MRSA in the Middle-East and Tedizolid

(Discovery & Microbiology / Pharmacokinetics / Pharmacodynamics Pre-clinical Safety)

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Louvain Drug Research Institute
Catholic University of Louvain, Brussels, Belgium

- Co-founder and Past President of the International Society of Anti-infective Pharmacology (ISAP)
- Member of General Assembly (2006-) and of the Steering Committee (2008-2010) of the European Committee on Antimicrobial Susceptibility Testing (EUCAST)

Anti-Infective Bayer Middle East Forum
Dubai, UAE, 5th November 2015

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Disclosures and slides availability

• Research grants
  – Theravance, Astellas, Targanta, Cerexa/Forest, AstraZeneca, Bayer, GSK, Trius, Rib-X, Eumedica, Debiopharm
  – Belgian Science Foundation (F.R.S.-FNRS), Ministry of Health (SPF), Walloon and Brussels Regions, European Union (FP7 programme)

• Speaking fees
  – Bayer, GSK, Sanofi, Johnson & Johnson, OM-Pharma

• Decision-making and consultation bodies
  – European Committee for Antimicrobial Susceptibility Testing [EUCAST] (General Assembly and steering committee (2010-2012))
  – European Medicines Agency (external ad-hoc expert)
  – US National Institutes of Health (grant reviewing)
  – Drive-AB [Driving reinvestment in R&D and responsible use for antibiotics] (governance)

Slides: http://www.facm.ucl.ac.be ➔ Lectures
Belgium

MRSA in the Middle-East

Tedizolid
Belgium
Belgium

10 million inhabitants …

10 Nobel prizes (10/850)

• Peace
  - Institute of International Law, Ghent (1904)
  - Auguste Beernaert (1909)
  - Henri Lafontaine (1913)
  - Father Dominique Pire (1958)

• Literature
  - Maurice Maeterlinck, Ghent (1911)

• Medicine
  - Jules Bordet, Brussels (1919)
  - Corneille Heymans, Ghent (1938)
  - Christian de Duve, Louvain (1974)
  - Albert Claude, Brussels (1974)

• Chemistry
  - Ilya Prigogyne, Brussels (1977)

• Physics
  - François Englert, Brussels (2013)
The Catholic University of Louvain in brief (1 of 4)

- Originally founded in 1425 in the city of Louvain (in French and English; known as Leuven in Flemish)
The Catholic University of Louvain in brief (2 of 4)

- It was one of the major University of the so-called "Low Countries" in the 1500–1800 period, with famous scholars and discoverers (Vesalius for anatomy, Erasmus for philosophy…). Teaching was in Latin, Greek and Hebrew (College of the 3 languages…)

The University in the 1500s

Erasmus

Vesalius
The Catholic University of Louvain in brief (3 of 4)

- In the 19th century, teaching was in French but in the early 1900s, a Flemish-speaking section was opened. Courses were given in both languages, attracting many students and celebrities...

- In 1968, the University was divided into:
  - a French-speaking *Université catholique de Louvain*
  - a Flemish-speaking *Katholieke Universiteit Leuven*...
The Catholic University of Louvain in brief (4 of 4)

- The Flemish-speaking *Katholieke Universiteit Leuven* has remained in Louvain (Leuven) and is named officially in English “KU-Leuven”.
- The French-speaking *Université catholique de Louvain* has moved about 25 km South to a place called “Louvain-la-Neuve”, with the "Health Sciences Sector" located in Brussels (Woluwe)

Together, the two Universities have about **55,000 students**
What do we do?

- Teaching of Pharmacology and Pharmacotherapy
- Post-graduate training on Drug Development
- Launching of Clinical Pharmacy in Europe
- Web-based courses on anti-infective Pharmacology
- 30 graduate students, doctoral fellows and post-graduate fellows working on anti-infective therapy (laboratory and clinical applications)

- Toxicity, medicinal chemistry and improved schedules of aminoglycosides
- Novel antibiotics
  - beta-lactams (ceftaroline…)
  - fluoroquinolones (finafloxacine…)
  - ketolides (solithromycin…)
  - oxazolidinones (tedizolid …)

www.facm.ucl.ac.be

- Editorial board of AAC and IJAA
- Member of the General Committee of EUCAST (for ISC) and of its Steering committee (2008–10)
- Member of the Belgian Antibiotic Policy Coordination Committee
- Founder and Past President of the International Society of Anti-infective Pharmacology (ISAP)

www.isap.org

A partial view of our University Clinic (900 beds) and the Education and Research buildings (5,000 students), in the outskirts of Brussels, Belgium
Why should a Belgian travel to Dubai to speak to you?
To speak about MRSA in the Middle-East

and then about tedizolid…
What about MRSA in the Middle East?

Egypt:

- *Staphylococcus aureus* isolates are the major pathogens responsible for wound and surgical site infections at MUH and MRSA are a potential threat for wound patients in Egypt.


<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Sensitive No. (%)</th>
<th>Intermediate No. (%)</th>
<th>Resistant No. (%)</th>
<th>MIC&lt;sub&gt;90&lt;/sub&gt; in mcg/mL</th>
<th>MIC&lt;sub&gt;90&lt;/sub&gt; in mcg/mL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ampicillin</td>
<td>0</td>
<td>0</td>
<td>31 (100%)</td>
<td>128</td>
<td>32</td>
</tr>
<tr>
<td>Amoxicillin</td>
<td>0</td>
<td>0</td>
<td>31 (100%)</td>
<td>128</td>
<td>16</td>
</tr>
<tr>
<td>Cephalaxin</td>
<td>5 (16.1%)</td>
<td>0</td>
<td>26 (83.9%)</td>
<td>256</td>
<td>64</td>
</tr>
<tr>
<td>Cefuroxime</td>
<td>6 (19.3%)</td>
<td>2 (6.5%)</td>
<td>23 (74.2%)</td>
<td>256</td>
<td>12</td>
</tr>
<tr>
<td>Cefoperazone</td>
<td>4 (12.9%)</td>
<td>3 (9.7%)</td>
<td>24 (77.4%)</td>
<td>256</td>
<td>64</td>
</tr>
<tr>
<td>Cefepime</td>
<td>10 (32.2%)</td>
<td>3 (9.7%)</td>
<td>18 (58.1%)</td>
<td>256</td>
<td>64</td>
</tr>
<tr>
<td>Cefotaxime</td>
<td>6 (19.3%)</td>
<td>2 (6.5%)</td>
<td>23 (74.2%)</td>
<td>256</td>
<td>64</td>
</tr>
<tr>
<td>Ampicillin-sulbactam</td>
<td>5 (16.1%)</td>
<td>1 (3.2%)</td>
<td>25 (80.6%)</td>
<td>12</td>
<td>46</td>
</tr>
<tr>
<td>Amoxicillin-clavulanic acid</td>
<td>4 (12.9%)</td>
<td>0</td>
<td>27 (87.1%)</td>
<td>32</td>
<td>16</td>
</tr>
<tr>
<td>Gentamicin</td>
<td>18 (58%)</td>
<td>0</td>
<td>13 (41.9%)</td>
<td>32</td>
<td>4</td>
</tr>
<tr>
<td>Amikacin</td>
<td>28 (90.3%)</td>
<td>0</td>
<td>3 (9.7%)</td>
<td>16</td>
<td>2</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>11 (35.5%)</td>
<td>4 (12.9%)</td>
<td>16 (51.6%)</td>
<td>32</td>
<td>2</td>
</tr>
<tr>
<td>Norfloxacin</td>
<td>8 (25.9%)</td>
<td>5 (16.1%)</td>
<td>18 (58.1%)</td>
<td>64</td>
<td>16</td>
</tr>
<tr>
<td>Ofloxacin</td>
<td>11 (35.5%)</td>
<td>6 (19.3%)</td>
<td>14 (45.2%)</td>
<td>16</td>
<td>2</td>
</tr>
<tr>
<td>Levofloxacin</td>
<td>15 (48.4%)</td>
<td>9 (29%)</td>
<td>7 (22.6%)</td>
<td>8</td>
<td>1</td>
</tr>
<tr>
<td>Gatifloxacin</td>
<td>17 (54.9%)</td>
<td>12 (38.7%)</td>
<td>2 (6.5%)</td>
<td>1</td>
<td>0.5</td>
</tr>
<tr>
<td>Erythromycin</td>
<td>6 (19.3%)</td>
<td>3 (9.7%)</td>
<td>22 (70.9%)</td>
<td>128</td>
<td>8</td>
</tr>
<tr>
<td>Clindamycin</td>
<td>8 (25.9%)</td>
<td>2 (6.5%)</td>
<td>21 (67.7%)</td>
<td>64</td>
<td>8</td>
</tr>
<tr>
<td>Tetracycline</td>
<td>2 (6.5%)</td>
<td>1 (3.2%)</td>
<td>28 (90.3%)</td>
<td>256</td>
<td>64</td>
</tr>
<tr>
<td>Vancomycin</td>
<td>25 (70.9%)</td>
<td>8 (25.9%)</td>
<td>1 (3.2%)</td>
<td>8</td>
<td>2</td>
</tr>
<tr>
<td>Chloramphenicol</td>
<td>8 (25.9%)</td>
<td>4 (12.9%)</td>
<td>19 (61.3%)</td>
<td>256</td>
<td>32</td>
</tr>
<tr>
<td>Rifampicin</td>
<td>12 (38.7%)</td>
<td>4 (12.9%)</td>
<td>15 (48.4%)</td>
<td>16</td>
<td>2</td>
</tr>
</tbody>
</table>

The 31 methicillin resistant *S. aureus* isolates collected from 208 wound patients at Minia University were tested for their resistance to different antimicrobial agents. The percentage of sensitive, intermediate sensitive and resistant isolates, the MIC<sub>90</sub> and MIC<sub>90</sub> are shown. MIC = minimum inhibitory concentration.
But what about MRSA in the Middle East?

Egypt:

• *Staphylococcus aureus* isolates are the major pathogens responsible for wound and surgical site infections at MUH and MRSA are a potential threat for wound patients in Egypt. Ahmed et al. Surg Infect (Larchmt). 2014; 15:404-11. PMID: 24815332.

• CA-MRSA skin infections are not common among Egyptian children…. Antibiogram testing from suppurative skin lesions are, however, better to be recommended to guide individual therapy. Abdel Fattah & Darwish Int J Dermatol. 2012; 51:1441-7. PMID: 22928620.

