New Drug Update 2016: A Formulary Approach

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Disclosure

Dr. May has nothing to disclose concerning possible financial or personal relationships with commercial entities (or their competitors) mentioned in this presentation.
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 Under Consideration

- Sacubitril/Valsartan (Entresto®) by Novartis
- Idarucizumab (Praxbind®) by Boehringer Ingelheim
- Cariprazine (Vraylar®) by Actavis
- Brexpiprazole (Rexulti®) by Otsuka
- Secukinumab (Cosentyx®) by Novartis
- Insulin degludec injection (Tresiba®) by Novo Nordisk
- Isavuconazonium sulfate (Cresemba®) by Astellas
- Indacaterol and glycopyrrolate (Utibron Neohaler®) by Novartis
- Sugammadex (Bridion®) by Merck
- Reslizumab (Cinqair®) by Teva Pharmaceuticals
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
Sacubitril/Valsartan (Entresto®)

Pharmacology

- Neprilysin inhibitor and an angiotensin receptor blocker fixed dose combination
  - Neprilysin degrades vasoactive peptides:
    - Natriuretic peptides
    - Bradykinin
    - Adrenomedullin
  - Inhibition increases these peptides: decreased
    - Vasoconstriction
    - Sodium retention
    - Maladaptive remodeling
- Indication: reduce the risk of CV death and heart failure hospitalization in CHF patients with reduced ejection fraction.
- Note: 103 mg of valsartan in Entresto® = 160 mg of valsartan in Diovan® (different salts)
**Sacubitril/Valsartan (Entresto®)**

**Pharmacokinetics**
- Sacubitril metabolized to LBQ657 (active form)
- **Tmax**
  - Sacubitril = 0.5 hours
  - LBQ657 = 2 hours
  - Valsartan = 1.5 hours
- **Metabolism**
  - Sacubitril metabolized by esterases
- **Half-life**
  - Sacubitril = 1.4 hours
  - LBQ657 = 11.5 hours
  - Valsartan = 9.9 hours
- **Elimination**
  - Sacubitril: Urine 52 – 68%, feces 37 – 48%
  - Valsartan: primarily feces
Efficacy

- Double-blind, randomized trial, n = 8442
  - Entresto® versus enalapril
    - both in addition to other drugs
  - Class II – IV heart failure and reduced ejection fraction
  - Study stopped early: lower cardiovascular mortality in Entresto®
    group
    - Composite first hospitalization/CV death:
      - 21.8% vs 26.5%
    - First hospitalization due to worsening CHF
      - 12.8% vs 15.6%
    - Death from CV causes
      - 13.3% VS 16.5%
    - All cause mortality
      - 17.0% vs 19.8%

Sacubitril/Valsartan (Entresto®)

Safety

• **BLACK BOX WARNING**
  • Fetal toxicity – discontinue as soon as pregnancy detected
  • Symptomatic hypotension – 14%
    • Study excluded patients with baseline hypotension
  • Elevated serum creatinine – 3.3%
  • Cough – 11.3%
  • Angioedema – 0.5%

• Drug interactions
  • Do not combine with an ACE inhibitor (angioedema)
  • Potassium sparing diuretics/potassium supplements (hyperkalemia)
  • NSAIDS (worsening of renal function possible)
**Dosage and Cost**

- Combo 49/51 mg twice daily
  - Doubled after 2 – 4 weeks as tolerated to reach
    - 97/103 mg twice daily
- Stop ACE inhibitor treatment 36 hours before starting this regimen
- If not on ACEI or ARB or if GFR <30
  - Start on 24/26 mg twice daily and titrate up

**Cost:**
- Entresto® = $450/month
- Ivabradine = $450/month
Sacubitril/Valsartan (Entresto®)

Criteria

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

Well then Praxbind or Prayer
Idarucizumab (Praxbind®)

