Tedizolid: a novel treatment for Gram + infections and its potential role in clinical practice

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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)

Tedizolid Launch Symposium
Jeddah, Saudi Arabia – 26 November 2016

With approval of the Belgian Common Ethical Health Platform – visa no. 16/V1/8979/084651
Disclosures

Financial support from

• Non-profit Institutions:
  – the Belgian *Fonds de la Recherche Scientifique* for basic research on pharmacology antibiotics and related topics
  – The European Union for applied research on optimization of β-lactams treatments through on-line monitoring of free serum levels
  – *Université catholique de Louvain* for past personal support

• Industry:
  – AstraZeneca, GSK, Sanofi-Aventis, Bayer HealthCare, Cempra Pharmaceuticals, The Medicines Company, Northern Antibiotics, RibX, Cubist, Galapagos, …

Other relationships in relation to this talk

– Belgian Antibiotic Policy Coordination Committee,
– European Committee for Antibiotic Susceptibility Testing (EUCAST)
– European Medicines Agency (EMA)

Slides: http://www.facm.ucl.ac.be ➔ Lectures
The programme…

• A short view of Belgium and of where I work…

• What is tedizolid?
  – discovery, main properties…

• What are our current choices for treatment of ABSSSI
  – a brief overview of the pros and cons of currently available antibiotics for treatment of ABSSSI (other than tedizolid)

• How does tedizolid compares clinically to linezolid?
  – registration studies
  – potential roles in daily therapy

• Questions, objections, suggestions …
Belgium

10 millions inhabitants …

10 Nobel prizes (10/850) for activities in Belgium

• 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)

source: http://www.nobelprize.org/
Last accessed: 10 May 2016
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)

- Created in 1425, 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 1500's

Erasmus

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

- In the 19th century, teaching was in French but in the early 1900's, 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…

Prof. G. Lemaitre, professor of Physics and Mathematics at the University who, in the 1930's, made the first suggestion of the continuous expansion of the Universe ("big bang")
(here in conversation with A. Einstein)

Professor C. de Duve, Professor of Biochemistry, obtained the Nobel Prize (Physiology and Medicine) in 1974 for his work on intracellular organelles (lysosomes, peroxisomes…) 
(here in front of a centrifuge)
The Catholic University of Louvain in brief (4 of 4)

- The Flemish-speaking *Katholieke Universiteit Leuven* has remained in Louvain (Leuven) and is named in English "Catholic Universiteit Leuven".

- The French-speaking *Université catholique de Louvain* has moved about 25 km South in a place called "Louvain-la-Neuve, with the "Health Sciences Sector" located in Brussels (Woluwe)

- Together, the two sister Universities have about **60,000 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 graduating 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 (delafloxacin *…)
  - ketolides (solithromycin *…)
  - oxazolidinones (tedizolid …)
  * in development

- re-assessment of older antibiotics

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 Antiinfective Pharmacology (ISAP)

www.isap.org
Why should a Belgian come to Jeddah to speak about tedizolid?

and find the sun?

to leave this?
We have been working on tedizolid since 2007 …

called "torezolid"
or TR-700
at that time…

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
But where does tedizolid come from?
The programme...

• A short view of Belgium and of where I work...

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  – discovery, main properties...

• What are our current choices for treatment of ABSSSI
  – a brief overview of the pros and cons of currently available antibiotics for treatment of ABSSSI (other than tedizolid)

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  – potential roles in daily therapy

• Questions, objections, suggestions ...
From linezolid to tedizolid: the basics

Linezolid (LZD)

Tedizolid (TR-700)

Substantial differences that DO impact on
- **intrinsic activity** (*more potent*)
- activity against LZD-resistant strains
- half-life (*longer*)

**acetamido vs. free -OH**

additional methyl-tetrazoyl

pyridinyl replacing the morpholinyl

**From linezolid to tedizolid: the basics**

**Linezolid (LZD)**

**Tedizolid (TR-700)**
Tedizolid is more potent because of more interactions with the target ...

W.B. Im et al. / European Journal of Medicinal Chemistry 46 (2011) 1027–1039 PMID: 21392356

Fig. 2. Models of 11 (blue) and linezolid (yellow) binding to the Escherichia coli ribosome.

tedizolid
Tedizolid is systematically 3-4-x more active than linezolid against LSDS strains.

Table 1. Susceptibility of the strains of *S. aureus, L. monocytogenes* and *L. pneumophila* used in this study to linezolid and torezolid

<table>
<thead>
<tr>
<th>Species, phenotype and strain no.</th>
<th>MIC (mg/L)(^a)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>linezolid</td>
</tr>
<tr>
<td><em>Staphylococcus aureus</em></td>
<td></td>
</tr>
<tr>
<td>MSSA ATCC 25923(^b)</td>
<td>2</td>
</tr>
<tr>
<td>HA-MRSA ATCC 33591(^b)</td>
<td>1</td>
</tr>
<tr>
<td>SA 233(^c)</td>
<td>2</td>
</tr>
<tr>
<td>CM 05(^d)</td>
<td>8</td>
</tr>
<tr>
<td>CA-MRSA NRS 192(^e)</td>
<td>2</td>
</tr>
<tr>
<td>NRS 384 (US300)(^e)</td>
<td>2</td>
</tr>
<tr>
<td>VISA NRS 52(^e)</td>
<td>2</td>
</tr>
<tr>
<td>VRSA VRS 1(^e)</td>
<td>1–2</td>
</tr>
<tr>
<td>VRS 2(^e)</td>
<td>1–2</td>
</tr>
<tr>
<td>animal MRSA N7112046(^f)</td>
<td>2</td>
</tr>
<tr>
<td><em>Listeria monocytogenes</em></td>
<td></td>
</tr>
<tr>
<td>EGD(^g)</td>
<td>1–2</td>
</tr>
<tr>
<td><em>Legionella pneumophila</em></td>
<td></td>
</tr>
<tr>
<td>ATCC 33153(^b)</td>
<td>4–8</td>
</tr>
</tbody>
</table>

LZD\(^h\), resistant to linezolid.

\(^{a}\)Representative values of at least two determinations.

\(^{b}\)From the American Tissue Culture Collection (Manassas, VA, USA).

\(^{c}\)Provided by P. C. Appelbaum.\(^36\)

\(^{d}\)Provided by J. P. Quinn, John H. Stroger Jr. Hospital, Rush University, Chicago, IL, USA.

\(^{e}\)From the Network on Antimicrobial Resistance in *Staphylococcus aureus* (NARSA) programme (operated by Eurofins Medinet, Inc., Hendon, VA, USA; supported under NIAID/NIH contract no. HHSN27220070005C); details on each strain are available at http://www.narsa.net/content/home.jsp.

\(^{f}\)Provided by Y. Glupczynski, Cliniques universitaires UCL de Mont Godinne, Yvoir, Belgium.

\(^{g}\)Provided by P. Berche, Hôpital Necker, Paris, France.\(^28\)

And also for a large-scale survey of different Gram-positive organisms from multiple US and European sites

S. aureus (n=4499)

Coagulase (-) staphylococci (n=537)

Enterococci (n=873)

β-hemolytic streptococci (n=975)

And also for another large-scale survey of different Gram-positive organisms from Asia-Pacific, Eastern Europe, and Latin American Countries in 2014

Activities of Tedizolid and Linezolid Determined by the Reference Broth Microdilution Method against 3,032 Gram-Positive Bacterial Isolates Collected in Asia-Pacific, Eastern Europe, and Latin American Countries in 2014

Michael A. Pfaller, Robert K. Flamm, Ronald N. Jones, David J. Farrell, Rodrigo E. Mendes

JMI Laboratories, North Liberty, Iowa, USA; University of Iowa College of Medicine, Iowa City, Iowa, USA
And also for a another large-scale survey of different Gram-positive organisms from Asia-Pacific, Eastern Europe, and Latin American Countries in 2014

### TABLE 1 Numbers of organisms included in this study stratified by site of infection

<table>
<thead>
<tr>
<th>Organism or group</th>
<th>BSI</th>
<th>PIHP</th>
<th>SSSI</th>
<th>Other</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>S. aureus</td>
<td>263</td>
<td>208</td>
<td>484</td>
<td>1,427</td>
<td>2,382</td>
</tr>
<tr>
<td>MSSA</td>
<td>193</td>
<td>134</td>
<td>372</td>
<td>982</td>
<td>1,681</td>
</tr>
<tr>
<td>MRSA</td>
<td>70</td>
<td>74</td>
<td>112</td>
<td>445</td>
<td>701</td>
</tr>
<tr>
<td>S. pyogenes</td>
<td>16</td>
<td>5</td>
<td>62</td>
<td>175</td>
<td>258</td>
</tr>
<tr>
<td>S. agalactiae</td>
<td>25</td>
<td>2</td>
<td>8</td>
<td>110</td>
<td>145</td>
</tr>
<tr>
<td>S. anginosus group$^a$</td>
<td>5</td>
<td>6</td>
<td>6</td>
<td>37</td>
<td>54</td>
</tr>
<tr>
<td>E. faecalis</td>
<td>60</td>
<td>0</td>
<td>52</td>
<td>81</td>
<td>193</td>
</tr>
</tbody>
</table>

$^a$ S. constellatus (23 isolates), S. anginosus group not otherwise specified (4 isolates), S. anginosus (26 isolates), S. intermedius (1 isolate).