Iran

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- *Staphylococcus aureus* isolates are the major pathogens responsible for wound and surgical site infections at MUH and MRSA are a potential threat for wound patients in Egypt. 
- CA-MRSA skin infections are not common among Egyptian children. 

Iran
- Emergence of MRSA with SCCmec type III and with spa types t12311, t10740, t1234, t1991, and t2651 with different phenotypic and genotypic antimicrobial resistance in the west of Iran. 

### Table 1

<table>
<thead>
<tr>
<th>Antibiotics</th>
<th>HA-MRSA (n=62), n (%)</th>
<th>CA-MRSA (n=38), n (%)</th>
<th>Total (n=100), n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Penicillin</td>
<td>62 (100)</td>
<td>38 (100)</td>
<td>100 (100)</td>
</tr>
<tr>
<td>Oxacillin</td>
<td>62 (100)</td>
<td>38 (100)</td>
<td>100 (100)</td>
</tr>
<tr>
<td>Vancomycin</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Clindamycin</td>
<td>18 (29.0)</td>
<td>9 (23.7)</td>
<td>27 (27)</td>
</tr>
<tr>
<td>Erythromycin</td>
<td>32 (51.6)</td>
<td>18 (47.4)</td>
<td>50 (50)</td>
</tr>
<tr>
<td>Gentamicin</td>
<td>12 (19.3)</td>
<td>6 (15.8)</td>
<td>18 (18)</td>
</tr>
<tr>
<td>Amikacin</td>
<td>12 (19.3)</td>
<td>5 (13.1)</td>
<td>17 (17)</td>
</tr>
<tr>
<td>Kanamycin</td>
<td>12 (19.3)</td>
<td>6 (15.8)</td>
<td>18 (18)</td>
</tr>
<tr>
<td>Tobramycin</td>
<td>12 (19.3)</td>
<td>6 (15.8)</td>
<td>18 (18)</td>
</tr>
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</tr>
<tr>
<td>Tetracycline</td>
<td>16 (25.8)</td>
<td>10 (26.3)</td>
<td>26 (26)</td>
</tr>
<tr>
<td>Quinupristin–dalfopristin</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Linezolid</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Tigecycline</td>
<td>1 (1.6)</td>
<td>0</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Imipenem</td>
<td>3 (4.8)</td>
<td>0</td>
<td>3 (3)</td>
</tr>
</tbody>
</table>

MRSA, methicillin-resistant *Staphylococcus aureus*; HA, hospital-acquired; CA, community-acquired.
But what about MRSA in the Middle East?

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Iran


  - **High frequency of MRSA found not only in HA *S. aureus* but also in CA *S. aureus* isolates**; therefore, the strategic goals is to optimize antimicrobial use … Sabouni et al. J Prev Med Hyg. 2013; 54:205-7. PMID: 24779281.

Iraq

- Burn patients with sepsis in Iraq were commonly found to have bloodstream pathogens resistant to most antibiotics available locally. Ronat et al. PLoS One. 2014; 9:e101017. PMID: 25111170.
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Jordan:
• Methicillin-resistant *Staphylococcus aureus* (MRSA) is a major cause of infections that are becoming increasingly difficult to combat because of emerging resistance.

Libya
• The results provide evidence that Libyan health care workers could serve as MRSA carriers and play a role in the dissemination of MRSA to the public and other workers.
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• **MRSA prevalence in our hospital was high** and this may be the case for other hospitals in Libya.

Qatar

• **The high prevalence of CA-MRSA, especially including USA300, in this setting** underscores the importance of global epidemiological monitoring to better understand and hopefully help prevent the emergence and spread of these problem pathogens in patient populations.
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But what about MRSA in the Middle East?

Saudi Arabia

Antimicrobial Original Research Paper

National surveillance of antimicrobial resistance among Gram-positive bacteria in Saudi Arabia

Atef M. Shibl\textsuperscript{1,2}, Ziad A. Memish\textsuperscript{2,3}, Abdelmageed M. Kambal\textsuperscript{4}, Yazid A. Ohaly\textsuperscript{5}, Abdulrahman Ishaq\textsuperscript{6}, Abiola C. Senok\textsuperscript{2}, David M. Livermore\textsuperscript{7}

\textsuperscript{1}College of Pharmacy, King Saud University, Riyadh, Saudi Arabia, \textsuperscript{2}Department of Pathology and Pharmacology, College of Medicine, Alfaisal University, Riyadh, Saudi Arabia, \textsuperscript{3}Ministry of Health, Riyadh, Saudi Arabia, \textsuperscript{4}Microbiology Department, King Khalid University Hospital, Riyadh, Saudi Arabia, \textsuperscript{5}Department of Medicine, King Faisal Specialist Hospital and Research Centre, Riyadh, Saudi Arabia, \textsuperscript{6}Ministry of Health, Riyadh, Saudi Arabia, \textsuperscript{7}Norwich Medical School, University of East Anglia, Norwich, UK

Journal of Chemotherapy 2014; 2:13-18
But what about MRSA in the Middle East?
But what about MRSA in the Middle East?

### Table 2  Antimicrobial resistance rates among different Gram-positive species during the study

<table>
<thead>
<tr>
<th></th>
<th>S. aureus</th>
<th>Coagulase-negative staphylococci</th>
<th>Enterococci</th>
<th>S. pneumoniae</th>
<th>Beta-haemolytic streptococci (group A)</th>
<th>Beta-haemolytic streptococci (others)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>T (N)</td>
<td>R (%)</td>
<td>T (N)</td>
<td>R (%)</td>
<td>T (N)</td>
<td>R (%)</td>
</tr>
<tr>
<td>Penicillins*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Penicillin G</td>
<td>4741</td>
<td>93%</td>
<td>781</td>
<td>88%</td>
<td>119</td>
<td>55%</td>
</tr>
<tr>
<td>Oxacillin</td>
<td>8568</td>
<td>32%</td>
<td>913</td>
<td>63%</td>
<td>386</td>
<td>33%</td>
</tr>
<tr>
<td>Ampicillin</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amox/Clav</td>
<td>139</td>
<td>12%</td>
<td>242</td>
<td>4%</td>
<td>103</td>
<td>0%</td>
</tr>
<tr>
<td>Other beta-lactams</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ceftriaxone</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Imipenem</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aminoglycosides</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amikacin</td>
<td>2197</td>
<td>32%</td>
<td>211</td>
<td>23%</td>
<td>177</td>
<td>11%</td>
</tr>
<tr>
<td>Gentamicin</td>
<td>5744</td>
<td>32%</td>
<td>887</td>
<td>48%</td>
<td>250</td>
<td>6%</td>
</tr>
<tr>
<td>Others</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vancomycin</td>
<td>4428</td>
<td>0%</td>
<td>905</td>
<td>0%</td>
<td>149</td>
<td>1%</td>
</tr>
<tr>
<td>Erythromycin</td>
<td>6737</td>
<td>48%</td>
<td>910</td>
<td>65%</td>
<td>369</td>
<td>89%</td>
</tr>
<tr>
<td>Clindamycin</td>
<td>4581</td>
<td>31%</td>
<td>693</td>
<td>35%</td>
<td>393</td>
<td>17%</td>
</tr>
<tr>
<td>Chloramphenicol</td>
<td>4368</td>
<td>14%</td>
<td>878</td>
<td>16%</td>
<td>292</td>
<td>58%</td>
</tr>
<tr>
<td>Tetracycline</td>
<td>4173</td>
<td>49%</td>
<td>209</td>
<td>25%</td>
<td>312</td>
<td>88%</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>2168</td>
<td>32%</td>
<td>530</td>
<td>26%</td>
<td>32</td>
<td>63%</td>
</tr>
<tr>
<td>Rifampicin</td>
<td>2957</td>
<td>6%</td>
<td>779</td>
<td>10%</td>
<td>87</td>
<td>5%</td>
</tr>
<tr>
<td>TMP-SMX</td>
<td>3318</td>
<td>27%</td>
<td>893</td>
<td>48%</td>
<td>406</td>
<td>38%</td>
</tr>
</tbody>
</table>

Note: Data were included only for relevant antibiotics tested in more than 20% of all isolates and at least 20 isolates of individual Gram-positive species were tested.  
*N*, the number of tested isolates; *R*, resistance rate; Amox/Clav: amoxicillin/clavulanicacid; TMP-SMX, trimethoprim/sulfamethoxazole.
But what about MRSA in the Middle East?

### Table 2: Antimicrobial resistance rates among different Gram-positive species during the study

<table>
<thead>
<tr>
<th>Antibiotics</th>
<th>S. aureus</th>
<th>Coagulase-negative staphylococci</th>
<th>Enterococci</th>
<th>S. pneumoniae</th>
<th>Beta-haemolytic streptococci (group A)</th>
<th>Beta-haemolytic streptococci (others)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>T (N)</td>
<td>R (%)</td>
<td>T (N)</td>
<td>R (%)</td>
<td>T (N)</td>
<td>R (%)</td>
</tr>
<tr>
<td>Penicillins*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Penicillin G</td>
<td>4741</td>
<td>93%</td>
<td>119</td>
<td>55%</td>
<td>866</td>
<td>0%</td>
</tr>
<tr>
<td>Oxacillin</td>
<td>8568</td>
<td>32%</td>
<td>781</td>
<td>88%</td>
<td>386</td>
<td>33%</td>
</tr>
<tr>
<td>Ampicillin</td>
<td>139</td>
<td>12%</td>
<td>913</td>
<td>63%</td>
<td>242</td>
<td>4%</td>
</tr>
<tr>
<td>Amox/Clav</td>
<td>98</td>
<td>4%</td>
<td>210</td>
<td>4%</td>
<td>103</td>
<td>0%</td>
</tr>
<tr>
<td>Other beta-lactams</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ceftriaxone</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Imipenem</td>
<td>250</td>
<td>6%</td>
<td>177</td>
<td>11%</td>
<td>881</td>
<td>0%</td>
</tr>
<tr>
<td>Aminoglycosides</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amikacin</td>
<td>2197</td>
<td>32%</td>
<td>76</td>
<td>3%</td>
<td>205</td>
<td>0%</td>
</tr>
<tr>
<td>Gentamicin</td>
<td>5744</td>
<td>32%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Others</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vancomycin</td>
<td>4428</td>
<td>0%</td>
<td>419</td>
<td>1%</td>
<td>149</td>
<td>1%</td>
</tr>
<tr>
<td>Erythromycin</td>
<td>5737</td>
<td>48%</td>
<td>474</td>
<td>1%</td>
<td>414</td>
<td>0%</td>
</tr>
<tr>
<td>Clindamycin</td>
<td>4581</td>
<td>31%</td>
<td>729</td>
<td>26%</td>
<td>864</td>
<td>8%</td>
</tr>
<tr>
<td>Chloramphenicol</td>
<td>3468</td>
<td>14%</td>
<td>393</td>
<td>17%</td>
<td>855</td>
<td>8%</td>
</tr>
<tr>
<td>Tetracycline</td>
<td>4173</td>
<td>49%</td>
<td>456</td>
<td>6%</td>
<td>331</td>
<td>4%</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>2168</td>
<td>32%</td>
<td>417</td>
<td>51%</td>
<td>403</td>
<td>88%</td>
</tr>
<tr>
<td>Rifampicin</td>
<td>2957</td>
<td>6%</td>
<td>378</td>
<td>79%</td>
<td>38</td>
<td>53%</td>
</tr>
<tr>
<td>TMP-SMX</td>
<td>3318</td>
<td>27%</td>
<td></td>
<td></td>
<td>133</td>
<td>91%</td>
</tr>
</tbody>
</table>

Note: Data were included only for relevant antibiotics tested in more than 20% of all isolates and at least 20 isolates of individual Gram-positive species were tested.