**Pharmacology**
- Humanized monoclonal antibody fragment that binds to dabigatran and its metabolites
  - Neutralizes anticoagulant effect
  - Binds to dabigatran with higher affinity than dabigatran binds to thrombin
  - Does NOT reverse other Factor Xa inhibitors
- **Indication**
  - For urgent reversal of the anticoagulant effect of dabigatran
Idarucizumab (Praxbind®)

Pharmacokinetics

- Given intravenously
- Metabolized by protein catabolism in kidney
- Idarucizumab-dabigatran complex renally cleared
- Half-life ~ 10.3 hours
Idarucizumab (Praxbind®)

**Efficacy**

- Accelerated FDA approval based on interim analysis of study
- Patients on dabigatran $n = 90$
  - Overt, uncontrolled, or life-threatening bleeding or needed urgent procedure that could not be delayed for $>8$ hours
  - Unbound serum dabigatran levels fell below 20 ng/ml (little or no anticoagulant effect) in all but one patient
  - Normal intraoperative hemostasis in 92% undergoing urgent procedures
  - At 12 hours: 93% still had unbound dabigatran levels $< 20$ ng/ml
  - At 24 hours: 79% still had unbound dabigatran levels $< 20$ ng/ml

Idarucizumab (Praxbind®)

Safety

• From clinical trial in ≥ 5% of patients:
  • Hypokalemia
  • Delirium
  • Pyrexia
  • Pneumonia
    • Drug-related or condition-related: unknown
• From health volunteer study in ≥ 5% of patients:
  • Headache
Idarucizumab (Praxbind®)

Dosage and Cost

- 5 gm (as 2 consecutive 2.5 gm doses) IV infusion or bolus
- Do not restart dabigatran for at least 24 hours after dose

- Cost: $3500 per 5 gm dose
Idarucizumab (Praxbind®)

Criteria

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

- Atypical antipsychotic
- Actual mechanism of action unknown, but thought to be:
  - Partial agonist activity at central dopamine D2 and serotonin 5-HT$_{1A}$ receptors
  - Antagonist activity at serotonin 5-HT$_{2A}$ receptors
- Indication
  - Treatment of schizophrenia
  - Acute treatment of manic or mixed episodes associated with bipolar I disorder
Cariprazine (Vraylar®)

Pharmacokinetics

• 2 active metabolites
• Half-life: 2 – 4 days, metabolites: 1 to 3 weeks
• Metabolized by CYP 3A4 primarily
  • Reduce dose by half if given with strong 3A4 inhibitors
  • Moderate 3A4 inhibitors…???
• Excreted in urine ~21%
Cariprazine (Vraylar®)

Efficacy

- **Schizophrenia**: three, 6-week, randomized, double-blind, placebo-controlled studies two with active control (measuring PANSS)
  - Study 1 (n = 711) - cariprazine and risperidone superior to placebo
  - Study 2 (n = 604) - cariprazine and aripiprazole superior to placebo
  - Study 3 (n = 439) - cariprazine with flexible doses superior to placebo
  - Baseline PANSS = 97 with reductions from -19 to -25

- **Bipolar I Disorder**: three, 3-week, randomized, double-blind, placebo-controlled studies (measuring YMRS)
  - Study 1 (n = 332) - superior to placebo
  - Study 2 (n = 118) - superior to placebo
  - Study 3 (n = 158) - superior to placebo
  - Baseline YMRS score = 30 – 33 with reductions from -18 to -19
Cariprazine (Vraylar®)

Safety

- In schizophrenia trials (≥ 5% and at least twice the rate of placebo):
  - Akathisia: 9 – 14%
  - Extrapyramidal symptoms: 15 – 20%
- In bipolar mania trials (≥ 5% and at least twice the rate of placebo):
  - Akathisia: 20 - 21%
  - Extrapyramidal symptoms: 26 - 29%
  - Dyspepsia: 7 – 9%
  - Vomiting: 8 – 10%
  - Somnolence: 7 – 8%
  - Restlessness: 7%
Cariprazine (Vraylar®)

