NEW DRUGS 2009

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Disclosures

Gerry Barber

• Is a member of the speaker's bureau for Cubist Pharmaceuticals

• Does not own individual stock in pharmaceutical companies

Goals / Objectives

• Review selected new agents approved in 2009, or "on the horizon"

• Describe agent profiles
  - MOA, PK, common SE, noted / potential Dis

• Examine
  - Key trial results
  - Potential advantages place in therapy
  - Disadvantages
New Drug Development

- Continuing Trend: for Chronic Diseases
  - 70's – 80's: not a single new antibiotic class
  - Resistant infxns, iatrogenic issues: new ABX
- Enormous Costs to Reach Approval
  - $802 million per new entity – DiMasi
  - Others: $500 million +
    - Vary by therapy (ie, RA vs. GU)
    - Vary by regulatory policy


Probability of Market Entry, Costs

<table>
<thead>
<tr>
<th>Disease</th>
<th>Entry probability (%)</th>
<th>Baseline (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute MI</td>
<td>90</td>
<td>77</td>
</tr>
<tr>
<td>Ischemic heart disease</td>
<td>75</td>
<td>65</td>
</tr>
<tr>
<td>RA</td>
<td>74</td>
<td>61</td>
</tr>
<tr>
<td>GU</td>
<td>73</td>
<td>61</td>
</tr>
<tr>
<td>None</td>
<td>63</td>
<td>53</td>
</tr>
</tbody>
</table>

Varying factors:
- Market failure
- Technology
- Regulatory

Adams CP, et. al. Health Affairs 2006; 25:420-428

Prasugrel HCl (Effient™)
Daiichi Sankyo / Lilly

Indications:
- ACS patients: to reduce thrombotic CV events, including stent thrombosis who are managed w/ perc. coronary interventions

MOA:
- Inhibits PLT activation / aggregation mediated by P2Y12 ADP receptor
**Thienopyridines**

1. Meadows, et. al. *Circulation Research*. 2007;100;1261‐1275

- **Prasugrel HCl**
  - Pharmacology
    - Inhibits adenosine 5’-diphosphate (ADP)-induced platelet activation and aggregation
    - Thienopyridine prodrug (also clopidigrel) – active metabolite selectively & irreversibly binds to PY12 ADP platelet receptors
    - Prasugrel conversion to active metabolites in a single oxidative step through CYP(6) 3A4, 3A5, 2B6, 2C9, 2C19

**Prasugrel HCl Primary Metabolic Pathways**

Prasugrel HCl

- Pharmacokinetics
  - Linear
  - Half-life: 8-9 hours
  - Bioavailability: ~80%
  - Elimination: 70% urine; 25% feces

- Drug Interactions
  - Ketoconazole (CYP3A4 inhibitor)
    - No sig. effect on prasugrel’s inhibiting PLT aggregation
    - No sig. effect of exposure to prasugrel active metabolites

- Contraindications
  - Hypersensitivity to prasugrel/ingredients
  - Active bleeding

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Prasugrel HCl

TRITON-TIMI 38

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prasugrel</td>
<td>LD 60mg, then 10mg daily</td>
</tr>
<tr>
<td>Clopidogrel</td>
<td>LD 300mg, then 75mg daily</td>
</tr>
</tbody>
</table>

- Outcomes:
  - Efficacy: 1st CV event – non-fatal MI or stroke, CV death: 9.9%
    - prasugrel vs. 11.1% clopidogrel (HR=0.81; 95% CI 0.73 – 0.9; P< 0.001)
  - Safety: Major bleeding
    - Composite: 2.4% prasugrel vs. 1.8% clopidogrel (P= 0.03)
    - Fatal bleeds: 0.4% prasugrel vs. 0.1% clopidogrel (P=0.002)

<table>
<thead>
<tr>
<th>Prasugrel HCl</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Advantages</strong></td>
</tr>
<tr>
<td>• Metabolic pathways</td>
</tr>
<tr>
<td>- ~10 x potency of clopidogrel</td>
</tr>
<tr>
<td>• Lacks DI with CYP 3A4 (so far, per ketoconazole)</td>
</tr>
<tr>
<td><strong>Disadvantages</strong></td>
</tr>
<tr>
<td>• &gt;3x risk: Bleeding</td>
</tr>
<tr>
<td>• Exclude pts. with RFs for bleeding</td>
</tr>
<tr>
<td>- Hx. Stroke, TIA</td>
</tr>
<tr>
<td>- Weight ≤ 60 kg</td>
</tr>
<tr>
<td>- Age ≥ 75 yrs</td>
</tr>
<tr>
<td><strong>Place in Therapy:</strong></td>
</tr>
<tr>
<td>Clopidogrel alternative – non-responders, allergies</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Dronedarone HCl (Multaq™)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sanofi-Aventis</strong></td>
</tr>
<tr>
<td><strong>Indications:</strong></td>
</tr>
<tr>
<td>• Reduce CV hospitalization</td>
</tr>
<tr>
<td>- Persistent or paroxysmal AF / AFL w/ recent AF / AFL and CV risk factors in sinus rhythm or to be cardioverted</td>
</tr>
<tr>
<td>• MOA:</td>
</tr>
<tr>
<td>- Unknown; mostly inhibits K+ channels → prolonging action potential duration</td>
</tr>
<tr>
<td>- Primarily class III, antiarrhythmic properties of all four Vaughan-Williams classes</td>
</tr>
</tbody>
</table>