N, the number of tested isolates; R, resistance rate; Amox/Clav: amoxicillin/clavulanicacid; TMP-SMX, trimethoprim/sulfamethoxazole.
and now tedizolid…

but, again, why?
Because we have been working on tedizolid since 2007...

doi:10.1093/jac/dkp267
Advance Access publication 16 September 2009

**Cellular pharmacokinetics and intracellular activity of torezolid (TR-700): studies with human macrophage (THP-1) and endothelial (HUVEC) cell lines**

Sandrine Lemaire¹, Françoise Van Bambeke¹, Peter C. Appelbaum² and Paul M. Tulkens¹*¹

¹Unité de Pharmacologie cellulaire et moléculaire & Louvain Drug Research Institute, Université catholique de Louvain, Brussels, Belgium; ²Hershey Medical Center, Hershey, PA 17033, USA

*at that time, tedizolid was called “torezolid” … and even TR-700 or DA-7157*
But where does tedizolid come from?
Tedizolid discovery
Dong-A Pharmaceuticals and Tedizolid

Synthesis and antibacterial activity of oxazolidinones containing pyridine substituted with heteroaromatic ring

Yeong Woo Jo, a,b Weon Bin Im, b Jae Keol Rhee, b Mi Ja Shim, c Won Bae Kim b and Eung Chil Choi a,*

a College of Pharmacy and Research Institute of Pharmaceutical Sciences, Seoul National University, Seoul 151-742, Korea
b Dong-A Pharmaceutical Co., Ltd., Research Laboratories, Yongin, Kyungki 449-905, Korea
c Department of Life Science, The University of Seoul, Seoul 130-743, Korea

Received 29 July 2004; revised 18 August 2004; accepted 18 August 2004
Available online 11 September 2004

Original article

Discovery of torezolid as a novel 5-hydroxymethyl-oxazolidinone antibacterial agent

Weon Bin Im a,b, Sun Ho Choi b, Ju-Young Park a, Sung Hak Choi b, John Finn c, Sung-Hwa Yoon a,*

a Department of Molecular Science and Technology, Ajou University, San 5, Woncheon, Yeongtong, Suwon 443-749, Republic of Korea
b Dong-A Pharmaceutical Co., Ltd., Research Laboratories, Yongin 449-905, Republic of Korea
c Trius Therapeutics, 6310 Nancy Ridge Drive Suite 101, San Diego, CA 92121, USA
Dong-A pharmaceuticals and tedizolid: step #1

1. Replacing the morpholinyl by a **pyridinyl** and adding a **methyl-tetrazolyl** moiety
   - increases activity
   - prolongs half-life

![Chemical structures of Linezolid and DA-7867](image)

**Table:**

<table>
<thead>
<tr>
<th>MIC</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>MSSA</td>
<td>0.78 µg/ml</td>
</tr>
<tr>
<td>MRSA</td>
<td>0.78 µg/ml</td>
</tr>
<tr>
<td>VRE</td>
<td>0.125 µg/ml</td>
</tr>
<tr>
<td>PRSP</td>
<td>0.39 µg/ml</td>
</tr>
</tbody>
</table>

**Potency of lead compound (DA-7867).**
Tedizolid has more interactions with the ribosome...

W.B. Im et al. / European Journal of Medicinal Chemistry 46 (2011) 1027–1039

Fig. 2. Models of 11 (blue) and linezolid (yellow) binding to the Escherichia coli ribosome.
Tedizolid is systematically ≥ 4-x more active than linezolid against LZDS strains and the LZD cfr+ resistant strain.

![Chemical structures of Tedizolid and Linezolid](image)

**Potential role of the methyl-tetrazolyl moiety**

<table>
<thead>
<tr>
<th>Species, phenotype and strain no.</th>
<th>linezolid</th>
<th>torezolid</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Staphylococcus aureus</em></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MSSA ATCC 25923&lt;sup&gt;b&lt;/sup&gt;</td>
<td>2</td>
<td>0.25</td>
</tr>
<tr>
<td>HA-MRSA ATCC 33591&lt;sup&gt;b&lt;/sup&gt;</td>
<td>1</td>
<td>0.125–0.25</td>
</tr>
<tr>
<td>SA 238&lt;sup&gt;c&lt;/sup&gt;</td>
<td>2</td>
<td>0.25–0.5</td>
</tr>
<tr>
<td>CM 05&lt;sup&gt;d&lt;/sup&gt;</td>
<td>8</td>
<td>0.25–0.5</td>
</tr>
<tr>
<td>CA-MRSA NRS 192&lt;sup&gt;e&lt;/sup&gt;</td>
<td>2</td>
<td>0.125–0.25</td>
</tr>
<tr>
<td>NRS 384 (US300)&lt;sup&gt;e&lt;/sup&gt;</td>
<td>2</td>
<td>0.25</td>
</tr>
<tr>
<td>VISA NRS 52&lt;sup&gt;e&lt;/sup&gt;</td>
<td>2</td>
<td>0.125</td>
</tr>
<tr>
<td>VRSA VRS 1&lt;sup&gt;e&lt;/sup&gt;</td>
<td>1–2</td>
<td>0.125–0.25</td>
</tr>
<tr>
<td>VRS 2&lt;sup&gt;e&lt;/sup&gt;</td>
<td>1–2</td>
<td>0.25</td>
</tr>
<tr>
<td>animal MRSA N7112046&lt;sup&gt;f&lt;/sup&gt;</td>
<td>2</td>
<td>0.125</td>
</tr>
<tr>
<td><em>Listeria monocytogenes</em></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EGD&lt;sup&gt;g&lt;/sup&gt;</td>
<td></td>
<td>0.125</td>
</tr>
<tr>
<td><em>Legionella pneumophila</em></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ATCC 33153&lt;sup&gt;b&lt;/sup&gt;</td>
<td>4–8</td>
<td>0.25–0.5</td>
</tr>
</tbody>
</table>

LZD<sup>k</sup>, resistant to linezolid.

<sup>a</sup>Representative values of at least two determinations.
<sup>b</sup>From the American Tissue Culture Collection (Manassas, VA, USA).
<sup>c</sup>Provided by P. C. Appelbaum.<sup>36</sup>
<sup>d</sup>Provided by J. P. Quinn, John H. Stroger Jr. Hospital, Rush University, Chicago, IL, USA.
<sup>e</sup>From the Network on Antimicrobial Resistance in *Staphylococcus aureus* (NARS) programme (operated by Eurofins Medinet, Inc., Hendon, VA, USA; supported under NIAID/NIH contract no. HHSN272200700055C); details on each strain are available at http://www.narsa.net/content/horne.jsp.
<sup>f</sup>Provided by Y. Glupczynski, Cliniques universitaires UCL de Mont Godinne, Yvoir, Belgium.
<sup>g</sup>Provided by P. Berche, Hôpital Necker, Paris, France.<sup>28</sup>

And even for *S. aureus* of different epidemiological origin...

---

Activity of Tedizolid (TR-700) against Well-Characterized Methicillin-Resistant *Staphylococcus aureus* Strains of Diverse Epidemiological Origins

Kenneth S. Thomson, Richard V. Goering
Creighton University, Omaha, Nebraska, USA

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**TABLE 1** Drug activity against all MRSA isolates and epidemiological groups

<table>
<thead>
<tr>
<th>Isolate(s)</th>
<th>Drug(s)</th>
<th>MIC range (μg/ml)</th>
<th>MIC&lt;sub&gt;90&lt;/sub&gt; (μg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All isolates (n = 111)</td>
<td>Tedizolid</td>
<td>0.12 to 0.5</td>
<td>0.5</td>
</tr>
<tr>
<td></td>
<td>Linezolid</td>
<td>0.5 to 4</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Trimethoprim/sulfamethoxazole</td>
<td>≤0.5/9.5 to &gt;2/38</td>
<td>&gt;2/38</td>
</tr>
<tr>
<td></td>
<td>Tigecycline</td>
<td>0.06 to &gt;1</td>
<td>0.5</td>
</tr>
<tr>
<td></td>
<td>Levofloxacin</td>
<td>0.12 to &gt;4</td>
<td>&gt;4</td>
</tr>
<tr>
<td></td>
<td>Clindamycin</td>
<td>0.06 to &gt;16</td>
<td>&gt;16</td>
</tr>
<tr>
<td></td>
<td>Vancomycin</td>
<td>≤0.25 to 4</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Daptomycin</td>
<td>≤0.5 to 2</td>
<td>≤0.5</td>
</tr>
<tr>
<td></td>
<td>Oxacillin</td>
<td>0.12 to &gt;4</td>
<td>&gt;4</td>
</tr>
<tr>
<td></td>
<td>Erythromycin</td>
<td>0.12 to &gt;8</td>
<td>&gt;8</td>
</tr>
<tr>
<td></td>
<td>Gentamicin</td>
<td>≤0.06 to &gt;16</td>
<td>&gt;16</td>
</tr>
</tbody>
</table>
As also with strains from clinical trials

