Avycaz: ceftazidime/avibactam

A NOVEL CEPHALOSPORIN/BETA-LACTAMASE INHIBITOR

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Disclosure Statement

• I do not have any disclosures to report or conflicts of interest
Timeline of Antibiotic Resistance

Nearly as quickly as life-saving antibiotics are created, new drug-resistant infections appear.

**Antibiotics Introduced**
- **Penicillin** 1943
- **Tetracycline** 1950
- **Erythromycin** 1953
- **Methicillin** 1960
- **Gentamicin** 1967
- **Vancomycin** 1972
- **Imipenem and Ceftazidime** 1985
- **Levofoxacin** 1996
- **Linezolid** 2000
- **Ceftaroline** 2010

**Antibiotic Resistance Identified**
- 1959: Tetracycline-R Shigella
- 1962: Methicillin-R Staphylococcus
- 1965: Penicillin-R pneumococcus
- 1968: Erythromycin-R Streptococcus
- 1979: Gentamicin-R Enterococcus
- 1987: Ceftazidime-R Enterobacteriaceae
- 1988: Vancomycin-R Enterococcus
- 1996: Levofoxacin-R pneumococcus
- 1998: Imipenem-R Enterobacteriaceae
- 2001: Linezolid-R Staphylococcus
- 2002: Vancomycin-R Staphylococcus

**Yearly Antibiotic-Resistant Infections**
- 2,000,000 infections
- 23,000 deaths

More than 2 million people in the U.S. are sickened every year with antibiotic-resistant infections. At least 23,000 die as a result.

**Antibiotics in Agriculture**
- Of all antibiotics sold in the U.S. each year, 80 percent by weight are used in agriculture, primarily to fatten and protect animals.

**Before Antibiotics**
- 5 women died out of every 1,000 who gave birth.
- Three out of 10 who contracted pneumonia died.
- One out of every 10 people who got a skin infection from a scrape, a cut, or scratching a bite lost a limb.

*Penicillin-resistant Staphylococcus appeared in 1943, three years before widespread use of the drug.

Source: Centers for Disease Control and Prevention
Credits: Switched Media and Food & Environment Reporting Network

Generating Antibiotics Incentives Now Act

- GAIN Act was passed July 2012
- An attempt to address the growing need of new antibiotics
- Grants Qualified Infectious Disease Product (QIDP) status to antibiotics for MDR pathogens

Woodcock J “Three encouraging new steps towards new antibiotics.”
Objectives

• Describe the pharmacological properties of ceftazidime/avibactam

• Compare the safety and efficacy of ceftazidime/avibactam to other agents used to treat complicated gram negative bacterial infections
Avycaz Background

• FDA approval February 2015
• Combination antibiotic: ceftazidime/avibactam (CAZ-AVI)
• Ceftazidime – third generation cephalosporin
• Avibactam – new beta-lactamase inhibitor
• Designated as a QIDP under the Generating Antibiotic Incentives Now (GAIN) Act
  • 5th agent approved under the GAIN Act
FDA Indications

Complicated IAI

• Used in combination with metronidazole
• Susceptible organisms
  • *E. coli*
  • *K. pneumoniae*
  • *P. mirabilis*
  • *P. stuartii*
  • *E. cloacae*
  • *K. oxytoca*
  • *P. aeruginosa*

Complicated UTI

• Including pyelonephritis
• Susceptible organisms
  • *E. coli*
  • *K. pneumoniae*
  • *C. koseri*
  • *E. aerogenes*
  • *E. cloacae*
  • *C. freundii*
  • *Proteus spp.*
  • *P. aeruginosa*
Mechanism of Action

- Ceftazidime – inhibits bacterial cell wall synthesis
- Avibactam – inhibits beta-lactamase
# Avibactam Resistance Patterns