**Dosage and Cost**

- **Schizophrenia:**
  - Starting dose 1.5 mg once daily
  - Recommended dose 1.5 – 6 mg once daily

- **Bipolar mania:**
  - Starting dose 1.5 mg once daily
  - Recommended dose 3 – 6 mg once daily

- **Cost:** All strengths - $1006 per one month supply
Cariprazine (Vraylar®)

Criteria

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

Pharmacology
- Atypical antipsychotic
- Actual mechanism of action unknown, but thought to be:
  - Partial agonist activity at central dopamine D2 and serotonin 5-HT1A receptors
  - Antagonist activity at serotonin 5-HT2A receptors
- Indication
  - Treatment of schizophrenia
  - Use as an adjunctive therapy to antidepressants for the treatment of major depressive disorder (MDD)
Brexpiprazole (Rexulti®)

Pharmacokinetics

- Oral bioavailability = 95%
- Metabolized by CYP 3A4 and 2D6
  - Strong 3A4 inhibitors: azole antifungals, clarithromycin
  - Strong 2D6 inhibitors: paroxetine, fluoxetine
- Half-life = 91 hours
- Elimination 25% urine and 46% feces
Brexpiprazole (Rexulti®)

Efficacy

• Adjunctive treatment for MDD:
  • Two, 6-week, double-blind, placebo-controlled trials
    (change in MADRS score. Mean baseline = 26)
    • Study 1  -8.4   Study 2  -7.6     both superior to placebo

• Schizophrenia
  • Two, 6-week, double-blind, placebo-controlled trials
    (change in PANSS score. Mean baseline = 95)
    • Study 1  -20   Study 2  -18     both superior to placebo
Brexipiprazole (Rexulti®)

Safety

- > 5% and twice the incidence seen with placebo:
  - Weight gain 6 – 8%
  - Akathisia 4 – 14%
- Check black box warning for all drugs in this class
Brexipiprazole (Rexulti®)

Dosage and Cost

- **MDD:**
  - Starting dose 0.5 mg to 1 mg once daily
  - Recommended dose 2 mg once daily
  - Maximum dose 3 mg once daily

- **Schizophrenia:**
  - Starting dose 1 mg once daily
  - Recommended dose 2 to 4 mg once daily
  - Maximum dose 4 mg once daily

- Cost: all doses $1038.60 for 30 tablets
Brexipiprazole (Rexulti®)

Criteria

• New Pharmacological Class
• More Efficacious
• Safer
• Pharmacokinetic Advantage (clinically relevant)
• More Cost Effective
Secukinumab (Cosentyx®)

Pharmacology

- The first human interleukin (IL)-17A antagonist
  - IL-17A naturally occurring pro-inflammatory cytokine
  - IL-17A involved with immunopathogenesis of plaque psoriasis
  - Secukinumab selectively binds and neutralizes IL-17A

- Indication
  - Treatment of moderate to severe plaque psoriasis in adults who are candidates for systemic therapy or phototherapy

- Other treatments
  - Mild: Corticosteroids, vitamin D analogs
  - Moderate to severe: phototherapy, methotrexate, cyclosporine, oral retinoids, TNF inhibitors, etc.
  - Note: Ixekizumab (Taltz®) – recently approved, IL-17 antagonist
    - Available “2nd quarter of 2016”
Secukinumab (Cosentyx®)

Pharmacokinetics

- Administered via subcutaneous injection
- Tmax = 6 days
- Half-life = 22 – 31 days
- Metabolism – not established
- Elimination – not established
Secukinumab (Cosentyx®)

Efficacy

- 4 double-blind, randomized, placebo-controlled studies (n = 2403 patients)
  - Primary endpoint: >75% reduction in Psoriasis Area and Severity Index
    - Secukinumab 150 mg  67.0% - 71.7% (PASI 75)
    - Secukinumab 300 mg  75.9% - 86.7% (PASI 75)
    - Enanercept 50 mg     44% (active control, PASI 75)
    - Placebo              0% - 4.9% (PASI 75)