<table>
<thead>
<tr>
<th>Isolate</th>
<th>Drug</th>
<th>MIC Range, mg/L</th>
<th>MIC&lt;sub&gt;50&lt;/sub&gt;, mg/L</th>
<th>MIC&lt;sub&gt;90&lt;/sub&gt;, mg/L</th>
</tr>
</thead>
<tbody>
<tr>
<td>MRSA (n = 285)</td>
<td>Tedizolid</td>
<td>0.12–0.5</td>
<td>0.25</td>
<td>0.25</td>
</tr>
<tr>
<td></td>
<td>Linezolid</td>
<td>1–4</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>USA300-0114 (n = 139)</td>
<td>Tedizolid</td>
<td>0.12–0.5</td>
<td>0.25</td>
<td>0.25</td>
</tr>
<tr>
<td></td>
<td>Linezolid</td>
<td>1–4</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>USA300-other (n = 95)</td>
<td>Tedizolid</td>
<td>0.12–0.5</td>
<td>0.25</td>
<td>0.25</td>
</tr>
<tr>
<td></td>
<td>Linezolid</td>
<td>1–2</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>PVL+ (n = 265)</td>
<td>Tedizolid</td>
<td>0.12–0.5</td>
<td>0.25</td>
<td>0.5</td>
</tr>
<tr>
<td></td>
<td>Linezolid</td>
<td>1–4</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>PVL− (n = 15)</td>
<td>Tedizolid</td>
<td>0.12–0.5</td>
<td>0.25</td>
<td>0.5</td>
</tr>
<tr>
<td></td>
<td>Linezolid</td>
<td>1–4</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>MSSA (n = 383)</td>
<td>Tedizolid</td>
<td>0.12–0.5</td>
<td>0.25</td>
<td>0.5</td>
</tr>
<tr>
<td></td>
<td>Linezolid</td>
<td>1–4</td>
<td>2</td>
<td>2</td>
</tr>
</tbody>
</table>

MIC, minimum inhibitory concentration; MIC<sub>50</sub>, minimum inhibitory concentration required to inhibit 50% of isolates; MIC<sub>90</sub>, minimum inhibitory concentration required to inhibit 90% of isolates; MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-susceptible *Staphylococcus aureus*; PVL, Panton-Valentine leucocidin.

*Includes both ABSSSI and blood isolates from some patients. Susceptibility and PVL data were not obtained for a small number of isolates.

Goering et al. ECCMID 2015; Poster EP086.
Tedizolid and linezolid resistance
Oxazolidinones: 1\textsuperscript{st} mechanism of resistance

Chloramphenicol-florfenicol resistance (Cfr)

- First identified in several staphylococcal species (cattle, swine) (Schwarz 2000; Kehrenberg 2006)
- CM05 (Colombia) - first clinical isolate documented to carry the cfr gene (Toh 2007)
- C-8 methylation of ribosome target at A2503 (Kehrenberg 2005; Giessing 2009)
- PhLOPS\textsubscript{A} phenotype leads to cross resistance to 6 drug classes!
  - Phenicols, Lincosamides, Oxazolidinones, Pleuromutilins, Streptogramin A and 16 membered
    macrolides (Long, 2006; Smith & Mankin 2008)
- Tedizolid retains potency against cfr strains and demonstrates 8 fold better activity than
  linezolid (Shaw 2008, Jones 2009, Livermore 2009, Locke 2009)
Activity against $cfr^+$ resistant strains...

## Oxazolidinone MICs for *S. aureus cfr* strains

<table>
<thead>
<tr>
<th>Strain</th>
<th>Reference</th>
<th>Presence of $cfr$</th>
<th>MIC (μg/ml)$^a$</th>
<th>Linezolid</th>
<th>Tedizolid</th>
</tr>
</thead>
<tbody>
<tr>
<td>RN4220(pLI50)</td>
<td>68</td>
<td>−</td>
<td>2</td>
<td></td>
<td>0.5</td>
</tr>
<tr>
<td>RN4220(pLXM1)$^b$</td>
<td>68</td>
<td>+</td>
<td>8</td>
<td></td>
<td>0.5</td>
</tr>
<tr>
<td>CM05Δ$^c$</td>
<td>44</td>
<td>−</td>
<td>2</td>
<td></td>
<td>0.5</td>
</tr>
<tr>
<td>CM05$^c$</td>
<td>68</td>
<td>+</td>
<td>8</td>
<td></td>
<td>0.5</td>
</tr>
<tr>
<td>29213</td>
<td>ATCC</td>
<td>−</td>
<td>2</td>
<td></td>
<td>0.5</td>
</tr>
<tr>
<td>29213(p42262)$^d$</td>
<td>45</td>
<td>+</td>
<td>16</td>
<td></td>
<td>0.5</td>
</tr>
<tr>
<td>42262$^e$</td>
<td>51</td>
<td>+</td>
<td>16</td>
<td></td>
<td>0.5</td>
</tr>
</tbody>
</table>

$^a$ MICs (broth microdilution: CLSI)

$^b$ The pLXM1 $cfr$-containing plasmid is isogenic to the empty pLI50 vector.

$^c$ CM05Δ is isogenic to the CM05 clinical $cfr$-positive strain but lacks $cfr$ and one copy of $ermB$.

$^d$ 29213(p42262) was generated through transformation of ATCC 29213

$^e$ 42262 is a clinical $cfr$-positive isolate from a 2008 hospital outbreak in Madrid, Spain.

Locke et al. Antimicrob Agent Chemother 2010;54:5337-5343
Why is tedizolid active against *cfr*(+) LZD<sup>R</sup> strains?

Locke et al. Antimicrob Agent Chemother 2010;54:5337-5343

FIG. 2. Structural analysis of oxazolidinone binding in the presence of Cfr methylation. (A) Crystal structure of LZD-bound *H. marismortui* 50S ribosome (30). (B) Model of LZD binding in the Cfr-methylated state. (C and D) Proposed models of TR-700 bound to wild-type (C) or Cfr-methylated (D) ribosome. Substantial steric hindrance between the LZD C-5 acetamide group and the 23S rRNA base A2503 carbon-8 methyl (bonds shown in brown) likely contributes to reduced binding affinity (B). As modeled, the TR-700 hydroxymethyl substituent does not display this steric clash with the A2503 methyl group (D), explaining its retained activity against *cfr* strains. A group of PTC bases were removed from the images to improve clarity. Images were generated with PyMOL (16).
Why is tedizolid active against cfr(+) LZDR strains?

Locke et al. Antimicrob Agent Chemother 2010;54:5337-5343
Oxazolidinones: 2\textsuperscript{nd} mechanism of resistance

Cromosomal 23S rRNA mutations

- Low frequency, but local outbreaks have been observed
- First clinical cases of resistant staphylococci and enterococci reported soon after linezolid approval in 2000 (Gonzales 2001; Tsiodras 2001)
- Tedizolid demonstrates 8-fold better potency against these strains (Shaw 2008, Jones 2009, Livermore 2009, Locke 2009)
- Mutations also observed in ribosomal proteins L3 and L4

But the MIC may exceed the EUCAST breakpoints
### Tedizolid (TR-700 / TZD) and ribosomal mutations

**TABLE 1. Oxazolidinone MICs for S. aureus ribosomal mutants**

<table>
<thead>
<tr>
<th>Strain&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Source or reference</th>
<th>Resistance mechanism&lt;sup&gt;b&lt;/sup&gt;</th>
<th>MIC (µg/ml)&lt;sup&gt;c&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>LZD</td>
</tr>
<tr>
<td>29213</td>
<td>ATCC</td>
<td>23S (G2447T ×3)</td>
<td>2</td>
</tr>
<tr>
<td>29213-1</td>
<td>43</td>
<td>23S (T2500A ×2)</td>
<td>32</td>
</tr>
<tr>
<td>29213-2</td>
<td>43</td>
<td>L3 (ΔPhe127-His146)</td>
<td>8</td>
</tr>
<tr>
<td>29213-3</td>
<td>43</td>
<td></td>
<td>8</td>
</tr>
<tr>
<td>33591</td>
<td>ATCC</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>33591-1</td>
<td>43</td>
<td>23S (G2576T ×3)</td>
<td>16</td>
</tr>
<tr>
<td>33591-2</td>
<td>43</td>
<td>23S (G2576T/T2571C ×3)</td>
<td>16</td>
</tr>
<tr>
<td>33591-3</td>
<td>43</td>
<td>L4 (Lys68Gln)</td>
<td>2</td>
</tr>
<tr>
<td>NRS127</td>
<td>NARSA&lt;sup&gt;d&lt;/sup&gt;</td>
<td>L3 (ΔSer145)</td>
<td>8</td>
</tr>
</tbody>
</table>

---

<sup>a</sup> ATCC 29213 and ATCC 33591 isogenic mutant panels were generated through selection in the presence of LZD and/or TR-700. NRS127 is an LZD<sup>e</sup> clinical isolate.

<sup>b</sup> Mutations in 23S rRNA genes (and mutant allele copy number) or in the ribosomal protein L3 or L4 are shown.

<sup>c</sup> MICs (broth microdilution; CLSI) were determined against the oxazolidinone panel.

<sup>d</sup> Network of Antimicrobial Resistance in *Staphylococcus aureus*.

---

*Locke et al. Antimicrob Agent Chemother 2010;54:5337-5343*
Emerging linezolid-resistant S. aureus: STAR Global Surveillance in 2011-2012*

The Surveillance of Tedizolid Activity and Resistance (STAR) Programme compares the *in vitro* activity of tedizolid and other antimicrobials against a variety of clinically relevant Gram-positive pathogens and monitors for the emergence of resistance. The Gram-positive pathogens chosen represent those relevant to ABSSSI, including those with significant resistance phenotypes such as MRSA and VRE.

*The Surveillance of Tedizolid Activity and Resistance (STAR) Programme compares the *in vitro* activity of tedizolid and other antimicrobials against a variety of clinically relevant Gram-positive pathogens and monitors for the emergence of resistance. The Gram-positive pathogens chosen represent those relevant to ABSSSI, including those with significant resistance phenotypes such as MRSA and VRE.*

But could tedizolid induce resistance?
Tedizolid is less capable of inducing resistance...

- Spontaneous frequency of resistance is 16-fold lower for tedizolid vs linezolid
- Serial passage experiment (30 cycles of selection)
  - Much more difficult to select resistance to tedizolid vs linezolid

**Linezolid**

Single mutation leads to resistance

Mutation frequency = $3 \times 10^{-9}$

**Tedizolid**

Double mutation required

Mutation frequency = $2 \times 10^{-10}$

To sum up: what are the main differences between linezolid and tedizolid of interest at this point?