<table>
<thead>
<tr>
<th>Ambler class</th>
<th>Bush–Jacoby–Medeiros class</th>
<th>Characteristics</th>
<th>No. of enzymes</th>
</tr>
</thead>
<tbody>
<tr>
<td>C</td>
<td>1</td>
<td>Mostly chromosomal enzymes in Gram-negatives. Some are plasmid-coded. Resistant to clavulanic acid.</td>
<td>51</td>
</tr>
<tr>
<td>A</td>
<td>2a</td>
<td>Staphylococcal and enterococcal penicillinases.</td>
<td>23</td>
</tr>
<tr>
<td></td>
<td>2b</td>
<td>Broad-spectrum β-lactamas, including TEM-1 and SHV-1, mainly occurring in Gram-negatives.</td>
<td>16</td>
</tr>
<tr>
<td></td>
<td>2be</td>
<td>Extended-spectrum β-lactamas (ESBLs).</td>
<td>200</td>
</tr>
<tr>
<td></td>
<td>2br</td>
<td>Inhibitor-resistant TEM (IRT) β-lactamas.</td>
<td>24</td>
</tr>
<tr>
<td></td>
<td>2c</td>
<td>Carbenicillin-hydrolyzing enzymes.</td>
<td>19</td>
</tr>
<tr>
<td></td>
<td>2d</td>
<td>Cloxacillin (oxacillin) hydrolyzing enzymes.</td>
<td>31</td>
</tr>
<tr>
<td></td>
<td>2e</td>
<td>Cephalosporinases inhibited by clavulanic acid.</td>
<td>20</td>
</tr>
<tr>
<td></td>
<td>2f</td>
<td>Carbapenem-hydrolyzing enzymes inhibited by clavulanic acid.</td>
<td>4</td>
</tr>
<tr>
<td>B</td>
<td>3</td>
<td>Metallo-enzymes that hydrolyze carbapenemns and other β-lactams except monobactams. Not inhibited by clavulanic acid. Miscellaneous enzymes.</td>
<td>24</td>
</tr>
<tr>
<td>D</td>
<td>4</td>
<td></td>
<td>9</td>
</tr>
</tbody>
</table>

Rahal JJ. CID 2009; 49:S4-10
Avibactam’s Extended Spectrum

- Avibactam expands ceftazidime's spectrum of activity to include many ceftazidime- and carbapenem-resistant Enterobacteriaceae and Pseudomonas aeruginosa

- Increased potency and expanded spectrum of inhibition of class A and C beta-lactamases
  - ESBL
  - AmpC
  - KPC
  - Does NOT work against metallo-beta-lactamases

- Avycaz has the same efficacy against Acinetobacter as ceftazidime

Zasowski EJ. Pharmacotherapy. 2015;35(8):755-70
Bush K. AAC. 2010;54(3):969-76
# Pharmacokinetics

| **Absorption** | Immediate (IV administration only)  
|               | Low protein binding (21%, 8%) |
| **Distribution** | Vd = 17, 22  
|                 | No observed interactions between ceftazidime and Avibactam  
|                 | Good lung and CNS penetration |
| **Metabolism** | No metabolism |
| **Elimination** | Half-life = 2.7 hours  
|                 | Primarily excreted unchanged in the urine  
|                 | Reduced clearance in renal insufficiency |
## Dosing

<table>
<thead>
<tr>
<th>Infection</th>
<th>Dosage</th>
<th>Frequency</th>
<th>Infusion Time</th>
<th>Duration of Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>cIAI [with metronidazole]</td>
<td>2.5 grams (2g/0.5g)</td>
<td>q8h</td>
<td>2 hours</td>
<td>5-14 days</td>
</tr>
<tr>
<td>cUTI</td>
<td>2.5 grams (2g/0.5g)</td>
<td>q8h</td>
<td>2 hours</td>
<td>7-14 days</td>
</tr>
<tr>
<td>For CrCl &gt; 50 mL/min</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Avycaz (ceftazidime-avibactam) [prescribing information]. Cincinnati, OH; Forest Pharmaceuticals, Inc; 2015
## Renal Dosing

<table>
<thead>
<tr>
<th>CrCl (mL/min)</th>
<th>Recommended Dosing</th>
</tr>
</thead>
<tbody>
<tr>
<td>31-50</td>
<td>1.25 grams (1/0.5) q8h</td>
</tr>
<tr>
<td>16-30</td>
<td>0.94 grams (0.75/0.19) q12h</td>
</tr>
<tr>
<td>6-15</td>
<td>0.94 grams (0.75/0.19) q24h</td>
</tr>
<tr>
<td>≤5</td>
<td>0.94 grams (0.75/0.19) q48h</td>
</tr>
</tbody>
</table>

Avycaz (ceftazidime-avibactam) [prescribing information]. Cincinnati, OH; Forest Pharmaceuticals, Inc; 2015
Ceftazidime/Avibactam Dosing Error

• Similar to the ceftolozane/tazobactam dosing errors

• Dose was prepared based off of ceftazidime component alone instead of the combination of the two products
  • Patient dosed to receive 1.25 grams of Avycaz actually received 1.57 grams
  • The manufacturer reported that the label is under revision to list the strength of the product as the total of the ingredients combined
Ceftazidime-Avibactam Activity Tested against Enterobacteriaceae Isolates from U.S. Hospitals (2011 to 2013) and Characterization of β-Lactamase-Producing Strains