BSI: bloodstream infections  
PIHP: pneumonia in hospitalized patients  
SSSI: skin and skin structures infection  

And also for a another large-scale survey of different Gram-positive organisms from Asia-Pacific, Eastern Europe, and Latin American Countries in 2014

And also for a another large-scale survey of different Gram-positive organisms from Asia-Pacific, Eastern Europe, and Latin American Countries in 2014.

Activities of Tedizolid Broth Microdilution Isolates Collected in Countries in 2014

E. faecalis (n=193)

Oxazolidinones: 1st 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_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)
Tedizolid is also active against linezolid-resistant isolates (cfr+).

<table>
<thead>
<tr>
<th>Species, phenotype and strain no.</th>
<th>linezolid</th>
<th>torezolid</th>
</tr>
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<tr>
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<tr>
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<td>2</td>
<td>0.25</td>
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<td>1</td>
<td>0.125–0.25</td>
</tr>
<tr>
<td>SA 238(^c)</td>
<td>2</td>
<td>0.25–0.5</td>
</tr>
<tr>
<td>CM 05(^d)</td>
<td>8</td>
<td>0.25–0.5</td>
</tr>
<tr>
<td>CA-MRSA NRS 192(^e)</td>
<td>2</td>
<td>0.125–0.25</td>
</tr>
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<td>NRS 384 (US300)(^e)</td>
<td>2</td>
<td>0.25</td>
</tr>
<tr>
<td>VISA NRS 52(^e)</td>
<td>2</td>
<td>0.125</td>
</tr>
<tr>
<td>VRSA VRS 1(^e)</td>
<td>1–2</td>
<td>0.125–0.25</td>
</tr>
<tr>
<td>VRS 2(^e)</td>
<td>1–2</td>
<td>0.25</td>
</tr>
<tr>
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<td>0.125</td>
</tr>
<tr>
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<tr>
<td>EGD(^g)</td>
<td>1–2</td>
<td>0.125</td>
</tr>
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</tr>
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<td>ATCC 33153(^b)</td>
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LZD\(^h\), resistant to linezolid.

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\(^g^\) Provided by P. Berche, Hôpital Necker, Paris, France.\(^28\)

Activity against Cfr$^+$ resistant strains … (cfr$^+$ bacteria)

<table>
<thead>
<tr>
<th>Strain</th>
<th>Reference</th>
<th>Presence of cfr</th>
<th>MIC (μg/ml)$^a$</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Lzd</td>
<td>TR-700</td>
<td></td>
</tr>
<tr>
<td>RN4220(pLI50)</td>
<td>68</td>
<td>−</td>
<td>2</td>
<td>0.5</td>
<td></td>
</tr>
<tr>
<td>RN4220(pLXM1)$^b$</td>
<td>68</td>
<td>+</td>
<td>8</td>
<td>0.5</td>
<td></td>
</tr>
<tr>
<td>CM05Δ$^c$</td>
<td>44</td>
<td>−</td>
<td>2</td>
<td>0.5</td>
<td></td>
</tr>
<tr>
<td>CM05$^c$</td>
<td>68</td>
<td>+</td>
<td>8</td>
<td>0.5</td>
<td></td>
</tr>
<tr>
<td>29213</td>
<td>ATCC</td>
<td>−</td>
<td>2</td>
<td>0.5</td>
<td></td>
</tr>
<tr>
<td>29213(p42262)$^d$</td>
<td>45</td>
<td>+</td>
<td>16</td>
<td>0.5</td>
<td></td>
</tr>
<tr>
<td>42262$^e$</td>
<td>51</td>
<td>+</td>
<td>16</td>
<td>0.5</td>
<td></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.

Why is tedizolid active against LZD$^R$ strains (cfr)?


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 LZD^R strains (cfr)?

Chemistry and microbiology

- Tedizolid is 3-4 x more potent than linezolid
- Tedizolid is active against $cfr^+$ linezolid-resistant strains
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 **active moiety TR-700**
Oral and IV tedizolid phosphate yield similar systemic conversion to tedizolid (high bioavailability)

Mean tedizolid plasma concentration after a single dose of IV or oral 200 mg tedizolid phosphate (log time scale; n=8).

Percentage bioavailability of tedizolid after oral tedizolid phosphate dosing: 91.5%

Flanagan et al. Pharmacotherapy 2014;34:891-900. PMID: 24989138
Tedizolid clinical presentations

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

Tablets can be crushed in water and tedizolid phosphate remains stable for at least 4h

Tedizolid has a longer half-life than linezolid → once-daily dosing is possible

Tedizolid:
- mean t_{1/2} ∼ 2 x that of linezolid
- 18h presence > breakpoint (0.5 mg/L) vs. 12h for linezolid (4 mg/L).

Muñoz et al. ECCMID 2010 P1594
Tedizolid elimination is largely **not** through the kidney …

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

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

\[
\text{No need of adjustment for decreased renal function}
\]

Ong *et al.* Drug Metab Dispos. 2014;42:1275-84.
Impact of variations in excretory functions on tedizolid pharmacokinetics

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** conditions

Flanagan et al Pharmacotherapy 2014;34:240–50 – PMID 23926058
Data on file, Bayer.
Sivextro (tedizolid phosphate) [prescribing information]. Whitehouse Station, NJ: Merck & Co., Inc.; 2015.
PK parameters governing the activity of antibiotics

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

Concentration vs. Time (h)

- $C_{\text{max}}$
- $fT > \text{MIC}$
- $\text{AUC}_{24\text{h}}$
- MIC
AUC$_{24h}$ and activity tedizolid

TZD activity depends on actual fAUC$_{24h}$/MIC value, and is independent of the dosing schedule (in the limits investigated)

Tedizolid breakpoints (200 mg/once daily)...

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

**Table 5 Susceptibility Test Interpretive Criteria for SIVEXTRO**

<table>
<thead>
<tr>
<th>Pathogen</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>
</tr>
<tr>
<td><em>Streptococcus pyogenes</em></td>
<td>≤0.5</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td><em>Streptococcus agalactiae</em></td>
<td>≤0.5</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td><em>Streptococcus anginosus Group</em></td>
<td>≤0.25</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td><em>Enterococcus faecalis</em></td>
<td>≤0.5</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

S=susceptible, I=intermediate, R=resistant
* Includes *S. anginosus, S. intermedius, S. constellatus*
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 (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 eukaryotic cells

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

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¹Unité de Pharmacologie cellulaire et moléculaire & Louvain, Brussels, Belgium; ²Hershey Medical Center, USA

doi:10.1093/jac/dkp267
Advance Access publication 16 September 2009
Tedizolid is more active (3 – 4 x) 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)

Lemaire et al. JAC 2010; 64:1035–1043
Tedizolid is active intracellularly against MRSA disregarding resistance phenotypes

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

Lemaire et al. JAC 2010; 64:1035–1043
Tedizolid accumulates in lung macrophages (and fluid) of healthy adults volunteers (200 mg dose)

Tedizolid distributes equally in muscle and adipose tissue (microdialysis) compared to plasma

- Subjects administered a single oral dose of 600 mg tedizolid phosphate (prodrug)
- Microdialysis probes into the subcutaneous adipose tissue and into the muscle
- Analysis by high-performance liquid chromatography with UV detection

A summary for tedizolid at this point?

Chemistry and microbiology

• 3-4 x more potent than linezolid
• active against $cfr^+$ linezolid-resistant strains

Pharmacokinetics, breakpoints, tissue distribution…

• longer half-life than linezolid → once daily dosing
• No need of dose readjustment (renal or hepatic failure, weight…)
• 200 mg/day covers for MICs up to 0.5 mg/L (EU) or 1 mg/L (USA)
• accumulates and show activity in macrophages…

but what about safety?