**Linezolid (LZD)**

Substantial differences that DO impact on:
- **intrinsic activity** *(more potent)*
- full activity against *cfr*+ resistant strains
- MICs < LZD for ribosomal mutants

**Tedizolid (TR-700)**

additional methyl-tetrazolyl

morpholinyl vs pyridinyl

acetamido vs free -OH
Tedizolid pharmacokinetics
Tedizolid is presented as a prodrug to increase its solubility

- **Tedizolid phosphate (TR-701)** is a water soluble phosphate prodrug of TR-700 (compound 11)
- **Phosphatases** rapidly cleave TR-701 *in vivo* to the *active moiety* TR-700
Tedizolid is quickly formed from tedizolid phosphate

- **Tedizolid phosphate (TR-701)** is a water soluble prodrug of TR-700 (compound 11)
- **Phosphatases** rapidly cleave TR-701 in vivo

---

Tedizolid formulations in the clinical setting

Tedizolid phosphate

- Active pharmaceutical ingredient: stable at room temp for >2 yrs
- 2 formulations:
  - IV Lyophile: TR-701 FA Lyophilized Vial for Injection, 200 mg
  - Oral Tablet: TR-701 FA Immediate Release Tablet, 200 mg
Tedizolid vs linezolid human pharmacokinetics

Oral therapeutic doses (200mg tedizolid q24h versus 600mg linezolid q12h for 21 days)

Tedizolid:
- Mean $t_{1/2}$ >2 x greater than linezolid
- Longer initial presence at >0.5 µg/mL (vs 4 µg/mL for linezolid)
- Tedizolid concentrations were similar on Day 21 compared with Day 1
- No evidence of accumulation of tedizolid while linezolid showed a 47% increase in exposure from Day 1 (AUC=65.9 µg•hr/mL) to Day 21 (AUC=114.57 µg•hr/mL)


This allows for a once daily dosing
Tedizolid concentrations were generally similar on Day 7 compared with Day 1 after intravenous 200 mg multiple dosing.

A slight accumulation of ~28% was observed following multiple dosing.

Absolute bioavailability of tedizolid was 91.7% in US subjects (82.6% in Japanese subjects; 85.5% in Chinese subjects).

When using $^{14}$C-labelled tedizolid phosphate in humans, most of the radioactivity is excreted in feces.
Tedizolid elimination...

- When using $^{14}$C-labelled tedizolid phosphate in humans, most of the radioactivity is excreted in feces as tedizolid sulfate (inactive).

Mean cumulative percentage of radioactive dose was recovered in urine and feces after single 204 mg (100-µCi) oral $^{14}$C-tedizolid phosphate to healthy male subjects (+/− SD).

**TABLE 6**

Mean metabolite percentage of administered dose in excreta

<table>
<thead>
<tr>
<th></th>
<th>Urine</th>
<th>Feces</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>S.D.</td>
<td>Mean</td>
</tr>
<tr>
<td>Desmethyl tedizolid</td>
<td>1.069</td>
<td>0.697</td>
<td>N.D.</td>
</tr>
<tr>
<td>Carboxy tedizolid</td>
<td>3.583</td>
<td>0.831</td>
<td>4.188</td>
</tr>
<tr>
<td>Tedizolid sulfate</td>
<td>10.197</td>
<td>2.386</td>
<td>69.117</td>
</tr>
<tr>
<td>Tedizolid</td>
<td>1.017</td>
<td>0.415</td>
<td>1.963</td>
</tr>
</tbody>
</table>

N.D., not detected; S.D., standard deviation (for 6 subjects).
No Need for Dose Adjustment in Special Populations

Tedizolid pharmacokinetics for patients with severe renal impairment (eGFR < 30 mL/min/1.73 m²)

Tedizolid has been shown to have predictable PKs in the following patient groups:

- **Severe renal impairment** (eGFR < 30 mL/min/1.73 m²)
- **Moderate hepatic impairment** (Child-Pugh score 7-9)
- **Severe hepatic impairment** (Child-Pugh score 10-15)
- **Elderly** (age 66-78)
- **Obese and morbidly obese**
- **Ethnic populations**
- No exposure difference between **fasted** and **fed** statuses


Data on file, Bayer.

Anti-Infective Bayer Middle East Forum, Dubai, UAE
Pharmacokinetics/Pharmacodynamics
Why pharmacokinetics/pharmacodynamics?

• It helps to understand why an antibiotic may (or may not) be effective

• It allows a faster and more efficient move from preclinical to phase II – phase III studies

• It is a key element in the setting of clinical breakpoints

• It is now required by regulatory authorities to better assess the real interest of a new drug (and to re-scrutinize old ones)

• It helps to guide the clinician for a better use of the drug

• Reimbursement committees use it to ensure that what they pay for is valid!
How did it start and evolve...?

not too long ago...

since 1999... and again this year

and to clinical practice
PK parameters governing the activity of antibiotics

- $C_{\text{max}} / \text{MIC}$
- $fT > \text{MIC}$
- $\text{AUC}_{24h} / \text{MIC}$

Concentration vs Time (h)

- $C_{\text{max}}$
- $fT > \text{MIC}$
- $\text{MIC}$

$C_{\text{max}}$ and $fT > \text{MIC}$ are critical for maintaining effective antibiotic activity.
TZD activity depends on actual AUC/MIC value, and independent of the dosing schedule.
# Tedizolid vs linezolid: human pharmacokinetics

<table>
<thead>
<tr>
<th>drug</th>
<th>dosage</th>
<th>$C_{max}$ (mg/L)</th>
<th>apparent $t_{1/2}$ (h)</th>
<th>Clearance (ml/min)</th>
<th>Total AUC$_{24h}$ (mg·h/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>linezolid IV</td>
<td>600 mg Q12 h</td>
<td>15.1 ± 2.5</td>
<td>4.8 ± 1.7</td>
<td>123 ± 40</td>
<td>89.7 ± 31.0</td>
</tr>
<tr>
<td>tedizolid IV</td>
<td>200 mg Q 24h</td>
<td>3.0 ± 0.7</td>
<td>12.4 ± 1.2</td>
<td>5.9 ± 1.4</td>
<td>29.2 ± 6.2</td>
</tr>
<tr>
<td>tedizolid oral</td>
<td>200 mg Q 24h</td>
<td>2.2 ± 0.6</td>
<td>11.2 ± 2.6</td>
<td>8.4 ± 2.1</td>
<td>25.6 ± 8.4</td>
</tr>
</tbody>
</table>

1. Zyvox US Prescription Information (multiple doses)
2. FDA briefing documents (steady state)

3-fold difference with linezolid

but MICs are 3-4 fold lower
Tedizolid and murine *S. aureus* pneumonia (Craig's model)

Relationship between linezolid and tedizolid (TR-700) plasma 24 h $f$AUC/MIC ratios and *in vivo* efficacy against multiple strains of *S. aureus* (5 and 11) in a 24 h treatment

<table>
<thead>
<tr>
<th></th>
<th>mean $AUC_{24h}/MIC$</th>
</tr>
</thead>
<tbody>
<tr>
<td>24h static dose</td>
<td>24 h 1-log kill</td>
</tr>
<tr>
<td>LZD</td>
<td>19.0 ± 11.4</td>
</tr>
<tr>
<td>TZD</td>
<td>20.0 ± 12.9</td>
</tr>
</tbody>
</table>

Similar values when taking MIC into account

Towards a breakpoint (FDA / EUCAST)

- A tedizolid $AUC_{0-24h}/MIC$ ratio of 15 was determined as the PK/PD target associated with the activity of tedizolid against *S. aureus* in the non-neutropenic mouse thigh model of infection…¹

Calculation of the probability of reaching the necessary $AUC/MIC$ ratio for increasing MICs in humans…

---

**Figure 2-1: Probability of PK/PD target attainment for tedizolid at the target $AUC_{0-24}/MIC$ Ratio of 15**

- FDA briefing document: anti-infective drug advisory committee meeting
- March 31, 2014
- Last accessed: May 17, 2015
Tedizolid breakpoints… a matter of dispute?

<table>
<thead>
<tr>
<th>Organism group</th>
<th>Breakpoint (mg/L)</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>S ≤ (mg/L)</td>
<td>R &gt; (mg/L)</td>
<td></td>
</tr>
<tr>
<td>Staphylococcus spp.</td>
<td>0.5</td>
<td>0.5</td>
<td></td>
</tr>
<tr>
<td>Enterococcus spp.</td>
<td>IE</td>
<td>IE</td>
<td></td>
</tr>
<tr>
<td>Streptococcus groups A,B,C,G</td>
<td>0.5</td>
<td>0.5</td>
<td></td>
</tr>
<tr>
<td>Viridans group streptococci (Streptococcus aginosis group only)</td>
<td>0.25</td>
<td>0.25</td>
<td></td>
</tr>
<tr>
<td>PK/PD breakpoints</td>
<td>IE</td>
<td>IE</td>
<td></td>
</tr>
</tbody>
</table>

1 mg/L for *S. aureus* is resistant

1 mg/L for *S. aureus* is intermediate

Table 5  Susceptibility Test Interpretive Criteria for SIVEXTRO

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Minimum Inhibitory Concentrations (mcg/mL)</th>
<th>S</th>
<th>I</th>
<th>R</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Staphylococcus aureus</em> (methicillin-resistant and methicillin-susceptible isolates)</td>
<td>≤0.5</td>
<td>1</td>
<td>≥2</td>
<td></td>
</tr>
<tr>
<td><em>Streptococcus pyogenes</em></td>
<td>≤0.5</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td><em>Streptococcus agalactiae</em></td>
<td>≤0.5</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td><em>Streptococcus anginosus Group</em></td>
<td>≤0.25</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td><em>Enterococcus faecalis</em></td>
<td>≤0.5</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

*S=susceptible, I=intermediate, R=resistant
* Includes *S. anginosus, S. intermedius, S. constellatus*
Intracellular pharmacokinetics and activity
Activity of tedizolid towards intracellular bacteria

doi:10.1093/jac/dkp267
Advance Access publication 16 September 2009

Cellular pharmacokinetics and intracellular activity of torezolid (TR-700): studies with human macrophage (THP-1) and endothelial (HUVEC) cell lines

Sandrine Lemaire¹, Françoise Van Bambeke¹, Peter C. Appelbaum² and Paul M. Tulkens¹*