Mariana Castanheira, Janet C. Mills, Sarah E. Costello, Ronald N. Jones, Helio S. Sader
JMI Laboratories, North Liberty, Iowa, USA

AN ORGANISM DATA-BASED STUDY
Methods

• Collected over 20,000 *Enterobacteriaceae* isolates from 79 US hospitals
  • From blood, respiratory tract, tissue, urine, intra-abdominal infections

• Compared ceftazidime/avibactam to: ceftazidime, ceftriaxone, ampicillin/sulbactam, piperacillin/tazobactam, meropenem, levofloxacin, gentamicin, tigecycline, and colistin
Results

• 99.9% of isolates were susceptible to ceftazidime/Avibactam
  • MIC\textsubscript{50}: 0.12; MIC\textsubscript{90}: 0.25
  • 743 isolates displayed ESBL
  • 120 isolates carried serine-based carbapenemases
    • Traditionally have resistance to all beta-lactams and monobactams
    • About 97% of isolates were susceptible to ceftazidime/Avibactam compared to meropenem (1.7%) and gentamicin (36.7%)
Phase II Trials
Phase II Study (cIAI)

• RCT of adult subjects with cIAI
  • Stratified by baseline severity of disease (APACHE II score ≤ 10, and > 10 to ≤ 25) and randomized 1:1 to receive CAZ-AVI + MTZ or meropenem

• Dose: CAZ-AVI 2.5 g q8h + MTZ 0.5 g q8h or meropenem 1 g q8h

• Duration: 5-14 days
  • Investigator could DC study drug after 5 days if the subject had improved clinical outcomes

• Primary outcome– clinical cure rate at test-of-cure

Lucasti C. AAC 2013;68(5):1183–92
## Phase II Study (cIAI)

<table>
<thead>
<tr>
<th><strong>Inclusion Criteria</strong></th>
<th><strong>Exclusion Criteria</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>• 18-90 years old</td>
<td>• APACHE score ≥ 25</td>
</tr>
<tr>
<td>• cIAI meeting specific criteria</td>
<td>• ABX administration within 72 hours</td>
</tr>
<tr>
<td>• Evidence of SIRS</td>
<td>• Estimated CrCl &lt; 50 mL/min</td>
</tr>
<tr>
<td>• Physical exam findings consistent with cIAI</td>
<td>• Abnormal liver function</td>
</tr>
</tbody>
</table>

Lucasti C. AAC 2013;68(5):1183–92
Phase II Study (cIAI) Results

- 204 patients were enrolled in the study
  - 174 patients were included in the mMITT population (CAZ-AVI 85, Meropenem 89)

- Most common diagnosis was peritonitis

- More than 1/3 patients had a polymicrobial infection
  - *E. coli* was the most common pathogen

- Outcomes were similar for both treatment groups

Lucasti C. AAC 2013;68(5):1183–92
## Phase II Study (cIAI)

<table>
<thead>
<tr>
<th>mMITT Population Efficacy Response</th>
<th>CAZ-AVI + MTZ N=85 n (%)</th>
<th>Meropenem N=89 n (%)</th>
<th>Difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cure</td>
<td>70 (82.4)</td>
<td>79 (88.8)</td>
<td>-6.4 (-17.3, 4.2)</td>
</tr>
<tr>
<td>Failure</td>
<td>7* (8.2)</td>
<td>5** (5.6)</td>
<td>2.6</td>
</tr>
<tr>
<td>Indeterminate</td>
<td>8 (9.4)</td>
<td>5 (5.6)</td>
<td>3.8</td>
</tr>
</tbody>
</table>

*4 of 7 failures in the CAZ-AVI group had polymicrobial cIAI that included *Enterococcal* species or anaerobes

**All 5 meropenem failures had monomicrobial cIAI caused by aerobic gram negative organisms
Phase II Study (cIAI) Results

- Study not statistically powered to demonstrate non-inferiority to the comparator
- Efficacy in the mMITT Population was compared with results from contemporary Phase III cIAI clinical trials

Lucasti C. AAC 2013;68(5):1183–92
Adverse Events

- CNS: anxiety (10%), dizziness (6%)
- Gastrointestinal: constipation (10%), abdominal pain (7%)
You are the next class of drug-resistant bacteria. As humans continue to abuse and overuse antibiotics, your ranks will swell. So, go out there and mutate! And remember: that which does not kill us makes us stronger!!
Questions?
References

- Avycaz (ceftazidime-avibactam) [prescribing information]. Cincinnati, OH; Forest Pharmaceuticals, Inc; 2015