivacaftor (Symdeko®) – cystic fibrosis
- Coagulation factor Xa, inactiviated-zhzo (Andexxa®)
  - Reversal of factor Xa inhibitors
- Deutetrabenezine (Austedo®) – treatment of tardive dyskinesia
- Ertugliflozin (Steglatro®) - diabetes
- Semaglutide (Ozempic®) - diabetes
- Benralizumab (Fasenra®) – severe eosinophilic asthma
- Fremanezumab (Ajovy®) – migraine prevention
- Galcanezunab (Emgality®) – migraine prevention
- Prucalopride (Motegrity®) – chronic idiopathic constipation
- Eravacycline (Xerava®) – complicated intra-abdominal infections
- Brexanolone (Zulresso®) – post-partum depression

Most Exciting Drugs in the Pipeline: 2019-2020 (in no particular order)

- **VX-659 + Tezacaftor + Ivacaftor** – Treatment of cystic fibrosis. Expands patients who may benefit
- **Aducanumab** – Treatment of Alzheimer's Disease. Monoclonal antibody that clears beta-amyloid
- **Bremelanotide** – treatment of hypoactive sexual desire disorder: activates endogenous melanocortin pathways involved in sexual desire and response: disposable SC auto injector
  - Unrelated to flibanserin
  - No interactions with alcohol
- **Romosozumab** – Treatment of osteoporosis in postmenopausal women. Inhibits the protein sclerostin.

Most Exciting Drugs in the Pipeline: 2019-2020 (in no particular order)

- **Viaskin Peanut** – Immunotherapy for the treatment of peanut allergy
- **NKTR-181** – AN opioid with a lower risk of dependence
  - Less euphoria produced
  - Low permeability across the blood/brain barrier
- **Risankizumab** – Treatment of moderate to severe plaque psoriasis
  - Early data show greater efficacy compared to competitors
  - This is a $7.5 billion market
- **Sotagliflozin** – SGLT-1 and SGLT-2 inhibitor used in addition to insulin therapy in Type I diabetes
  - First **oral** treatment for Type I diabetes

Other Drugs in the Pipeline 2019+

- Antimicrobials
  - **New class: formicamycins** – produced by bacterial found on African ants – potential against MRSA
  - **Cefiderocol:** new cephalosporin – demonstrated superiority over imipenem/cilastatin for gram negative cUTI
  - **ANS 100**: combination of 2 monoclonal antibodies – to prevent S. aureus pneumonia in ventilated patients
  - **Ramoplantin**: new drug class for C. difficle associated diarrhea
  - **Solithromycin:** next generation macrolide for MRSA

Other Drugs in the Pipeline 2019+

- Psychiatry
  - **Eglumegad** – treatment of anxiety and drug addition
    - Oral bioavailability has been a problem so a pro-drug is now being studied
  - **Bitopertin** – treatment of schizophrenia
    - Not looking good: “not promising” based on early studies
  - Other drugs for major depressive disorder
    - 2 drugs in phase III

Self Assessment Question #1

- True or False
  - Baloxavir is administered with a similar dosing regimen to oseltamivir.

Self Assessment Question #2

- True or False
  - Erenumab is the only monoclonal antibody against calcitonin gene-related peptide (CGRP) receptor on the market for migraine prophylaxis

Self Assessment Question #3

- True or False
  - Plazomicin’s spectrum of activity is identical to that of the other aminoglycosides

Questions?





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For a “Formulary Approach” review of new drugs listed, just e-mail…

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