¹Unité de Pharmacologie cellulaire et moléculaire & Louvain Drug Research Institute, Université catholique de Louvain, Brussels, Belgium; ²Hershey Medical Center, Hershey, PA 17033, USA

Accumulation and activity of tedizolid in macrophages

doi:10.1093/jac/dkp267
Advance Access publication 16 September 2009

Cellular pharmacokinetics and intracellular activity of torezolid (TR-700): studies with human macrophage (THP-1) and endothelial (ECV304) cells

Sandrine Lemaire¹, Françoise Van Bambeke¹
¹Unité de Pharmacologie cellulaire et moléculaire & Laboratoire d’Hémato-oncologie, Université Libre de Bruxelles, Brussels, Belgium; ²Hershey Medical Center, Hershey, PA, USA

Tedizolid accumulates more in macrophages than linezolid in vitro

Accumulation of linezolid (LZD) and of torezolid (TR-700) in THP-1 macrophages
(a) Uptake kinetics
(b) Influence of the temperature (2 h incubation; blocks with different letters are significantly different from each other with p < 0.05)

Tedizolid is more active (4x) than linezolid against intracellular *S. aureus*

Concentration-dependent effects of linezolid (LZD) and torezolid (TR-700) towards *S. aureus* ATCC 25923 after phagocytosis by THP-1 macrophages or HUVECs (endothelial cells)

**Tedizolid is active intracellularly against MRSA disregarding resistance phenotypes (cfr+ for LZD)**

Concentration-dependent effects of torezolid (TR-700) towards *S. aureus* with different resistance phenotypes after phagocytosis by THP-1 macrophages

Distribution of tedizolid in tissues
Tedizolid accumulates in lung macrophages and epithelial lining fluid of healthy adult volunteers (200 mg dose)

Is tedizolid intracellular accumulation useful?

• The simple answer: *if you accumulate, you could be active*
• The pharmacologist's answer:
  – *No penetration → no activity* (e.g. aminoglycosides in short term experiments)
  – *Accumulation → may not be necessarily correlate with activity* (e.g. macrolides) but may help (e.g. telavancin, oritavancin, …)
  – *Subcellular bioavailability: this may be the critical point – drugs must be able to reach all targets* (e.g. fluoroquinolones)

Tedizolid may share the properties of fluoroquinolones in showing:
• a significant accumulation (about 10-fold)
• a subcellular distribution that suggests a full subcellular bioavailability
• an activity against both phagolysosomal (*S. aureus*), phagosomal (*L. pneumophila*) and cytosolic (*L. monocytogenes*) organisms
Tedizolid safety
(preclinical and "experimental human")
Linezolid adverse effects

• Drug interactions:
  – cytochrome P450: no special effect
  – antibiotics: rifampin causes a 21 % reduction in LZD serum levels
  – Monoamine oxidase inhibition (reversible, nonselective inhibitor):
    adrenergic and serotonergic agents (PRECAUTIONS)

• Myelosuppression (including anemia, leukopenia, pancytopenia and thrombocytopenia) (WARNING)

• Hypoglycemia

• Lactic acidosis (PRECAUTION – Immediate medical attention)

• Peripheral and optic neuropathy (>28 days)

• Convulsions
Linezolid adverse effects

- Drug interactions:
  - cytochrome P450: no special effect
  - antibiotics: rifampin causes a 21% decrease in LZD serum levels
  - Monoamine oxidase inhibition (reversible, nonselective inhibitor): may interact with adrenergic and serotonergic agents (PRECAUTIONS)

- Myelosuppression (including anemia, leukopenia, pancytopenia and thrombocytopenia) (WARNING)
- Hypoglycemia
- Lactic acidosis (PRECAUTION – Immediate medical attention)
- Peripheral and optic neuropathy (>28 days)
- Convulsions

Monoamine oxidase (MAO) substrate specificity

Consequences of MAO-A Inhibition

Serotonin Syndrome

Hypertensive crisis

MAO-A

- Serotonin
- Noradrenaline
  - Adrenaline
  - Octopamine
- Dopamine
  - Tyramine
  - Tryptamine
  - Kynuramine
  - 3-methoxytyramine

MAO-B

- Benzylamine
- Phenylethylamine
- N-phenylamine
- Octylamine
- N-acetylputrescine
- Milacemide
- N-methyl-4-phenyl-1,2,3,6-tetrahydropyridine

**Note:** MAO-A is the predominate form for oxidation of tyramine

Is serotonergic syndrome an important problem?

FIG 1 Spectrum of clinical findings. Manifestations of the serotonin syndrome range from mild to life threatening. The vertical arrows suggest the approximate point at which clinical findings initially appear in the spectrum of the disease, but all findings may not be consistently present in a single patient with serotonin syndrome. Severe signs may mask other clinical findings. For example, muscular hypertonicity can overwhelm tremor and hyperreflexia. Reprinted from reference 14 with permission from Massachusetts Medical Society.

This is what we tell the pharmacists in Belgium….

Interactions linezolid - médicaments

- Anti-migraineux
  - triptans
  - dihydroergotamine

- Anti-Parkinsoniens
  - L-Dopa
  - bromocryptine
  - selegiline

- Sympathomimétiques
  - bronchodilatateurs
  - pseudoéphèdrine

- Analgésiques
  - dextropropoxyphène
  - fentanyl
  - tramadol

- Anti-psychotiques
  - clozapine
  - olanzapine
  - risperidone
  - lithium

- Anti-dépresseurs
  - tricycliques
  - IMAO
  - ISRS

- Anxiolytiques
  - buspirone

- Vasopresseurs
  - (nor)adrénaline

- Anti-émétiques
  - setrons
  - metoclopramide

*Lawrence et al., CID (2006) 42:1578-83*
Linezolid contraindications

Monoamine oxidase inhibitors
Drugs that elevate blood pressure
Serotonergic drugs

Precaution
Tyramine-containing food
Tedizolid and monoamine-oxidase...

*In Vitro, In Vivo, and Clinical Studies of Tedizolid To Assess the Potential for Peripheral or Central Monoamine Oxidase Interactions*

S. Flanagan, K. Bartiza, S. L. Minassian, E. Fang, P. Prokocimer

Trius Therapeutics, Inc., San Diego, California, USA; Minassian Biostatistics, Inc., San Diego, California, USA
Tedizolid at exposure up to 30x human equivalent exposure did not cause serotonergic response in mice

FIG 3 Mouse head twitch rate following tedizolid phosphate, linezolid, fluoxetine, or moclobemide treatment. Twitch frequency is shown as means ± SD (n = 8 mice/group). Tedizolid refers to tedizolid phosphate. *, P < 0.05 versus the control group.

Lack of MAO interactions at multiples ~30-fold above therapeutic tedizolid clinical peak exposure in the model, while 1X linezolid produced ~5-fold increases over vehicle control
Human data for blood pressure elevation

FIG 2 Blood pressure response to 60 mg pseudoephedrine in placebo- and tedizolid phosphate-pretreated study populations. Patients \((n = 18)\) were randomized to oral placebo or oral tedizolid phosphate doses of 200 mg per day for 4 days; on the fifth day, 60 mg pseudoephedrine was administered with the morning dose of placebo or tedizolid phosphate, and blood pressure was recorded over the subsequent 24 h. Blood pressure was measured within 15 min prior to drug administration (Pre), every hour for 8 h after study drug administration, and at 10, 12, and 24 h.

Linezolid adverse effects

• Drug interactions:
  – cytochrome P450: no special effect
  – antibiotics: rifampin causes a 21 % decrease in LZD serum levels
  – Monoamine oxidase inhibition (reversible, nonselective inhibitor):
    ➤ adrenergic and serotonergic agents (PRECAUTIONS)

• Myelosuppression (including anemia, leukopenia, pancytopenia and thrombocytopenia)
  (WARNING)

• Hypoglycemia

• Lactic acidosis (PRECAUTION – Immediate medical attention)

• Peripheral and optic neuropathy (>28 days)

• Convulsions

Thrombocytopenia caused by linezolid may be more frequent than previously thought

(Pharmacotherapy 2010;30(9):895–903)

Analysis of Linezolid-Associated Hematologic Toxicities in a Large Veterans Affairs Medical Center

Quentin Minson, Pharm.D., and Chris A. Gentry, Pharm.D.

Patients. Four hundred forty-four patients (mean age 63.7 yrs) who received 544 courses of linezolid from 2004–2007.

Conclusion. The overall rates of thrombocytopenia and anemia for patients receiving linezolid were found to be higher than those in phase III clinical trials. This may be attributable in part to the inclusion of patients with comorbidities that were exclusion criteria in the phase III clinical trials. Clinicians should be aware of variables associated with the development of severe thrombocytopenia and anemia in patients receiving linezolid so that they may predict which patients are likely to develop these toxicities and consider potential alternative therapies in those patients.

Linezolid-induced thrombocytopenia is indeed frequent ...

<table>
<thead>
<tr>
<th>Patients with thrombocytopenia</th>
<th>no (87.2%)</th>
<th>yes (12.8%)</th>
<th>grade 1-2 (7.6%)</th>
<th>grade 3-4 (5.2%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>435</td>
<td>64</td>
<td>38</td>
<td>26</td>
<td></td>
</tr>
</tbody>
</table>

| grade 1: 75–99.9 x 10³/mm³; grade 2: 50–74.9 x 10³/mm³; grade 3: 20–49.9 x 10³/mm³; grade 4: < 20 x 10³/mm³. |
...and related to initial low platelet levels

<table>
<thead>
<tr>
<th>Patients with thrombocytopenia</th>
<th>no</th>
<th>yes</th>
<th>grade 1-2</th>
<th>grade 3-4</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>435</td>
<td>64</td>
<td>38</td>
<td>26</td>
</tr>
<tr>
<td></td>
<td>(87.2%)</td>
<td>(12.8%)</td>
<td>(7.6%)</td>
<td>(5.2%)</td>
</tr>
</tbody>
</table>

Figure 1. Mean ± SD platelet count during and/or after linezolid therapy in patients who subsequently developed no thrombocytopenia, grade 1–2 thrombocytopenia, and grade 3–4 thrombocytopenia. Platelet counts were significantly different between the no thrombocytopenia group and each of two thrombocytopenia groups at each time point (p<0.0001 by Tukey-Kramer analysis of variance). Platelet counts were not significantly different between the grade 1–2 and grade 3–4 toxicity groups at any time point.
...and aggravated by renal failure...
TEDIZOLID Phase I: platelets at 21 days*

Tedizolid 200 mg QD effects on hematologic parameters over 21 days were comparable to placebo.