Secukinumab (Cosentyx®)

Safety

- Most common:
  - Nasopharyngitis, diarrhea, upper respiratory infections
- Screen for tuberculosis prior to treatment
- Exacerbations of Crohn’s disease seen during trials
- Pregnancy category B
- No drug interactions detected to date
- No live vaccines
Secukinumab (Cosentyx®)

Dosage and Cost

• 300 mg SC at weeks 0, 1, 2, 3, and 4
• Followed by 300 mg SC every 4 weeks
• Each 300 mg dose is given as two 150 mg injections
• Patients taught to self-inject

• COST – Carton with 2 x 150mg pens:
  • $10,260 for 12 weeks treatment
• Other options:
  • Humira® - $8740 Enbrel® - $8920 Remicade® - $5842
Secukinumab (Cosentyx®)

Criteria

• New Pharmacological Class
• More Efficacious ?
• Safer
• Pharmacokinetic Advantage (clinically relevant)
• More Cost Effective
Tresiba insulin
“ultra long-acting”
Insulin Degludec Injection (Tresiba®)

Pharmacology

• Long-acting human insulin
• Synthesized using recombinant DNA technology
• Other long acting insulins:
  • Insulin detemir
  • Insulin glargine
• Indication
  • Treatment of adults with type I or type 2 diabetes
Insulin Degludec Injection (Tresiba®)

Pharmacokinetics

- Forms multihexamers in subcutaneous tissue
  - Delays absorption
- Binds to circulating albumin… delays elimination
- Duration of action >42 hours
- Tmax = 9 hours
- Half-life = 25 hours
Insulin Degludec Injection (Tresiba®)

Efficacy

• Approval based on results of NINE open-label, active-controlled trials
  • 8 trials – non-inferior to insulin glargine or detemir
  • Rate of nocturnal hypoglycemia less in some studies
  • 1 trial – superior in lowering HbA1c compared to sitagliptin but had more episodes of hypoglycemia

*The Medical Letter*, December 7 2015
Insulin Degludec Injection (Tresiba®)

Safety

- Allergic reactions
- Lipodystrophy
- Pruritus
- Rash
- Edema
- All insulins cause hypoglycemia and weight gain
- May cause less nocturnal hypoglycemia
Insulin Degludec Injection (Tresiba®)

Dosage and Cost

• Give SC once daily
• Rotate sites
• Note: Does not have to be given the same time each day (clinically relevant pharmacokinetic advantage?)
• Cost:
  • Tresiba® 3ml pen $355
  • Levemir® 3 ml pen $298
  • Lantus® 3 ml pen $298
Insulin Degludec Injection (Tresiba®)

Criteria

• New Pharmacological Class
• More Efficacious
• Safer ?
• Pharmacokinetic Advantage (clinically relevant) ?
• More Cost Effective
NEW CRESEMBA®
(isavuconazonium sulfate)
372 mg for injection • 186 mg capsules
Isavuconazonium Sulfate (Cresemba®)

**Pharmacology**

- A broad-spectrum, triazole antifungal
- Inhibits the synthesis of ergosterol, an essential component of the fungal cell membrane
- **Indication:**
  - IV and oral treatment of invasive aspergillosis
  - Current guidelines list voriconazole as 1st choice
  - IV and oral treatment of invasive mucormycosis
  - Current guidelines list a lipid formulation of amphotericin B and surgical debridement as 1st choice
**Isavuconazonium Sulfate (Cresemba®)**

**Pharmacokinetics**

- Isavuconazonium sulfate is a prodrug of isavuconazole
- Bioavailability = 98% (IV to PO conversion easy)
- Tmax (oral) = 2 – 3 hours
- Half-life = 130 hours
- Metabolized via CYP 3A4 and 3A5
- < 1% eliminated via urine
Isavuconazonium Sulfate (Cresemba®)