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<thead>
<tr>
<th>Dronedarone HCl</th>
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</thead>
<tbody>
<tr>
<td><strong>Pharmacology</strong></td>
</tr>
<tr>
<td>• Non-iodinated benzofurane derivative of amiodarone</td>
</tr>
<tr>
<td>• Reduced lipophilicity (methane sulphonyl group)</td>
</tr>
<tr>
<td>- Shorter half-life</td>
</tr>
<tr>
<td>- Less tissue accumulation</td>
</tr>
</tbody>
</table>
**Amiodarone**

Amiodarone and Dronedarone

![Chemical Structure](image)

**Pharmacokinetics**
- Non-linear
- Half-life: 13 – 19 hours
- Bioavailability: ~15% with food, distributes well
- Metabolism: primarily hepatic (P450 CYP3A)
- Elimination: ~84% feces; 6% urine

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**Drug-Drug Interactions**
- Modest inhibitor CYP3A4 & 2D6
- Inhibits PGP - ↓ digoxin dose
- ↓ exposure w/ CYP3A inducers
- Potent inhibitors of CYP3A
  - Ketoconazole: ↓ dronedarone exposure 57-fold

**Drug – Food Interactions**
- Grapefruit juice
  - ↑ dronedarone exposure 3-fold

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Dronedarone

ATHENA Trial

Dronedarone 400mg po BID v. placebo


Dronedarone

- Advantages
  - Pulmonary
  - Thyroid

- Caution / Intolerance
  - QTc prolongation
  - Nausea, diarrhea

- Avoid
  - NYHA Class III or IV

Place in Therapy:
Thyroid- or pulmonary-toxic amiodarone patients

Influenza A (H1N1) Vaccine
GSK, Sinovac ???
Oseltamivir-Resistant Novel Influenza A (H1N1) Virus Infection in Two Immunosuppressed Patients — Seattle, Washington, 2009

Influenza A (H1N1) Vaccine

Scenarios
- H1N1 Flu Arrives Before Vaccine is Available
  - Wreaks havoc, serious illness & death
  - Strain remains relatively mild
    - Late August 2009: 7,983 admits / 522 deaths*
- Vaccine Provokes Adverse Events
  - Real: GBS 1:100,000 of 1976 swine flu vaccinees
  - Myths/Perceived: 1 in 7 pregnancies —*miscarriage

* [http://www.cdc.gov/h1n1flu/](http://www.cdc.gov/h1n1flu/) Accessed August 20, 2009

H1N1 Vaccine

ACIP Guidelines
- Five General Population Groups
  - Pregnant women
  - HH contacts, caregivers of infants < 6 mo.
  - Healthcare, EM personnel
  - Children & young adults, 6 mo. – 24 yrs.
  - Adults, 25 – 64 yrs. with >er risk for flu complications
- Shortage — prioritize above subsets
- Available — administer to other adults

**H1N1 Vaccine**

**Additional ACIP Recommendations**
- 1 – 2 doses? Undetermined
  - Do not stockpile supply for 1st dose vaccinees
  - Anticipate increased availability over time
  - Appears 2-dose regimen is 6 weeks apart
- Inactivated seasonal & H1N1 simultaneously
  - In different anatomic injection sites
  - *Not recommended: simultaneous live attenuated vaccines*
- All recommended for seasonal vaccine → ASAP

http://www.cdc.gov/h1n1flu/ Accessed August 21, 2009

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**On the horizon…**
- Telavancin
- Rivaroxaban
**Telavancin (Theravance™)**

**Astellas**

- **Indications** (proposed):
  - Treatment of complicated skin, skin-structure infections (cSSSI)

**Pharmacology / MOA:**

- Lipoglycopeptide, semi-synthetic derivative of vancomycin;
- Concentration-dependent dissipation of cell membrane potential & increases cell membrane permeability.