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
Monoamine Oxidase (MAO) Substrate Specificity *

Consequences of MAO-A Inhibition

- Serotonin Syndrome
- Hypertensive crisis

MAO-A
- Serotonin
- Noradrenaline
- Adrenaline
- Octopamine

MAO-B
- Dopamine
- Tyramine\(^a\)
- Tryptamine
- Kynuramine
- 3-methoxytyramine
- Benzylamine
- Phenylethylamine
- N-phenylamine
- Octylamine
- N-acetylputrescine
- Milacemide
- N-methyl-4-phenyl-1,2,3,6-tetrahydropyridine

* Linezolid inhibits both enzymes, causing increased concentration of these bioamines ...

\(^a\) MAO-A is the predominant form for oxidation of tyramine

Is serotonergic syndrome an important problem?

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 the serotonin syndrome. Severe signs may mask other clinical findings. For example, muscular hypertonicity can overwhelm tremor and hyperreflexia.

5-HTP Mouse Head Twitch *  
(Model of Serotonergic Effects)

* The head-twitch response (HTR) is a rapid side-to-side head movement that occurs in mice and rats after the serotonin 5-HT2A receptor is activated (Nakagawasai et al. Neurotoxicology. 2004;25:223-32 - PMID: 14697897)

![Graph showing the head-twitch response](image)

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.

Human data for blood pressure response to pseudoephedrine (60 mg) vs placebo in tedizolid-pretreated patients

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 vs tedizolid effects on platelets (21 days [phase I trials])

* treatment duration of tedizolid in phase III is limited to 6 days

Prokocimer et al. ICAAC IDSA 2008; Poster F1-2069a.
Linezolid and tedizolid impairment of mitochondrial protein synthesis

1. Impairment of mitochondrial protein synthesis may explain linezolid-induced lactic acidosis and neuropathies

2. Both linezolid and tedizolid impair mitochondrial protein synthesis …. but this is reversible…¹

3. For linezolid, plasma concentrations of linezolid remain always > IC₅₀ → permanent inhibition ²

4. For tedizolid, free through concentrations fall < IC₅₀ → partial daily recovery ²


A summary of tedizolid preclinical safety attributes…

- **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) (see previous slides)
  - No serotonergic effect in head twitch model (see previous slides)

- **Other potential pharmacological issues**
  - 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 *

* not shown here but see registration data (FDA / EMA)
So, where are we now?

Examples of SSTIs

Superficial complicated SSTI

Simple superficial SSTI due to trauma

Deep simple SSTI

Deep complicated SSTI

Do you wish to treat THIS?
Do we need antibiotics?
The programme…

• A short view of Belgium and of where I work…

• What is tedizolid?
  – discovery, main properties…

• What are our current choices for treatment of ABSSSI
  – a brief overview of the pros and cons of currently available antibiotics for treatment of ABSSSI (other than tedizolid)

• How does tedizolid compares clinically to linezolid?
  – registration studies
  – potential roles in daily therapy

• Questions, objections, suggestions …
# MSSA SSTI: Available treatments

<table>
<thead>
<tr>
<th>Agent</th>
<th>Dose</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>(di/flu)cloxacillin oxacillin</td>
<td>500 mg every 6 h</td>
<td>• IV and oral agents (but low bioavailability !)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• short half life (must be compliant !)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• allergies</td>
</tr>
<tr>
<td>nafcillin</td>
<td>1-2 g every 4 h</td>
<td>• IV only</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• best choice but must be compliant</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• allergies</td>
</tr>
<tr>
<td>clindamycin *</td>
<td>600 mg every 8 h IV 450 mg every 6 h PO</td>
<td>• Bacteriostatic</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• active against MRSA but emergence of resistance (inducible)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• knowledge of local susceptibility is a must</td>
</tr>
<tr>
<td>doxycycline * minocycline *</td>
<td>100 mg BID PO</td>
<td>• Bacteriostatic</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• limited recent clinical experience</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• knowledge of local susceptibility is a must</td>
</tr>
<tr>
<td>TMP/SMX *</td>
<td>160/800 mg BID PO (or more …)</td>
<td>• Bactericidal</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• limited recent clinical experience</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• knowledge of local susceptibility is a must</td>
</tr>
</tbody>
</table>

* may also work on MRSA but requires documentation

## MRSA SSTI: Available treatments

<table>
<thead>
<tr>
<th>Agent</th>
<th>Dose</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>vancomycin</td>
<td>15 mg/kg every 12 h or continuous infusion</td>
<td>• long first choice for IV treatment of MRSA&lt;br&gt;• requires drug monitoring&lt;br&gt;• may cause nephrotoxicity&lt;br&gt;• beware of MICs ≥ 2 mg/L</td>
</tr>
<tr>
<td>linezolid</td>
<td>600 mg every 12 h IV OR PO</td>
<td>• bacteriostatic&lt;br&gt;• allows for efficient IV → PO switch&lt;br&gt;• toxicities</td>
</tr>
<tr>
<td>daptomycin</td>
<td>4 – 6 mg/kg Q24h IV</td>
<td>• bactericidal&lt;br&gt;• doses may need to be increased&lt;br&gt;• possible myopathy</td>
</tr>
<tr>
<td>ceftaroline</td>
<td>600 mg every 12 h IV</td>
<td>• bactericidal&lt;br&gt;• well tolerated but requires compliance&lt;br&gt;• IV only</td>
</tr>
<tr>
<td>oritavancin *</td>
<td>1200 mg once + 1000 mg + 500 mg at day 7</td>
<td>• bactericidal (VISA and VRSA not susceptible)&lt;br&gt;• convenient use but long infusion time (3h)&lt;br&gt;• prolonged tissue accumulation (risk ?)</td>
</tr>
<tr>
<td>dalbavancin *</td>
<td></td>
<td>* approved after publication of the guidelines</td>
</tr>
</tbody>
</table>

Important limits of vancomycin: 1. MIC-related failures

Relation of MIC to treatment failures

Important limits of vancomycin: 2. poor tissue penetration

- CNS: <10%
- Sternal bone: 57%
- Heart valve: 12%
- Lung tissue: 17%–24%
- Bone: 7%–13%
- Epithelial lining fluid: 18%
- Fat: 14%
- Muscle: 9%

Important limits of vancomycin: 3. unpredictable serum levels (at the level of individual patients and over time)

Continuous infusion of vancomycin:

target value: 27.5 mg/L

Ampe et al Intern J Antimicrob Agents 2013;41:439-446 – PMID 23523733
Important limits of vancomycin: 3. unpredictable serum levels (at the level of individual patients and over time)

Continuous infusion of vancomycin:
target value: 27.5 mg/L

Ampe et al Intern J Antimicrob Agents 2013;41:439-446 – PMID 23523733
Important limits of vancomycin: 4. nephrotoxicity

Incidence of nephrotoxicity as a function of the trough serum levels

The programme…

• A short view of Belgium and of where I work…

• What is tedizolid?
  – discovery, main properties…

• What are our current choices for treatment of ABSSSI
  – a brief overview of the pros and cons of currently available antibiotics for treatment of ABSSSI (other than tedizolid)

• How does tedizolid compares clinically to linezolid?
  – registration studies
  – potential roles in daily therapy

• Questions, objections, suggestions…
Tedizolid phase III studies

**Tedizolid Phosphate vs Linezolid for Treatment of Acute Bacterial Skin and Skin Structure Infections**
The ESTABLISH-1 Randomized Trial

Philippe Prokocimer, MD
Carisa De Anda, PharmD
Edward Fang, MD
Parvi Mehra, MD
Anita Das, PhD

*Importance* Acute bacterial skin and skin structure infections (ABSSIs), including cellulitis or erysipelas, major cutaneous abscesses, and wound infections, can be life-threatening and may require surgery and hospitalization. Increasingly, ABSSIs are associated with drug-resistant pathogens, and many antimicrobial agents have adverse effects restricting their use. Tedizolid phosphate is a novel oxazolidinone in development for the treatment of ABSSIs.