* data from phase I study; treatment duration in phase III was limited to 6 days

Linezolid adverse effects

- Drug interactions:
  - cytochrome P450: no special effect
  - antibiotics: rifampin causes a 21% reduction in LZD serum levels
  - Monoamine oxidase inhibition (reversible, nonselective inhibitor):
    ➔ adrenergic and serotonergic agents (PRECAUTIONS)
- Myelosuppression (including anemia, leukopenia, pancytopenia and thrombocytopenia) (WARNING)
- Hypoglycemia
- **Lactic acidosis** (PRECAUTION – Immediate medical attention)
- Peripheral and optic neuropathy (>28 days)
- Convulsions

Lactic acidosis and mitochondria…

- Linezolid clinical use has been associated with obvious signs of mitochondrial dysfunction (hyperlactatemia, metabolic acidosis)\(^1\)
- There is evidence of alterations of mitochondrial ultrastructure, mitochondrial respiratory chain enzyme activity and mitochondrial DNA\(^2\)


- Could the larger accumulation of tedizolid (shown on previous slides) be due to or be associated with a preferential accumulation in mitochondria?

Accumulation of linezolid (LZD) and of torezolid (TR-700) in THP-1 macrophages
(a) Uptake kinetics
(b) Influence of the temperature (2 h incubation; blocks with different letters are significantly different from each other with \(p < 0.05\))
Subcellular localization of tedizolid...

**Methods:** Murine J774 macrophages were exposed to TZD (2-50 mg/L) for 2h, collected and homogenized for fractionation by differential (peletting) and isopycnic (sucrose gradient) centrifugation (Tulkens et al. J Cell Biol 1974; 63:383-401; Renard et al. AAC 1987; 31:410-6). TZD was quantified after extraction with CHCl₃:CH₃OH (8:4) by liquid chromatography (reverse phase) coupled with mass-spectrometry (LC-MS; electrospray; selective ion monitoring at MW 370-372, with LZD as internal standard). TZD distribution was compared to that of marker enzymes for mitochondria (cytochrome c-oxidase [CYTOX]), lysosomes (N-acetyl-beta-hexosaminidase [NaBGase]) and cytosol (lactate dehydrogenase [LDH]).
Subcellular localization of tedizolid after isopycnic centrifugation...

Tedizolid subcellular distribution in extract from J774 macrophages

Delta Q/Delta p

- Tedizolid
- mitochondria
- lysosomes
- cytosol

Density

- TDZ
- LDH
- NAB
- CytOx

No stable association of tedizolid to mitochondria

Das et al. ICAAC 2012; Poster A-1291.
Highlights – Preclinical and PK/PD

Microbiology:

- Higher potency than for linezolid in wild-type and in mutant MRSA strains
- Retains activity against cfr+ strains

Pharmacokinetics

- Linear PKs, minimal accumulation and high oral bioavailability giving comparable exposure between IV and oral formulations
- Half-life (~10-11 hours) allows once-daily dosing
- High tissue concentrations in lung, adipose tissue and muscle (without evidence of stable association with mitochondria)
- No dose adjustment required for special populations

Safety

- no drug-drug interactions and lack of serotonergic effect
- Minimal effect on platelet counts
From here to “real world” clinical data

Dr Matthew Dryden
Clinical Director of Microbiology
Royal Hampshire Hospital,
Winchester

For further information and contact about this presentation:
mail: tulkens@facm.ucl.ac.be
web: http://www.facm.ucl.ac.be
Back-up
Tedizolid and cidal activity *in vivo*
Tedizolid is cidal *in vivo* ...
Tedizolid and granulocytes \textit{in vivo}

\textbf{Impact of Granulocytes on the Antimicrobial Effect of Tedizolid in a Mouse Thigh Infection Model}\textsuperscript{\textcopyright}

G. L. Drusano,\textsuperscript{*} Weiguo Liu, Robert Kulawy, and Arnold Louie

\textit{Emerging Infections and Pharmacodynamics Laboratory, Ordway Research Institute, Albany, New York 12208}

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Tedizolid (TR-700, formerly torezolid) is the active component of the new oxazolidinone prodrug tedizolid phosphate (TR-701). We had previously demonstrated that tedizolid possessed potent antistaphylococcal activity superior to that of linezolid in a neutropenic mouse thigh infection model (A. Louie, W. Liu, R. Kulawy, and G. L. Drusano, Antimicrob. Agents Chemother. 55:3453–3460, 2011). In the current investigation, we used a mouse thigh infection model to delineate the effect of an interaction of TR-700 and granulocytes on staphylococcal cell killing. We compared the antistaphylococcal killing effect of doses of TR-701 equivalent to human exposures ranging from 200 to 3,200 mg/day in both granulocytopenic and normal mice. The mice were evaluated at 24, 48, and 72 h after therapy initiation. In granulocytopenic mice, a clear exposure response in which, depending on the time point of evaluation, stasis was achieved at “human-equivalent” doses of slightly below 2,300 mg/day (at 24 h) to slightly below 2,000 mg/day (at 72 h) was observed. In immune-normal animals, stasis was achieved at human-equivalent doses of slightly greater than 100 mg/day or less. The variance in bacterial cell killing results was attributable to the presence of granulocytes (without drug), the direct effect of TR-700 on \textit{Staphylococcus aureus}, and the effect of the drug on \textit{Staphylococcus aureus} mediated through granulocytes. The majority of the bacterial cell killing in normal animals was attributable to the effect of TR-700 mediated through granulocytes. Additional studies need to be undertaken to elucidate the mechanism underlying this observation.
Tedizolid cooperates with granulocytes *in vivo*

Tedizolid becomes cidal at low doses (equivalent to human 200 mg dose) in the presence of PMN

Drusano et al. Antimicrob Agent Chemother 2011; 55-5300-5305
Tedizolid vs daptomycin in vivo

Dose-Ranging Studies

- Tedizolid has daptomycin-like “in vivo bactericidal” activity
- Linezolid at 160 mg/kg/day → did not achieve stasis in this model

Tedizolid and granulocytes cooperate *in vivo* upon each administration

TR701/700 200 mg-Equivalent Dose
With Granulocytes

Killing progresses over time at each administration of tedizolid...

AUC$_{24h}$ = 20.1
(equivalent to humans for a dose of 200 mg)

MIC = 0.5 mg/L

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Drusano et al. Antimicrob Agent Chemother 2011; 55-5300-5305
Human pharmacokinetics: linearity over increasing doses (single and multiple doses)

Pharmacokinetics of Tedizolid Following Oral Administration: Single and Multiple Dose, Effect of Food, and Comparison of Two Solid Forms of the Prodrug

Shawn D. Flanagan,¹ Paul A. Bien,¹ Kelly A. Muñoz,¹ Sonia L. Minassian,² and Philippe G. Prokocimer¹
¹Trius Therapeutics, San Diego, California; ²Minassian Biostatistics, San Diego, California

Tedizolid and penicillin-resistant *S. pneumoniae*

Activity of Tedizolid Phosphate (TR-701) in Murine Models of Infection with Penicillin-Resistant and Penicillin-Sensitive *Streptococcus pneumoniae*

Sunghak Chol,* Weonbin Im,* and Ken Bartiza

Dong-A Pharmaceutical Co., Yongin-Si, South Korea,* and Trius Therapeutics, Inc., San Diego, California, USA*¹

TABLE 1 MICs for tedizolid and linezolid against PRSP

<table>
<thead>
<tr>
<th>Antimicrobial agent</th>
<th>MIC (μg/ml)</th>
<th>Range</th>
<th>50%</th>
<th>90%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tedizolid</td>
<td></td>
<td>0.125–0.25</td>
<td>0.25</td>
<td>0.25</td>
</tr>
<tr>
<td>Linezolid</td>
<td></td>
<td>0.125–1</td>
<td>0.5</td>
<td>1</td>
</tr>
</tbody>
</table>

*² Twenty-eight isolates were tested. Penicillin resistance was determined on the basis of the oral penicillin resistance MIC breakpoint for nonmeningitis pneumococcal isolates (≥2 μg/ml). For penicillin G tested against these isolates, the MIC range was 2 to 4 μg/ml, the MIC<sub>50</sub> was 2 μg/ml, and the MIC<sub>90</sub> was 4 μg/ml.

FIG 1. Pneumococcal clearance from lungs of *S. pneumoniae*-infected mice by tedizolid phosphate. Oral antimicrobial treatment was started at 4 h postinfection. *P < 0.05 versus untreated control at the same time point; #, P < 0.001 versus uninfected control at the same time point.
And even with recent Chinese isolates

Zhao et al. ECCMID 2015; Poster P1318

![Image](PEKING UNIVERITY PEOPLE’S HOSPITAL)

**In vitro** antimicrobial activity of the novel oxazolidinone tedizolid against clinical common Gram-positive pathogens in China

Chunjian Zhao, Yu Guo, Hongbin Chen, Feifei Zhang, Qi Wang, Xiaojuan Wang, Xinya Zhang, Henan Li, Hui Wang, Hui WANG

**Table 1. Antimicrobial activities of tedizolid and linezolid against Gram-positive pathogens**

<table>
<thead>
<tr>
<th>Organisms</th>
<th>N</th>
<th>TEDIZOLID</th>
<th>LINEZOLID</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>MIC&lt;sub&gt;50&lt;/sub&gt; (µg/ml)</td>
<td>MIC&lt;sub&gt;90&lt;/sub&gt; (µg/ml)</td>
</tr>
<tr>
<td>S. aureus</td>
<td>581</td>
<td>0.25</td>
<td>0.25</td>
</tr>
<tr>
<td>MRSA</td>
<td>234</td>
<td>0.25</td>
<td>0.25</td>
</tr>
<tr>
<td>MSSA</td>
<td>347</td>
<td>0.25</td>
<td>0.25</td>
</tr>
<tr>
<td>CoNS</td>
<td>279</td>
<td>0.064</td>
<td>0.125</td>
</tr>
<tr>
<td>Enterococci</td>
<td>291</td>
<td>0.25</td>
<td>0.5</td>
</tr>
<tr>
<td>β-hemolytic Streptococcus</td>
<td>258</td>
<td>0.25</td>
<td>0.25</td>
</tr>
</tbody>
</table>