**Telavancin & Vancomycin Structures**

![Telavancin and Vancomycin Structures](image)

**Telavancin**

- **Pharmacokinetics**
  - $T_1/2$: 7-9 hours
  - Protein binding: 93 %
  - Elimination: primarily renal

- **Drug Interactions**:
  - None to date per literature

- **Contraindications**:
  - Hypersensitivity to telavancin, product ingredients
Telavancin

ATLAS Trial

- Complicated Skin & Skin-structure Infections (cSSSI)
  - Telavancin 10mg/kg iv daily vs. vancomycin 1g iv q12h
  - Telavancin achieves non-inferiority

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Telavancin treatment arm</th>
<th>Vancomycin treatment arm</th>
<th>Difference in cure rates 95% CI for the difference*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Staphylococcus aureus</td>
<td>265/279 (95.2%)</td>
<td>280/281 (99.6%)</td>
<td>-4.1 (-1.1 to 9.3)</td>
</tr>
<tr>
<td>MRSA</td>
<td>16/181 (9.0%)</td>
<td>4/178 (2.2%)</td>
<td>...</td>
</tr>
<tr>
<td>Enterococcus faecalis</td>
<td>25/27 (92.6%)</td>
<td>26/26 (100%)</td>
<td>...</td>
</tr>
<tr>
<td>Bacteroides fragilis</td>
<td>24/23 (104.3%)</td>
<td>23/23 (100%)</td>
<td>...</td>
</tr>
<tr>
<td>Staphylococcus epidermidis</td>
<td>13/13 (100%)</td>
<td>13/13 (100%)</td>
<td>...</td>
</tr>
</tbody>
</table>

NOTES: 95% confidence intervals refer to the number of occurrences in the observed numbers. MRSA, methicillin-resistant Staphylococcus aureus. MRSA, methicillin-sensitive Staphylococcus aureus.

Stryjewski et al. CID. 2008;46:1683-1693

Telavancin

- Dosing
  - 10 mg/kg IV daily x 7 – 14 days

- Renal Dosing
  - CrCl 30 – 50 mL/min: 7.5 mg/kg IV daily
  - CrCl < 30 mL/min or HD: 10 mg/kg IV q48h

- Hepatic Dosing
  - No adjustments needed

Telavancin

Common Side Effects

- Infusion-Related
  - Pruritis
  - Flushing
  - Urticaria
  - Nausea
  - Headache

- Other
  - QTc prolongation
  - Hypokalemia
  - Taste disturbances
  - H/A
  - Insomnia
  - Rash
  - Foamy urine
Telavancin

- Cautions
  - Vancomycin-like infusion ADRs
  - Resistance ??
- Place in Therapy:
  - Alternative for g(+) resistant organisms (vancomycin intolerance)
  - MRSA with higher vancomycin MICs or creep??
  - Stewardship, restricted use

Rivaroxaban (Xarelto™)

- Indication (proposed):
  - Prevention of deep vein thrombosis & pulmonary embolism in patients undergoing hip or knee replacement
- Contraindications:
  - Hypersensitivity to rivaroxaban or product ingredients

Rivaroxaban: a Selective Oral Direct Factor Xa Inhibitor

Adapted (slide series): Gibson CM. New approaches to anticoagulation: Factor Xa inhibition
Rivaroxaban

- Pharmacokinetics
  - Linear
  - Half-life: 5-9 hours (Elderly: 11 – 13h)
  - Peak / Onset: 2.5 – 4 hours
  - Bioavailability: ~60 - 80%
  - Elimination: 66% urine; 28% feces/biliary


Rivaroxaban

RECORD Trials

| RECORD 1-3  | Rivaroxaban 10mg PO daily | Enoxaparin 40mg SQ once daily |
| RECORD 4  | Rivaroxaban 10mg PO daily | Enoxaparin 30mg SQ twice daily |

- Outcomes:
  - No significant difference in bleeding
  - RECORD 1: Major VTE 0.2% rivaroxaban vs. 2% enoxaparin (P<0.001)
  - RECORD 2: Major VTE 0.6% rivaroxaban vs. 5.1% enoxaparin (P<0.001)
  - RECORD 3: Major VTE 1% rivaroxaban vs. 2.6% enoxaparin (P=0.01)
  - RECORD 4: Major bleeding 6.9% rivaroxaban vs. 10.1% enoxaparin


Rivaroxaban

- Side Effects
  - Bleeding
  - Anemia
  - Constipation
  - N/V
  - Fever
Rivaroxaban

- Place in Therapy???
  - Following total hip or knee arthroplasty, rivaroxaban appears more effective than enoxaparin in preventing venous thrombosis
  - Rates of bleeding episodes appear similar
  - RECORD 1, 2, & 4 data suggest that rivaroxaban may be associated with a higher risk of ischemic & CV events upon discontinuing the treatment cycle

Rivaroxaban

- Note
  - The Cardiovascular & Renal Drugs Advisory Committee of the FDA conducted a public hearing in March 2009 to further discuss safety & efficacy
  - Incr. risk bleeding, especially w/ other anti-PLT therapies
  - Incr. cerebrovascular events following d/c of rivaroxaban
  - Possible hepatotoxicity
  - Outcome: FDA suggests additional studies

So, Which are Keepers?

Time Will Tell...

- Increasing Population
  - Likely broader off-label indications
  - Application / receipt of new indications
  - Outcomes
  - ADRs
  - Drug interactions
  - User friendliness
  - Patent application strategies
Questions??