**Articles**

*Tedizolid for 6 days versus linezolid for 10 days for acute bacterial skin and skin-structure infections (ESTABLISH-2): a randomised, double-blind, phase 3, non-inferiority trial*

Gregory J Moran, Edward Fang, G Ralph Corey, Anita F Das, Carisa De Anda, Philippe Prokocimer

*Background* New antibiotics are needed to treat infections caused by drug-resistant bacteria. Tedizolid is a novel oxazolidinone antibacterial drug designed to provide enhanced activity against Gram-positive pathogens. We aimed to assess the efficacy and safety of intravenous to oral tedizolid for treatment of patients with acute bacterial skin and skin-structure infections.

# FDA new clinical guidance (2013)

<table>
<thead>
<tr>
<th></th>
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</tr>
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<tbody>
<tr>
<td>cSSSI</td>
<td>ABSSSI</td>
<td></td>
</tr>
<tr>
<td>Infection Type</td>
<td>Large Abscess, Wound, Cellulitis, DFI, Chronic Ulcer</td>
<td>Large Abscess, Wound, Cellulitis – min. 75 cm²</td>
</tr>
<tr>
<td>Infection Severity</td>
<td>Intermediate/Severe</td>
<td>Severe</td>
</tr>
<tr>
<td>Primary Endpoints</td>
<td>Subjective Clinicians Assessment at 7-14 Days After EOT</td>
<td>Objective ≥20% reduction in lesion size at 48–72 hours</td>
</tr>
</tbody>
</table>
| Secondary Endpoints | Varied | • Primary Endpoint Sustained to EOT  
• Clinician’s Assessment at EOT |
|                | Low Potential for Differentiation | Higher Potential for differentiation |

- ABSSSI = acute bacterial skin and skin structure infections
- cSSSI = complicated skin and skin structure infections; including chronic ulcers, diabetic foot infections, and burns – very different in nature, treated differently (polymicrobial) and chronic

* The 2010 FDA Guidance primary endpoint: "Cessation of lesion spread & fever at 48-72 h" was updated in 2013

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**Guidance for Industry: Acute Bacterial Skin and Skin Structure Infections: Developing Drugs for Treatment (FDA - CDER -- October 2013)**

### FDA new clinical guidance

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<td>Infection Severity</td>
<td>Intermediate/Severe</td>
<td>Severe</td>
</tr>
</tbody>
</table>

**Cellulitis/erysipelas**
- Diffuse skin infection characterized by spreading of edema, redness, and heat \(^1,2\)
- May accompany lymphangitis and regional lymph node inflammation \(^2\)
- Erysipelas may be differentiated with raised skin lesions and clear demarcation line of affected and unaffected areas \(^2\)

**Wound infection**
- Purulent drainage with edema, redness, and/or induration of the surrounding wound \(^1\)

**Cutaneous abscess**
- Involves the dermis and deeper skin tissues in the presence of pus collections \(^1,2\)

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1. see note * in the bottom of the slide

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Measurement of Lesions

Measurement for All Lesions
Head-to-toe vs largest perpendicular width

Additional Measurement for Abscesses and Wounds*
(at screening only)
Abscess/wound margin to perimeter of erythema, oedema, and/or induration/cellulitis

*Erythema extending at least 5cm in the shortest distance from the peripheral margin of the abscess or wound

Two Methods to Measure the Lesion Size
Ruler Technique (RT) and Digital Planimetry (DP)

- RT: the longest head-to-toe length and the greatest perpendicular width of a lesion; accurate for rectangular or square lesions
- DP: outline the edge of erythema with a surgical marker, then take photographic images of the lesions with digital camera.

Are these approaches in line with other clinical symptoms?
Are these approaches in line with other clinical symptoms?

Clinic-reported lesion measurements: Definitions, reliability, and association with treatment outcomes.

John H. Powers III MD, Anita F. Das

*George Washington University School of Medicine, Washington, DC, USA
**InClinc, San Mateo, CA, USA
***Merck & Co, Inc., Kenilworth, NJ, USA

Association of patient-reported pain with median ABSSSI lesion area in the Phase 3 trials, illustrating that pain decreases along with a reduction in lesion size, regardless of whether pain is measured by (A) the Visual Analog Scale or (B) Faces Rating Scale.

**ESTABLISH-1 (PO) and -2 (IV/PO)**

**Primary & Secondary Efficacy Endpoints**

### ESTABLISH-1 (PO)

**Primary Endpoint**
- ✔ Cessation of spread and afebrile at 48-72 hours after first dose of drug

**Key Secondary Endpoint**
- ✔ ≥ 20% Reduction in lesion area at 48-72 hours after first dose of drug
- ✔ Programmatic clinical response at EOT
- ✔ Investigator’s assessment of clinical response at PTE

### ESTABLISH-2 (IV/PO)

**Primary Endpoint**
- ✔ ≥ 20% Reduction in lesion area at 48-72 hours after first dose of drug

**Key Secondary Endpoint**
- ✔ Cessation of spread and afebrile at 48-72 hours after first dose of drug
- ✔ Programmatic clinical response at EOT
- ✔ Investigator’s assessment of clinical response at PTE

---

EOT: end of therapy;  
PTE: post-treatment evaluation  
IV: intravenous;  
PO: oral

ESTABLISH-1 (PO) and -2 (IV/PO) Phase 3 Trial Design: combining FDA and EMA endpoints

(double-blind, double-dummy)

**ESTABLISH-1 (112): All oral**
- N=667 ABSSSI patients
- 48–72 hours after initial dose
- 6 days, Oral Tedizolid QD
- 10 days, Oral Linezolid BID
- End of Therapy Day 11
- Post-Therapy Evaluation Day 18–25
- Late Follow-Up Day 29–36
- Post-treatment evaluations

**ESTABLISH-2 (113): IV initiated with option of switching to oral**
- N=666 ABSSSI patients
- 48–72 hours after initial dose
- 6 days IV/Oral Tedizolid QD
- 10 days, IV/Oral Linezolid BID
- End of Therapy Day 11
- Post-Therapy Evaluation Day 18–25
- Late Follow-Up Day 29–36
- Post-treatment evaluations

- Cessation of spread and absence of fever
- ≥20% decrease from baseline in lesion area
- FDA 1° endpoint
- Investigator’s assessment of clinical response
- EMA 1° endpoint
- Sustained clinical success
- EMA 2° endpoint

Tedizolid Launch Symposium, Jeddah, Saudi Arabia

26-11-2016
## Baseline Key Demographics and Infection Types

<table>
<thead>
<tr>
<th>All randomised patients *</th>
<th>ESTABLISH-1 &amp; ESTABLISH-2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Tedizolid 200mg QD for 6 days %, ITT (n=664)</td>
</tr>
<tr>
<td>Age (yrs), mean</td>
<td></td>
</tr>
<tr>
<td>&lt;65 years</td>
<td>44.6</td>
</tr>
<tr>
<td>≥65 years</td>
<td>89.2</td>
</tr>
<tr>
<td></td>
<td>10.8</td>
</tr>
<tr>
<td>Male, %</td>
<td></td>
</tr>
<tr>
<td></td>
<td>64.6</td>
</tr>
<tr>
<td>IV drug use</td>
<td></td>
</tr>
<tr>
<td></td>
<td>27.6</td>
</tr>
<tr>
<td>Diabetes</td>
<td></td>
</tr>
<tr>
<td></td>
<td>8.7</td>
</tr>
<tr>
<td>BMI (Range), kg/m²</td>
<td>14.2–69.9</td>
</tr>
<tr>
<td>Types of infection:</td>
<td></td>
</tr>
<tr>
<td>Cellulitis/erysipelas</td>
<td>45.3</td>
</tr>
<tr>
<td>Major abscess</td>
<td>25.3</td>
</tr>
<tr>
<td>Wound infection</td>
<td>29.4</td>
</tr>
<tr>
<td>Median Lesion Surface Area (cm²)</td>
<td>197.1</td>
</tr>
</tbody>
</table>

* Integrated data

Geographical distribution of patients similar between the two treatment arms from US, Canada, Europe, South Africa and Pacific Rim

Prokocimer et al. JAMA 2013;309(6):559–569
Moran et al. LID 2014;14(8):696–705
# Baseline Pathogen Distribution