Zhao et al. ECCMID 2015; Poster P1318
As also with strains from Europe

Table 2. Activity of Tedizolid and Comparators against *S. aureus*, MRSA, and MSSA Isolated from Skin Infections (2009–2013) in European Patients

<table>
<thead>
<tr>
<th>Pathogen (No.)</th>
<th>Drug</th>
<th>MIC Range</th>
<th>MIC&lt;sub&gt;50&lt;/sub&gt;</th>
<th>MIC&lt;sub&gt;90&lt;/sub&gt;</th>
<th>%S</th>
<th>%I</th>
<th>%R</th>
</tr>
</thead>
<tbody>
<tr>
<td>All <em>S. aureus</em> (592)</td>
<td>Tedizolid&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.06 to 1</td>
<td>0.25</td>
<td>0.5</td>
<td>99.8</td>
<td>0</td>
<td>0.2&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Linezolid</td>
<td>≤0.25 to 4</td>
<td>2</td>
<td>2</td>
<td>100</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>MRSA (125)</td>
<td>Tedizolid&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.06 to 0.5</td>
<td>0.25</td>
<td>0.5</td>
<td>100</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Linezolid</td>
<td>≤0.25 to 4</td>
<td>2</td>
<td>2</td>
<td>100</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>MSSA (467)</td>
<td>Tedizolid&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.12 to 1</td>
<td>0.25</td>
<td>0.5</td>
<td>99.8</td>
<td>0</td>
<td>0.2&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Linezolid</td>
<td>≤0.25 to 4</td>
<td>2</td>
<td>2</td>
<td>100</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

592 non-duplicate, non-consecutive isolates of *S. aureus* collected between 2009 and 2013 from patients with skin infections from 19 European countries (Austria, Belgium, Czech Republic, Denmark, France, Germany, Greece, Hungary, Ireland, Italy, Netherlands, Poland, Portugal, Romania, Russia, Spain, Sweden, Turkey, and the United Kingdom)

Goering et al. ECCMID 2015; Poster EP086.
Tedizolid human pharmacokinetics: ascending doses

- TR-700 has a PK profile allowing for once-a-day administration of TR-701
- Pharmacokinetics of TR-700 at steady state well predicted from single dose data and showed minimal accumulation
- The key pharmacodynamic driver for the efficacy of oxazolidinones is AUC/MIC. The value for TR-701 at 200 mg QD is 22.5/0.5=45
Tedizolid elimination...

- The majority of tedizolid elimination occurs via the liver (>80% of dose) as a tedizolid sulphate conjugate
- Tedizolid sulfonation can occur both in the liver and the intestinal tract through several SULT isoforms (SULT1A1, SULT1A2, and SULT2A1)
- SULT1A1 and SULT2A1 is highly expressed in liver and to a lesser extent in the small intestine
- Polymorphisms in SULT isoforms catalysing tedizolid metabolism in vitro are not known to date to significantly change the elimination of drugs

SULT = sulfotransferase

2. Niehues et al. ECCMID 2015; Poster P1321.
Tedizolid metabolism…

- The majority of tedizolid elimination occurs via the liver (>80% of dose) as a **tedizolid sulphate** conjugate

---

1 - Hydrolysis
2 - Demethylation
3 - Sulfation
4 - Oxidation
5 - Oxidation/Decarboxylation

**Fig. 4. Proposed biotransformation of tedizolid phosphate. Putative metabolites were identified by mass spectrometry.**
How to determine which PK parameter is critical?

- If you fractionate the daily dose, you change $C_{\text{max}}$ without changing $\text{AUC}_{24\text{h}}$. 

\[
\text{AUC}_{24\text{h}} = \frac{\text{Dose}_{24\text{h}}}{\text{Clearance}}
\]

$\text{AUC}_{24\text{h}}$ is independent of the schedule.
How to determine which PK parameter is critical?

- If you increase the dose without change of schedule, you increase BOTH $C_{\text{max}}$ and AUC$_{24\text{h}}$.
How do you do this with tedizolid?

TABLE 2. Calculated pharmacodynamic variables for 4 total daily dosages of TR-701 administered as one, two, or four equally divided doses over 24 h

| Total dosage (mg/kg/24 h) | Regimen<sup>a</sup> | $fC_{\text{max}}$/MIC ratio<sup>b</sup> | $f\text{AUC}$/MIC ratio<sup>c</sup> | $fT>\text{MIC}$ (%)<sup>d</sup> |
|---------------------------|-------------------|---------------------------------|---------------------------------|---------------------------------
| 10                        | 10 mg/kg q24h    | 2.62                            | 13.19                           | 21                              |
| 5 mg/kg q12h              |                   | 1.29                            | 12.82                           | 20                              |
| 2.5 mg/kg q6h             |                   | 0.64                            | 12.26                           | 0                               |
| 20                        | 20 mg/kg q24h    | 5.16                            | 26.03                           | 31                              |
| 10 mg/kg q12h             |                   | 2.62                            | 25.63                           | 43                              |
| 5 mg/kg q6h               |                   | 1.29                            | 24.51                           | 50                              |
| 36                        | 36 mg/kg q24h    | 9.29                            | 46.88                           | 39                              |
| 18 mg/kg q12h             |                   | 4.65                            | 46.14                           | 60                              |
| 9 mg/kg q6h               |                   | 2.32                            | 44.12                           | 87                              |
| 72                        | 72 mg/kg q24h    | 18.59                           | 93.76                           | 49                              |
| 36 mg/kg q12h             |                   | 9.29                            | 92.28                           | 79                              |
| 18 mg/kg q6h              |                   | 4.65                            | 88.24                           | 100                             |

<sup>a</sup> The first dose was administered 2 h after infection. All doses of TR-701 are provided as dose equivalents (mg/kg/day) of TR-700. Doses were given every 24 h (q24h), every 12 h (q12h), or every 6 h (q6h).

<sup>b</sup> $fC_{\text{max}}$/MIC ratio, maximum concentration of free drug in serum divided by the MIC. The MICs for the MRSA strain were 0.5 mg/liter in CA-MHB and 1 mg/liter in 80% mouse serum.

<sup>c</sup> $f\text{AUC}$/MIC ratio, area under the concentration-time curve over 24 h for the free, unbound fraction of a drug divided by the MIC.

<sup>d</sup> $fT>\text{MIC}$, calculated cumulative percentage of a 24-h period that the concentration of the free drug exceeded the MIC under steady-state pharmacokinetic conditions (expressed as a percentage of the dosing interval).

What do you see?

The correlation with $f_{C_{\text{max}}}$ is not excellent

The correlation with $f_{T > MIC}$ is worse!

## Tyramine sensitivity in humans

<table>
<thead>
<tr>
<th></th>
<th>Linezolid(^1)</th>
<th>Tedizolid(^2)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mean (SD) Tyr(_{30}) dose (mg)</strong></td>
<td>136 (42)</td>
<td>339 (69)</td>
</tr>
<tr>
<td><strong>Mean; Max Tyramine Sensitivity Factor (TSF)</strong></td>
<td>3.48; 5.0</td>
<td>1.28; 2.1</td>
</tr>
<tr>
<td><strong>Subjects with ≥2-fold TSF/total subjects</strong></td>
<td>8/10</td>
<td>1/7</td>
</tr>
</tbody>
</table>

TSF = Tyramine Sensitivity Factor = \(\frac{\text{Tyr}_{30} \text{ following Placebo or pretreatment}}{\text{Tyr}_{30} \text{ following TZD or LZD}}\).

Note: 2-fold increase in TSF is threshold for clinically meaningful change in response to tyramine. \(^1\)

2. Study TR701-105
## Vasopressor (pseudoephedrine) interaction in humans

<table>
<thead>
<tr>
<th></th>
<th>Mean (SD) Maximum SBP and SBP Changes (mm Hg)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Linezolid&lt;sup&gt;3&lt;/sup&gt;</td>
<td>Tedizolid&lt;sup&gt;4&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Mean Maximum SBP Change</td>
<td>Max SBP Value</td>
</tr>
<tr>
<td>Pseudoephedrine alone/+ placebo</td>
<td>18 (9)</td>
<td>133 (17)</td>
</tr>
<tr>
<td>Pseudoephedrine + drug</td>
<td>32 (10)</td>
<td>151 (15)</td>
</tr>
<tr>
<td>Difference</td>
<td>14</td>
<td>18</td>
</tr>
</tbody>
</table>

4. Study TR701-114
Is cellular accumulation of tedizolid of toxicological concern?

Methods: Murine J774 macrophages were exposed to TZD (2-50 mg/L) for 2h, collected and homogenized for fractionation by differential (peletting) and isopycnic (sucrose gradient) centrifugation (Tulkens et al. J Cell Biol 1974; 63:383-401; Renard et al. AAC 1987; 31:410-6). TZD was quantified after extraction with CHCl₃:CH₃OH (8:4) by liquid chromatography (reverse phase) coupled with mass-spectrometry (LC-MS; electrospray; selective ion monitoring at MW 370-372, with LZD as internal standard). TZD distribution was compared to that of marker enzymes for mitochondria (cytochrome c-oxidase [CYTOX]), lysosomes (N-acetyl-beta-hexosaminidase [NaBGase]) and cytosol (lactate dehydrogenase [LDH]).

Results: After both differential and isopycnic cell fractionation, TDZ was consistently recovered in fractions enriched in cytosol and not detected in those enriched in mitochondria or lysosomes.

Conclusions: In spite of a higher accumulation in eukaryotic cells compared to LZD, TDZ seems not associated in a stable fashion to mitochondria. Observing TDZ in the cytosol after cell fractionation may point to its ability to diffuse throughout the cell, explaining its higher activity against organisms harbored in distinct subcellular compartments while at the same time not necessarily implying a higher potential mitochondrial toxicity.

Das et al. ICAAC 2012; Poster A-1291.
Summary of tedizolid non-clinical safety attributes

**No Drug-Drug Interactions**

- No inhibition or induction of human hepatic cytochrome P450 activities at high concentrations
- No tyramine or noradrenergic "Pressor potentiation Effect" (vs significant effect for linezolid)
- No serotonergic effect in head twitch model

**No Safety Pharmacology Issues Identified**

- No effects in pivotal cardiovascular, neurobehavioral, respiratory, or gastrointestinal systems
- No IKr or QTc signal with TR-700 at highest soluble dose
- No non-clinical genetic toxicology signals: Ames, Chrom Ab, Micronucleus, UDS
- No genotoxicity or reprotoxicity issues
- No effect on spermatogenesis