Efficacy

- Invasive aspergillosis
  - Double-blind trial: isavuconazonium sulfate versus voriconazole (n = 516)
  - Treated for 84 days
  - All cause mortality similar (19% vs 20%)
  - Overall response rate similar (35% vs 36%)
- Invasive mucormycosis
  - Single arm trial for 84 days (n = 37)
  - All cause mortality = 43.2%
  - Complete response = 14.3%
- Candidemia and other invasive Candida infections
  - NOT non-inferior to caspofungin (n = 440)
Isavuconazonium Sulfate (Cresemba®)

Safety

- Generally well tolerated
- Most common: nausea, vomiting, diarrhea, headache, elevated hepatic transaminases, hypokalemia, constipation, cough, peripheral edema, and back pain
- Compared to voriconazole:
  - Fewer hepatobiliary adverse effects (9% vs 16%)
  - Fewer eye adverse effects (15% vs 27%)
  - Fewer skin and SC adverse effects (33% vs 42%)
  - Fewer overall adverse effects in study (42% vs 60%)
- Can shorten QTc interval
- Contraindicated with strong CYP 3A4 inhibitors
Isavuconazonium Sulfate (Cresemba®)

Dosage and Cost

- 372 mg IV or PO q8hr X 6 doses, then 372 mg daily
- IV: reconstitute, then further dilute in 250 ml, infuse over > 1 hour with inline filter
- PO: swallow capsules whole. Do not chew, dissolve, crush or open
- Cost (4 weeks of therapy)
  - Cresemba®: $6670 (IV), $3920 (PO)
  - Voriconazole, generic: $9570 (IV) (optimal oral dose not established)
Isavuconazonium Sulfate (Cresemba®)

Criteria

• New Pharmacological Class
• More Efficacious
• Safer?
• Pharmacokinetic Advantage (clinically relevant)?
• More Cost Effective
Indacaterol and Glycopyrrolate (Utibron Neohaler®)

**Pharmacology**

- Indacaterol – long acting beta2-adrenergic agonist (LABA)
- Glycopyrrolate – anticholinergic
  - NOTE: a product with just glycopyrrolate was also approved (Seebri Neohaler®)
- 3rd anticholinergic/LABA combination on the market
  - Umeclidinium/vilanterol (Anoro Ellipta®)
  - Tiotropium/olodaterol (Stiolto Respimat®)
- Patient counselling essential
- Indication
  - Long term maintenance treatment of COPD
Indacaterol and Glycopyrrolate (Utibron Neohaler®)

Pharmacokinetics

<table>
<thead>
<tr>
<th></th>
<th>Glycopyrrolate</th>
<th>Indacaterol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tmax</td>
<td>5 minutes</td>
<td>15 minutes</td>
</tr>
<tr>
<td>Metabolism</td>
<td>multiple CYP enzymes</td>
<td>UGT1A1 and CYP 3A4</td>
</tr>
<tr>
<td>Elimination</td>
<td>urine (60 – 70%)</td>
<td>feces (54% unchanged)</td>
</tr>
<tr>
<td>Half-life</td>
<td>33 – 53 hours</td>
<td>40 – 56 hours</td>
</tr>
</tbody>
</table>

- Dry powder inhaler, patient must be able to take deep breath
- Dosed twice daily
Indacaterol and Glycopyrrolate
(Utibron Neohaler®)

**Efficacy**

- 2 double-blind trials versus each agent alone and placebo (n = 2038)
  - At 12 weeks, combo increased FEV$_1$ AUC$_{0-12}$ significantly greater than individual agents and placebo
  - Rescue inhaler use was also decreased
  - QALY survey also showed improved scores over placebo
Indacaterol and Glycopyrrolate (Utibron Neohaler®)