<table>
<thead>
<tr>
<th>All randomised patients *</th>
<th>ESTABLISH-1 &amp; ESTABLISH-2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Tedizolid 200mg QD for 6 days</td>
</tr>
<tr>
<td></td>
<td>%, ITT (n=664)</td>
</tr>
<tr>
<td>No pathogen identified</td>
<td>38.9</td>
</tr>
<tr>
<td>Any Gram-positive pathogen</td>
<td>61.1</td>
</tr>
<tr>
<td><em>Staphylococcus aureus</em></td>
<td>49.5</td>
</tr>
<tr>
<td>MRSA</td>
<td>21.2</td>
</tr>
<tr>
<td>MSSA</td>
<td>28.3</td>
</tr>
<tr>
<td><em>Streptococcus pyogenes</em></td>
<td>5.0</td>
</tr>
<tr>
<td><em>S. anginosus-milleri group</em></td>
<td>4.5</td>
</tr>
</tbody>
</table>

* Integrated data

Prokocimer et al. JAMA 2013;309(6):559–569
Moran et al. LID 2014;14(8):696–705

26-11-2016 Tedizolid Launch Symposium, Jeddah, Saudi Arabia
Establish-1 and Establish-2
Integrated Efficacy Data


Can we do it?
ESTABLISH-1 and -2 Integrated Efficacy: All Efficacy Endpoints Achieved

ITT Analysis Set*

Patients with treatment response (%)

<table>
<thead>
<tr>
<th></th>
<th>Tedizolid N=664</th>
<th>Linezolid N=669</th>
</tr>
</thead>
<tbody>
<tr>
<td>48-72 hours</td>
<td>81.6</td>
<td>79.4</td>
</tr>
<tr>
<td>Early Clinical Response (≥20% lesion area Reduction)</td>
<td>2.2 (-2.0; 6.5)</td>
<td></td>
</tr>
<tr>
<td>Day 11</td>
<td>87.0</td>
<td>87.9</td>
</tr>
<tr>
<td>End of therapy (Programmatic clinical response)</td>
<td>-0.8 (-4.4; 2.7)</td>
<td></td>
</tr>
<tr>
<td>Days 7-14 post-EOT</td>
<td>86.7</td>
<td>86.8</td>
</tr>
<tr>
<td>(Investigator assessed response)</td>
<td>-0.1 (-3.8; 3.6)</td>
<td></td>
</tr>
</tbody>
</table>

* Pooled data

ESTABLISH-1 and -2 Integrated Efficacy: Non-inferiority Achieved in Each Infection Type

Early Clinical Response Rate at 48–72 h. ITT Analysis Set*

![Bar chart showing early clinical response rate for different infection types.](image)

- Cellulitis/erysipelas: Tedizolid 75.7%, Linezolid 74.3%
- Major cutaneous abscess: Tedizolid 85.7%, Linezolid 86.7%
- Wound infection: Tedizolid 87.2%, Linezolid 81.1%

* Pooled data

Non-inferiority was Achieved at 48-72 hours in All Subgroups

<table>
<thead>
<tr>
<th>ITT analysis set</th>
<th>Tedizolid, % (n/N)</th>
<th>Linezolid, % (n/N)</th>
<th>Treatment difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;65 years</td>
<td>82.6 (489/592)</td>
<td>79.5 (485/610)</td>
<td>3.1 (-1.3; 7.6)</td>
</tr>
<tr>
<td>≥65 years</td>
<td>73.6 (53/72)</td>
<td>78.0 (46/59)</td>
<td>-4.9 (-19.4; 10.1)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>83.0 (356/429)</td>
<td>80.1 (330/412)</td>
<td>2.8 (-2.4; 8.1)</td>
</tr>
<tr>
<td>Female</td>
<td>79.1 (186/235)</td>
<td>78.2 (201/257)</td>
<td>1.0 (-6.4; 8.2)</td>
</tr>
<tr>
<td>BMI</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;30 kg/m²</td>
<td>83.8 (389/464)</td>
<td>79.4 (347/437)</td>
<td>4.4 (-0.6; 9.5)</td>
</tr>
<tr>
<td>≥30 kg/m²</td>
<td>76.5 (153/200)</td>
<td>79.3 (184/232)</td>
<td>-2.8 (-10.8; 5.0)</td>
</tr>
<tr>
<td>IV drug use</td>
<td>82.5 (151/183)</td>
<td>79.6 (164/206)</td>
<td>2.9 (-5.0; 10.7)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>70.7 (41/58)</td>
<td>82.1 (55/67)</td>
<td>-10.9 (-26.1; 4.0)</td>
</tr>
<tr>
<td>Bacteraemia at baseline</td>
<td>100 (11/11)a</td>
<td>69 (11/16)</td>
<td>ND</td>
</tr>
</tbody>
</table>

Pathogens isolated included: *Staphylococcus aureus* (methicillin-resistant *S. aureus*, 2 patients; methicillin-sensitive *S. aureus*, 4 patients; eradication confirmed for all), *Streptococcus pyogenes* (2 patients), *Streptococcus constellatus* (1 patient), *Staphylococcus hominis* (1 patient), *Streptococcus agalactiae* (1 patient).

BMI = body mass index; CI = confidence interval; ND = not done; ITT = intent to treat; IV = intravenous.

ESTABLISH-1 and -2 Integrated Efficacy
(by relevant host and disease factors (A) and baseline severity measures (B) in the ITT population)

A
- Cellulitis/erysipelas [301/307]
- Wound infections [195/196]
- Major cutaneous abscess [168/166]
- BMI ≥30 kg/m² [200/232]
- Diabetes [58/67]
- IV drug users [183/206]
- ≥65 years [72/59]
- Moderate/severe renal impairment [20/29]

B
- Lesion area
  - >300 cm² [228/220]
  - ≤300 cm² [436/449]
- Fever at baseline
  - Yes [159/160]
  - No [505/509]
- Increased WBC
  - Yes [316/284]
  - No [348/385]
- SIRS
  - Yes [163/128]
  - No [501/541]
- Lymphadenopathy
  - Yes [524/524]
  - No [140/145]
- Bands
  - >10% [76/56]
  - ≤10% [588/613]

Favors DZO  Favors TZD

What about lesion localizations?
What about lesion localizations?

What about lesion localizations?

Conclusions: Post-therapy evaluations showed that the clinical response of lower-extremity ABSSSI to tedizolid and linezolid was comparable to that of ABSSSI in other locations. A short 6-day course of once-daily tedizolid was as effective as a 10-day course of twice-daily linezolid in treating patients with lower-extremity ABSSSI.

MRSA and MSSA eradication rates are equivalent for tedizolid 200 mg 6 days vs linezolid 600 mg 10 days

* Pooled data
ESTABLISH-1 and -2 Integrated Per-pathogen Microbiological Response at PTE

<table>
<thead>
<tr>
<th>MITT Analysis Set</th>
<th>ESTABLISH-1 &amp; ESTABLISH-2</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Tedizolid 200mg QD for 6 days % (n)</td>
<td>Linezolid 600mg BID for 10 days % (n)</td>
<td>95% CI</td>
<td></td>
</tr>
<tr>
<td><strong>Staphylococcus aureus</strong></td>
<td>88.8 (292/329)</td>
<td>88.9 (304/342)</td>
<td>-0.1 (-5.0; 4.7)</td>
<td></td>
</tr>
<tr>
<td><strong>MRSA</strong></td>
<td>84.4 (119/141)</td>
<td>82.2 (120/146)</td>
<td>2.2 (-6.6; 10.9)</td>
<td></td>
</tr>
<tr>
<td><strong>MSSA</strong></td>
<td>92.0 (173/188)</td>
<td>93.9 (186/198)</td>
<td>-1.9 (-7.4; 3.3)</td>
<td></td>
</tr>
<tr>
<td><strong>Streptococcus pyogenes</strong></td>
<td>90.9 (30/33)</td>
<td>95.0 (19/20)</td>
<td>-4.1 (-19.8; 16.1)</td>
<td></td>
</tr>
<tr>
<td><strong>S. anginosus-milleri group</strong></td>
<td>73.3 (22/30)</td>
<td>89.3 (25/28)</td>
<td>-15.7 (-35.4; 5.7)</td>
<td></td>
</tr>
</tbody>
</table>

High potency against Gram + pathogens

Establish-1 and Establish-2 Integrated Safety Data

are we safe with our patients?

### ESTABLISH-1 and -2 Integrated Safety: Overall Adverse Events

<table>
<thead>
<tr>
<th>Treatment-Emergent Adverse Event (TEAE)</th>
<th>Tedizolid % (n=662)</th>
<th>Linezolid % (n=662)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any TEAE</td>
<td>283 (42.7)</td>
<td>286 (43.2)</td>
</tr>
</tbody>
</table>

Most Adverse Events Reported were Mild or Moderate in Severity

Tedizolid N=662
- Mild: 29%
- Moderate: 58%
- Severe: 2%
- None: 11%

Linezolid N=662
- Mild: 29%
- Moderate: 57%
- Severe: 2%
- None: 12%

---

### ESTABLISH-1 and -2 Integrated Safety: Overall Adverse Events

<table>
<thead>
<tr>
<th>Treatment-Emergent Adverse Event (TEAE)</th>
<th>Tedizolid % (n=662)</th>
<th>Linezolid % (n=662)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug-related TEAE</td>
<td>148 (22.4)</td>
<td>185 (27.9)</td>
</tr>
<tr>
<td>TEAE leading to discontinuation of study drug</td>
<td>3 (0.5)</td>
<td>6 (0.9)</td>
</tr>
<tr>
<td>Serious TEAE</td>
<td>12 (1.8)</td>
<td>13 (2.0)</td>
</tr>
<tr>
<td>Drug-related serious TEAE</td>
<td>0 (0.0)</td>
<td>2 (0.3)</td>
</tr>
<tr>
<td>Any TEAE leading to death*</td>
<td>2 (0.3)</td>
<td>1 (0.2)</td>
</tr>
</tbody>
</table>

Overall TEAE rates were similar between tedizolid- and linezolid-treated patients

* Not related to study drug

---

ESTABLISH-1 and -2 Integrated Safety: TEAEs ≥ 1% in "Preferred Terms"

<table>
<thead>
<tr>
<th>System Organ Class &quot;Preferred Term&quot;</th>
<th>Tedizolid % (n=662)</th>
<th>Linezolid % (n=662)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrointestinal disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>106 (16.0)*</td>
<td>152 (23.0)</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>54 (8.2)*</td>
<td>81 (12.2)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>26 (3.9)</td>
<td>35 (5.3)</td>
</tr>
<tr>
<td></td>
<td>19 (2.9)*</td>
<td>37 (5.6)</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td>36 (5.4)</td>
<td>39 (5.9)</td>
</tr>
<tr>
<td>(IV site reactions &lt;2% both groups)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infections and infestations</td>
<td>91 (13.7)</td>
<td>78 (11.8)</td>
</tr>
<tr>
<td>Abscess</td>
<td>35 (5.3)</td>
<td>26 (3.9)</td>
</tr>
<tr>
<td>Cellulitis</td>
<td>17 (2.6)</td>
<td>14 (2.1)</td>
</tr>
</tbody>
</table>

*P<0.05

Lower incidence of gastrointestinal TEAEs in tedizolid- vs linezolid-treated patients

Tedizolid- and linezolid associated GI Adverse Events: time of appearance

Tedizolid was associated with a significantly lower incidence of GI adverse events irrespective of duration of therapy

GI = gastrointestinal.


Tedizolid was associated with a significantly lower incidence of GI adverse events irrespective of duration of therapy
**Tedizolid Use was Associated with Overall Reduced Risk of Myelosuppression**

Patients with reduced platelet counts during the entire study period

**FIG 3** Patients with platelet counts below the lower limit of normal (LLN) (<150,000 cells/mm³) over time. *, P < 0.05. EOT, end-of-therapy.

LLN = lower limit of normal.

Tedizolid was associated with a significantly lower risk of developing thrombocytopenia

Tedizolid is not known to increase the risk of anemia, leukopenia, or pancytopenia

Summary – clinical data * and perspectives

- Non-inferior to linezolid overall and in all infection types
  - with a shorter duration of therapy (6 days vs 10 days)
  - a lower daily dose (200 mg/day vs 1200 mg/day)
  - a simplified schedule of administration (once daily)

- High eradication rates against Gram-positive pathogens

- Well tolerated with no serious AE occurring related to tedizolid

- Significantly lower incidence of gastrointestinal adverse events vs linezolid; irrespective of treatment duration

- Significantly lower risk of developing thrombocytopenia vs linezolid

* as shown in this presentation
Summary – clinical data and perspectives

- Non-inferior to linezolid overall and in all infection types
  - with a shorter duration of therapy (6 days vs 10 days)
  - a lower daily dose (200 mg/day vs 1200 mg/day)
  - a simplified schedule of administration (once daily)
- High eradication rates against Gram-positive pathogens
- Well tolerated with no serious AE occurring related to tedizolid
- Significantly lower incidence of gastrointestinal adverse events vs linezolid; irrespective of treatment duration
- Significantly lower risk of developing thrombocytopenia vs linezolid

* as shown in this presentation

Compare also with the other available antibiotics that we have surveyed …
A recent expert opinion ...

Tedizolid in skin and skin structure infections: brave new world?

Periklis Panagopoulos\textsuperscript{a}, Nikolaos Papanas\textsuperscript{b} and Efstratios Maltezos\textsuperscript{a}

\textsuperscript{a}Unit of Infectious Diseases, Second Department of Internal Medicine, Democritus University of Thrace, Alexandroupolis, Greece; \textsuperscript{b}Diabetic Foot Clinic, Diabetes Centre, Second Department of Internal Medicine, Democritus University of Thrace, Alexandroupolis, Greece

"Tedizolid has demonstrated excellent activity against broad spectrum aerobic and facultative anaerobic gram-positive bacteria.

Other advantages include the availability of both oral and intravenous routes of administration, the short course of therapy, the convenient dosing scheme, and the trend toward less hematological toxicity.

Taken these advantages into consideration, tedizolid appears increasingly preferable to linezolid in ABSSSIs.''

Please, ask questions …

Vesalius - anatomy

be critical, ask for facts!

All slide are available on http://www.facm.ucl.ac.be → Lectures
Back up slides
Microbiology
And even with recent Chinese isolates

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

<table>
<thead>
<tr>
<th>Organisms</th>
<th>N</th>
<th>MIC&lt;sub&gt;50&lt;/sub&gt; (µg/ml)</th>
<th>MIC&lt;sub&gt;90&lt;/sub&gt; (µg/ml)</th>
<th>Range (µg/ml)</th>
<th>MIC&lt;sub&gt;50&lt;/sub&gt; (µg/ml)</th>
<th>MIC&lt;sub&gt;90&lt;/sub&gt; (µg/ml)</th>
<th>Range (µg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>S. aureus</em></td>
<td>581</td>
<td>0.25</td>
<td>0.25</td>
<td>0.064-0.125</td>
<td>2</td>
<td>2</td>
<td>0.5-2</td>
</tr>
<tr>
<td>MRSA</td>
<td>234</td>
<td>0.25</td>
<td>0.25</td>
<td>0.125-0.25</td>
<td>2</td>
<td>2</td>
<td>0.5-2</td>
</tr>
<tr>
<td>MSSA</td>
<td>347</td>
<td>0.25</td>
<td>0.25</td>
<td>0.064-0.25</td>
<td>2</td>
<td>2</td>
<td>0.5-2</td>
</tr>
<tr>
<td>CoNS</td>
<td>279</td>
<td>0.064</td>
<td>0.125</td>
<td>0.016-0.25</td>
<td>1</td>
<td>1</td>
<td>0.25-2</td>
</tr>
<tr>
<td>Enterococci</td>
<td>291</td>
<td>0.25</td>
<td>0.5</td>
<td>0.125-1</td>
<td>2</td>
<td>2</td>
<td>0.5-4</td>
</tr>
<tr>
<td>β-hemolytic</td>
<td>258</td>
<td>0.25</td>
<td>0.25</td>
<td>0.064-0.25</td>
<td>1</td>
<td>1</td>
<td>0.032-1</td>
</tr>
<tr>
<td>Streptococcus</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
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$_{50}$</th>
<th>MIC$_{90}$</th>
<th>%S</th>
<th>%I</th>
<th>%R</th>
</tr>
</thead>
<tbody>
<tr>
<td>All <em>S. aureus</em> (592)</td>
<td>Tedizolid$^a$</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$^b$</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$^a$</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$^a$</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$^b$</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)
Activity of tedizolid against staphylococci from difficult-to-treat infections

Antimicrobial Susceptibility Studies

**In vitro activity of tedizolid against staphylococci isolated from prosthetic joint infections**

Suzannah M. Schmidt-Malan b, Kerry E. Greenwood Quaintance b, Melissa J. Karau b, Robin Patel a,h,*

a Division of Infectious Diseases, Department of Medicine, Mayo Clinic, Rochester, MN 55905, USA
b Division of Clinical Microbiology, Department of Laboratory Medicine and Pathology, Mayo Clinic, Rochester, MN 55905, USA

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 Choi,* Weonbin Im,* and Ken Bartiza

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

**TABLE 1 MICs for tedizolid and linezolid against PRSP**

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

*a 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$_{50}$ was 2 µg/ml, and the MIC$_{90}$ 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.
Pharmacokinetics
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
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: Impact of renal and hepatic dysfunction


FIG 1 Plasma tedizolid concentrations over time in subjects with severe renal impairment and matched controls, shown on a semi-logarithmic scale (B).