Safety

- Most common
  - Upper respiratory infections
  - Nasopharyngitis
  - Hypertension
- Systemic absorption (minimal amount)
  - G = Urinary retention and increased IOP possible but rare
  - I = palpitations, tachycardia, chest pain, tremor, nervousness, insomnia
- Tolerance may occur over time to therapeutic effects
Indacaterol and Glycopyrrolate (Utibron Neohaler®)

Dosage and Cost

• Twice daily inhalation of one capsule
• Capsule placed in device.
• Push buttons on both sides
• Exhale fully, then take in deep, rapid, steady breaths until all powder in capsule is gone (usually 1 to 2 inhalations)
• Remove inhaler from mouth
• Wait 5 – 10 seconds before exhaling
• Cost (30 day supply)
  • Umeclidinium/vilanterol (Anoro Ellipta®) $315
  • Tiotropium/olodaterol (Stiolto Respimat®) $315
  • Indacaterol/glycopyrrolate (Utibron Neohaler®) $298
Indacaterol and Glycopyrrolate (Utibron Neohaler®)

Criteria

• New Pharmacological Class
• More Efficacious
• Safer
• Pharmacokinetic Advantage (clinically relevant)
• More Cost Effective
BRIDION EXPERIENCE DAY
Sugammadex (Bridion®)

Pharmacology

• A selective relaxant binding agent for reversal of neuromuscular blockade

• Forms complexes with rocuronium and vecuronium
  • Prevents them from binding to nicotinic receptors and inducing neuromuscular blockade

• Indication
  • Reversal of neuromuscular blockade induced by rocuronium bromide and vecuronium bromide in adults undergoing surgery
Sugammadex (Bridion®)

Pharmacokinetics

- $V_d = 11$ to $14$ liters with normal renal function
- Excreted unchanged in the urine
- Estimated half-life = 2 hours
  - Mild renal impairment = 4 hours
  - Moderate renal impairment = 6 hours
  - Severe renal impairment = 19 hours
## Sugammadex (Bridion®)

### Efficacy

<table>
<thead>
<tr>
<th>Blocking agent</th>
<th>Reversal regimen</th>
<th>Minutes to recovery</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Moderate blockade</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rocuronium (n = 98)</td>
<td>Sugammadex 2 mg/kg</td>
<td>1.5 (1.3 – 1.6)</td>
</tr>
<tr>
<td></td>
<td>Neostigmine 50 mcg/kg</td>
<td>18.6 (14.2 – 24.2)</td>
</tr>
<tr>
<td>Vecuronium (n = 93)</td>
<td>Sugammadex 2 mg/kg</td>
<td>2.7 (2.2 – 3.3)</td>
</tr>
<tr>
<td></td>
<td>Neostigmine 50 mcg/kg</td>
<td>17.9 (13.1 – 24.3)</td>
</tr>
<tr>
<td><strong>Deep blockade</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rocuronium (n = 98)</td>
<td>Sugammadex 4 mg/kg</td>
<td>2.7 (2.1 – 4.1)</td>
</tr>
<tr>
<td></td>
<td>Neostigmine 70 mcg/kg</td>
<td>49.0 (35.7 – 65.6)</td>
</tr>
<tr>
<td>Vecuronium (n = 93)</td>
<td>Sugammadex 4 mg/kg</td>
<td>3.3 (1.8 – 4.4)</td>
</tr>
<tr>
<td></td>
<td>Neostigmine 70 mcg/kg</td>
<td>58.9 (42.9 – 79.8)</td>
</tr>
</tbody>
</table>

Blobner et al. *Eur J Anaesthesia* 2010;27:874
Jones et al. *Anesthesiology* 2008;109:816
Khuenl-Brady et al. *Anesth Analg* 2010;110:64
Lemmens et al. *BMC Anesthesiol* 2010;10:15
Sugammadex (Bridion®)