FIG 2 Plasma tedizolid concentrations over time in subjects with impaired hepatic function and matched controls, shown on a semilogarithmic scale (B).
Tedizolid: Impact of renal (incl. dialysis and CCRT) and hepatic dysfunction

1. renal dysfunction

TABLE 1 Mean tedizolid pharmacokinetics in the renal-impairment study

<table>
<thead>
<tr>
<th>Study group</th>
<th>$C_{\text{max}}$ ($\mu$g/ml)</th>
<th>$T_{\text{max}}$ (h)</th>
<th>AUC$_{0-\infty}$ ($\mu$g · h/ml)</th>
<th>AUC$_{0-\infty}$ ($\mu$g · h/ml)</th>
<th>$t_{1/2}$ (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control ($n = 8$)</td>
<td>3.11 (0.75)</td>
<td>1.00 (1.00–2.50)</td>
<td>32.02 (9.32)</td>
<td>32.43 (9.53)</td>
<td>12.25 (2.04)</td>
</tr>
<tr>
<td>Severe renal impairment ($n = 8$)</td>
<td>3.12 (0.85)</td>
<td>1.26 (1.00–2.00)</td>
<td>29.69 (8.93)</td>
<td>29.99 (8.97)</td>
<td>12.85 (2.28)</td>
</tr>
<tr>
<td>Predialysis infusion ($n = 7$)</td>
<td>2.53 (0.95)</td>
<td>1.00 (0.50–1.50)</td>
<td>22.97 (8.02)</td>
<td>23.15 (8.10)</td>
<td>11.41 (1.78)</td>
</tr>
<tr>
<td>Postdialysis infusion ($n = 8$)</td>
<td>2.86 (1.01)</td>
<td>1.50 (1.00–1.50)</td>
<td>20.81 (4.65)</td>
<td>21.01 (4.71)</td>
<td>11.73 (2.33)</td>
</tr>
</tbody>
</table>

Additional information: at conventional Continuous Renal Replacement Therapy (CRRT) rates, tedizolid transmembrane clearance appears modest relative to total body clearance and is unlikely to require dose adjustments.

2. hepatic dysfunction

TABLE 2 Mean tedizolid pharmacokinetic parameters of the hepatic-impairment group

<table>
<thead>
<tr>
<th>Study group</th>
<th>$C_{\text{max}}$ ($\mu$g/ml)</th>
<th>$T_{\text{max}}$ (h)</th>
<th>AUC$_{0-\infty}$ ($\mu$g · h/ml)</th>
<th>AUC$_{0-\infty}$ ($\mu$g · h/ml)</th>
<th>$t_{1/2}$ (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moderate impairment ($n = 8$)</td>
<td>2.08 (0.74)</td>
<td>1.75 (0.50–3.00)</td>
<td>29.89 (16.76)</td>
<td>30.47 (17.50)</td>
<td>14.94 (3.49)</td>
</tr>
<tr>
<td>Matched controls ($n = 8$)</td>
<td>1.85 (0.49)</td>
<td>2.00 (1.00–4.00)</td>
<td>22.80 (5.63)</td>
<td>23.00 (5.70)</td>
<td>13.42 (3.93)</td>
</tr>
<tr>
<td>Severe impairment ($n = 8$)</td>
<td>2.20 (1.07)</td>
<td>2.00 (0.50–3.00)</td>
<td>34.80 (20.72)</td>
<td>35.23 (21.13)</td>
<td>14.19 (2.92)</td>
</tr>
<tr>
<td>Matched controls ($n = 8$)</td>
<td>2.12 (0.80)</td>
<td>3.00 (1.00–8.00)</td>
<td>24.37 (8.03)</td>
<td>24.56 (8.05)</td>
<td>13.68 (3.71)</td>
</tr>
</tbody>
</table>

Additional information: at conventional Continuous Renal Replacement Therapy (CRRT) rates, tedizolid transmembrane clearance appears modest relative to total body clearance and is unlikely to require dose adjustments.
### Similar pharmacokinetics in adolescents vs. adults

<table>
<thead>
<tr>
<th>Route</th>
<th>PK parameter</th>
<th>Geometric mean</th>
<th>Geometric mean ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>adolescents</td>
<td>adults *</td>
</tr>
<tr>
<td>IV</td>
<td>$C_{max}$ (mg/L)</td>
<td>3.66 (10)</td>
<td>2.55 (34)</td>
</tr>
<tr>
<td></td>
<td>$AUC_{0-\infty}$ (µg x h/mL)</td>
<td>26.95 (10)</td>
<td>29.11 (33)</td>
</tr>
<tr>
<td>oral</td>
<td>$C_{max}$ (mg/L)</td>
<td>2.17 (10)</td>
<td>2.23 (37)</td>
</tr>
<tr>
<td></td>
<td>$AUC_{0-\infty}$ (µg x h/mL)</td>
<td>23.94 (10)</td>
<td>28.3 (32)</td>
</tr>
</tbody>
</table>

* Historical data for adult PK parameters after IV dosing were pooled from studies TR701-107 \(^1\) and TR701-123 \(^2\). Oral dosing data for adults were obtained from study TR701-115 \(^3\).

\(^1\) Flanagan \textit{et al.} Pharmacotherapy 2014;34:891-900. PMID: 24989138

Tedizolid and cidal activity *in vivo*
Tedizolid is cidal \textit{in vivo} …

Louie et al. AAC 2011; 55:3453-3460
Impact of Granulocytes on the Antimicrobial Effect of Tedizolid in a Mouse Thigh Infection Model

G. L. Drusano,* Weiguo Liu, Robert Kulawy, and Arnold Louie

Emerging Infections and Pharmacodynamics Laboratory, Ordway Research Institute, Albany, New York 12208

Received 13 April 2011/Returned for modification 4 June 2011/Accepted 16 July 2011

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 Staphylococcus aureus, and the effect of the drug on 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. AAC 2011; 55-5300-5305
Tedizolid and granulocytes cooperate in vivo upon each administration

The graph shows the concentration of TR701/700 over time (hours) with granulocytes. The graph indicates that killing progresses over time at each administration of tedizolid. The AUC$_{24h} = 20.1$ (equivalent to humans for a dose of 200 mg) and the MIC = 0.5 mg/L.

Drusano et al. AAC 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

Louie et al. Antimicrob Agents Chemother. 2011;55::3453-60 (tedizolid) and data on file (daptomycin)
Pharmacodynamics and PK/PD breakpoint
How to determine which PK parameter is critical?

- If you fractionate the daily dose, you change $C_{\text{max}}$ without changing $AUC_{24h}$.
How to determine which PK parameter is critical?

- If you increase the dose without change of schedule, you increase BOTH $C_{\text{max}}$ and $\text{AUC}_{24\text{h}}$

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

$\text{AUC}_{24\text{h}}$ is proportional to the dose

Concentration

Time (h)
How do you do this with tedizolid?