Safety

• Most common
  • Pain, nausea, vomiting

• Hypersensitivity reactions
  • Anaphylaxis: 1 in 299 healthy volunteer study
  • FDA delayed approval over concerns about this

• Marked bradycardia – rare
  • Sometimes leading to cardiac arrest

• Drug interactions
  • Binds to progestogens: women on hormonal contraceptives should use non-hormonal contraception for 7 days after sugammadex use
Sugammadex (Bridion®)

Dosing and Cost

• Single IV bolus over 10 seconds
  • 2 mg/kg: moderate blockade
  • 4 mg/kg: deep blockade
• Not recommended in patients with severe renal impairment
• Recurrence of neuromuscular blockade after recovery is possible
  • Monitor respiratory function and ventilation
• Cost: 200 mg/2 ml single dose vial = $95
  500 mg/5 ml single dose vial = $174
Sugammadex (Bridion®)

Criteria

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

Pharmacology

• Humanized interleukin-5 (IL-5) antagonist monoclonal antibody
  • Note: 2nd IL-2 antagonist approved in US for this indication mepolizumab (Nucala®) approved in 2015

• IL-5 is a major cytokine responsible for growth, differentiation, recruitment, and activation of eosinophils
  • This antagonist binds IL-5, blocking its binding to IL-5 receptors on eosinophils: reduces the production and survival of eosinophils and decreasing airway inflammation

• Indication
  • As add-on maintenance treatment of severe asthma in adults who have an eosinophilic phenotype
Reslizumab (Cinqair®)

Pharmacokinetics

- Peak concentrations at the end of the infusion
- Vd ~ 5 liters
- Metabolized by proteolytic enzymes
- Half-life ~ 24 days
Reslizumab (Cinqair®)

Efficacy

- 4 randomized, placebo-controlled trials
  - Study 1 and 2 (n = 953) dosed q 4 weeks X 1 year
    - 12 – 75 year olds with moderate to severe asthma, inadequately controlled on medium dose inhaled corticosteroids, blood eosinophil count ≥400, and ≥1 exacerbation in last year
    - Decreased exacerbations by 54 % (results in 12-17 age group?)
    - FEV₁ increase from baseline 110 ml
  - Study 3 (n = 315) dosed q 4 weeks X 16 weeks
    - 12 – 75 years olds, similar characteristics
    - FEV₁ increase from baseline 160 ml
    - Improved QOL scores
  - Study 4 (n = 492) dosed q 4 weeks X 16 weeks (counts <400)
    - No difference from placebo

Corren et al. *Chest* 2016;March 24 (epub)
Bjermer et al. *Chest* 2016 April 4 (epub)
Reslizumab (Cinqair®)

Safety

• Musculoskeletal ADRs on infusion day 2.2%
• Oropharyngeal pain 2.6%
• CPK elevations 14%
• Myalgia 1%
• Anaphylaxis 0.3%
• Malignancy 0.6%
Reslizumab (Cinqair®)

Dosing and Cost

- 3 mg/kg IV every 4 weeks

Cost: Single treatment
- Cinqair® $2505 (for 70 kg patient)
- Nucala® $2500 (for 70 kg patient)
Reslizumab (Cinqair®)

Criteria

• New Pharmacological Class
• More Efficacious?
• Safer?
• Pharmacokinetic Advantage (clinically relevant)
• More Cost Effective
Other New Approvals of Interest…

- Daclatasvir (Daklinza®) - chronic HCV genotype 3
- Ombitasvir, paritaprevir, ritonivir (Technivie®) - chronic HCV genotype 4
- Patiromer (Veltassa®) – potassium binder
- Rolapitant (Varubi®) – chemotherapy induced nausea and vomiting
- Lumacaftor and ivacaftor (Orkambi®) - cystic fibrosis
- New class of cholesterol lowering agents (injectable)
  - PCSK9 inhibitors
  - Both likely > $14,000 per year
    - Alirocumab (Praluent®)
    - Evolocumab (Repatha®)
Pipeline Drugs 2016+

- Antimicrobials
  - Clostridium difficile monoclonal antibodies (Medarex)
    - *C. difficile* associated diarrhea
  - Ramoplanatin (Oscient)
    - *C. difficile* associated diarrhea
    - New drug class!
Pipeline Drugs 2016+

• **Other Antimicrobials**
  • **Omadacycline (Paratek)**
    • Skin and skin structure infections, CAP, UTIs
    • An aminomethylcycline (oral and IV)
    • A derivative of minocycline
  • **Solithromycin (Cempra, Inc)**
    • “highly potent next-generation macrolide, the first fluoroketolide, which has potent activity against most macrolide-resistant strains”
    • Activity against community-acquired MRSA
Pipeline Drugs 2016+

- **Antimicrobials in Phase II Studies (New Chemical Classes Only)**
  - **GSK 1322322** (GSK)
    - Peptide deformylase
    - Skin and skin structure infections
    - Abstract of Phase II study versus linezolid: [http://aac.asm.org/content/early/2014/08/12/AAC.03360-14](http://aac.asm.org/content/early/2014/08/12/AAC.03360-14)
  - **Brilacidin** (Polymedix)
    - “Defensin-mimetic” – small molecules that imitate natural human immunity
    - MRSA
    - Bacterial cell membrane lysis
    - Skin and skin structure infections
  - **NVC-422** (Actelion)
    - Oxidation
    - Ophthalmic use: did not meet primary or secondary endpoints in clinical trial

*Butler MS, Cooper MA. Journal of Antimicrobics. 2011;64:413-25*
Pipeline Drugs 2016+

Psychiatric Medications

• Eglumegad (Lilly): phase III
  • mGlu2/3 agonist (anxiety, drug addiction?)

• Bitopertin (Roche): phase III
  • Forbes Magazine, “Most Promising” Schizophrenia
  • Did not reach primary endpoints in 2 studies
  • 4 other studies ongoing
  • Major depressive disorder (Note: 2 other agents in phase III for MDD).
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Diabetes

• DiaPep277 – Phase III
  • Immune system modulator may preserve beta-cell function in new onset type 1 diabetes
  • [http://care.diabetesjournals.org/content/37/5/1392](http://care.diabetesjournals.org/content/37/5/1392)
  • UPDATE: this article has been retracted. The company has uncovered evidence that certain employees of Andromeda Biotech, Ltd., which Hyperion acquired in June 2014, engaged in serious misconduct, including collusion with a third-party biostatistics firm in Israel to improperly receive un-blinded DIA-AID 1 trial data and to use such data in order to manipulate the analyses to obtain a favorable result.
Pipeline Drugs 2016+

Cholesterol management (CETP inhibitors)

- **Evacetrapib** (Lilly):
  - Studies failed to show benefit.
  - Caused Lilly’s stock to drop.
  - Researchers now doubting this class will be successful.

- **Anacetrapib** (Merck)* (USAToday cover story!)
  - Safety data being collected through 2017
  - **Possible bad news…**
    - "And now analysts and experts are either writing off the last remaining CETP inhibitor at Merck, anacetrapib, or relegating it to a wild card position on the sidelines of drug development.”*
  - **Or maybe not…**
    - "Merck is still betting big on the outcome of its huge, 30,000-patient study for anacetrapib. Data are due in 2017.”*

Pipeline Drugs 2016+

- Reversal agents for other new anticoagulants in the pipeline
Self Assessment Question #1

True or False: Idarucizumab (Praxbind®) reverses all the Factor Xa inhibitors
Self Assessment Question #2

True or False: Insulin degludec injection (Tresiba®) must be given at the same time every day
Self Assessment Question #3

• True or False: Isavuconazonium sulfate has replaced voriconazole as the first drug of choice for invasive aspergillosis.
Questions?

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