<table>
<thead>
<tr>
<th>Total dosage (mg/kg/24 h)</th>
<th>Regimen&lt;sup&gt;a&lt;/sup&gt;</th>
<th>fC&lt;sub&gt;max&lt;/sub&gt;/MIC ratio&lt;sup&gt;b&lt;/sup&gt;</th>
<th>fAUC/MIC ratio&lt;sup&gt;c&lt;/sup&gt;</th>
<th>fT&gt;MIC (%)&lt;sup&gt;d&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>10 mg/kg q24h</td>
<td>2.62</td>
<td>13.19</td>
<td>21</td>
</tr>
<tr>
<td></td>
<td>5 mg/kg q12h</td>
<td>1.29</td>
<td>12.82</td>
<td>20</td>
</tr>
<tr>
<td></td>
<td>2.5 mg/kg q6h</td>
<td>0.64</td>
<td>12.26</td>
<td>0</td>
</tr>
<tr>
<td>20</td>
<td>20 mg/kg q24h</td>
<td>5.16</td>
<td>26.03</td>
<td>31</td>
</tr>
<tr>
<td></td>
<td>10 mg/kg q12h</td>
<td>2.62</td>
<td>25.63</td>
<td>43</td>
</tr>
<tr>
<td></td>
<td>5 mg/kg q6h</td>
<td>1.29</td>
<td>24.51</td>
<td>50</td>
</tr>
<tr>
<td>36</td>
<td>36 mg/kg q24h</td>
<td>9.29</td>
<td>46.88</td>
<td>39</td>
</tr>
<tr>
<td></td>
<td>18 mg/kg q12h</td>
<td>4.65</td>
<td>46.14</td>
<td>60</td>
</tr>
<tr>
<td></td>
<td>9 mg/kg q6h</td>
<td>2.32</td>
<td>44.12</td>
<td>87</td>
</tr>
<tr>
<td>72</td>
<td>72 mg/kg q24h</td>
<td>18.59</td>
<td>93.76</td>
<td>49</td>
</tr>
<tr>
<td></td>
<td>36 mg/kg q12h</td>
<td>9.29</td>
<td>92.28</td>
<td>79</td>
</tr>
<tr>
<td></td>
<td>18 mg/kg q6h</td>
<td>4.65</td>
<td>88.24</td>
<td>100</td>
</tr>
</tbody>
</table>

<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<sub>max</sub>/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> fAUC/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>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 $f_{T > \text{MIC}}$ is worse!

Louie et al. AAC 2011; 55:3453-3460
Safety
# Tyramine Sensitivity in humans

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

TSF = Tyramine Sensitivity Factor = (Tyr<sub>30</sub> following Placebo or pretreatment)/(Tyr<sub>30</sub> following TDZ or LZD).

Note: 2-fold increase in TSF is threshold for clinically meaningful change in response to tyramine.  
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>Linezolid³</th>
<th>Tedizolid⁴</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean Maximum SBP Change</td>
<td>Max SBP Value</td>
<td>Mean Maximum SBP Change</td>
</tr>
<tr>
<td>Pseudoephedrine alone/+ placebo</td>
<td>18 (9)</td>
<td>133 (17)</td>
<td>12 (6)</td>
</tr>
<tr>
<td>Pseudoephedrine + drug</td>
<td>32 (10)</td>
<td>151 (15)</td>
<td>11 (5)</td>
</tr>
<tr>
<td>Difference</td>
<td>14</td>
<td>18</td>
<td>-1</td>
</tr>
</tbody>
</table>

4. Study TR701-114
Other antibiotics (competitors)
What are the problems with available anti-Gram-positive antibiotics?

1. The emergence of MRSA…

→ what is the situation in your country?
What are the problems with available anti-Gram-positive antibiotics?

1. The emergence of MRSA…
   → **what is the situation in your country?**

2. Vancomycin is an old and "difficult" drug
   - IV only, at least twice daily, and 10 days or more…
   - monitoring is essential to avoid toxicity…
   - **beware of MICs > 2 mg/L** risk of failures!
What are the problems with available anti-Gram-positive antibiotics?

1. The emergence of MRSA…
   → what is the situation in your country?

2. Vancomycin is an old and "difficult" drug
   – IV only, at least twice daily, and 10 days or more…
   – monitoring is essential to avoid toxicity…
   – beware of MICs > 2 mg/L risk of failures!

3. Linezolid is fraught with toxicities
   – drug interactions (MAO inhibition)
   – myelosuppression, lactic acidosis…
   more frequent than originally reported!
Clinical development
What do you wish to see for tedizolid **clinically**?

- What is the human safety profile?
  - Phase I studies (ascending doses)

- What is the useful dose?
  - PK/PD (infected animal)
  - Phase II studies (patients)

- What are the efficacy and safety profiles against "standard of care" in a large meaningful population?
  - Phase III studies
A short overview of phase I studies: impact of ascending doses (global)

INCIDENCE OF ADVERSE EVENTS

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Overall Placebo (N = 10)</th>
<th>TR-701 200 mg (N = 6)</th>
<th>TR-701 400 mg (N = 6)</th>
<th>TR-701 600 mg (N = 6)</th>
<th>TR-701 800 mg (N = 6)</th>
<th>TR-701 1200 mg (N = 6)</th>
<th>TR-701 Overall (N = 30)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any Adverse Event (AE)</td>
<td>-</td>
<td>10 (n=4)</td>
<td>4 (n=2)</td>
<td>7 (n=3)</td>
<td>2 (n=1)</td>
<td>5 (n=3)</td>
<td>28 (n=13)</td>
</tr>
<tr>
<td>Mild</td>
<td>-</td>
<td>10 (n=4)</td>
<td>4 (n=2)</td>
<td>7 (n=3)</td>
<td>2 (n=1)</td>
<td>5 (n=3)</td>
<td>28 (n=13)</td>
</tr>
<tr>
<td>Moderate</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Severe</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Related AE</td>
<td>-</td>
<td>7 (n=3)</td>
<td>-</td>
<td>6 (n=3)</td>
<td>2 (n=1)</td>
<td>4 (n=3)</td>
<td>19 (n=10)</td>
</tr>
<tr>
<td>AE leading to Study Discontinuation</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Serious AE</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

no dose effect up to 1200 mg/day

presently proposed dosage

Prokocimer et al. ICAAC 2011 P1090
A short overview of phase I studies: impact of ascending doses (details)

ADVERSE EVENTS REPORTED BY AT LEAST 2 SUBJECTS IN TR-701 OVERALL

<table>
<thead>
<tr>
<th>System Organ Class Preferred Term</th>
<th>Overall Placebo (N = 10)</th>
<th>TR-701 200 mg (N = 6)</th>
<th>TR-701 400 mg (N = 6)</th>
<th>TR-701 600 mg (N = 6)</th>
<th>TR-701 800 mg (N = 6)</th>
<th>TR-701 1200 mg (N = 6)</th>
<th>TR-701 Overall (N = 30)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All System Organ Classes</td>
<td>-</td>
<td>4 (66.7%)</td>
<td>2 (33.3%)</td>
<td>3 (50.0%)</td>
<td>1 (16.7%)</td>
<td>3 (50.0%)</td>
<td>13 (43.3%)</td>
</tr>
<tr>
<td>Gastrointestinal Disorders</td>
<td>-</td>
<td>1 (16.7%)</td>
<td>1 (16.7%)</td>
<td>2 (33.3%)</td>
<td>-</td>
<td>3 (50.0%)</td>
<td>7 (23.3%)</td>
</tr>
<tr>
<td>Nausea</td>
<td>-</td>
<td>1 (16.7%)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>1 (16.7%)</td>
<td>3 (10.0%)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>-</td>
<td>-</td>
<td>1 (16.7%)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>2 (6.7%)</td>
</tr>
<tr>
<td>Nervous System Disorders</td>
<td>-</td>
<td>2 (33.3%)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>3 (10.0%)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>-</td>
<td>1 (16.7%)</td>
<td>1 (16.7%)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>2 (6.7%)</td>
</tr>
<tr>
<td>Respiratory, Thoracic and Mediastinal Disorders</td>
<td>-</td>
<td>1 (16.7%)</td>
<td>1 (16.7%)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>2 (6.7%)</td>
</tr>
<tr>
<td>Nasal Congestion</td>
<td>-</td>
<td>1 (16.7%)</td>
<td>1 (16.7%)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>2 (6.7%)</td>
</tr>
<tr>
<td>General Disorders</td>
<td>-</td>
<td>1 (16.7%)</td>
<td>-</td>
<td>1 (16.7%)</td>
<td>-</td>
<td>-</td>
<td>2 (6.7%)</td>
</tr>
</tbody>
</table>

- There were no deaths, Serious AEs, or discontinuations due to AEs.
- No clinically significant changes or findings were noted in clinical laboratory evaluations, vital sign measurements, 12-lead ECGs, and physical examinations.
- There was no dose-response relationship to the number of AEs and, overall, changes in safety evaluations were unremarkable.
Phase I: specific investigations: platelets (increasing doses)
What do you wish to see for tedizolid clinically?

- What is the human safety profile?
  - Phase I studies (ascending doses)

- What is the useful dose?
  - PK/PD (infected animal)
  - Phase II studies (patients)

- What are the efficacy and safety profiles against "standard of care" in a large meaningful population?
  - Phase III studies
Preclinical studies: definition of the "sufficient dose" in infected animals

Tedizolid maximal effect is obtained at the equivalent of 200 mg (human dose)

Drusano et al. AAC 2011; 55-5300-5305
Phase 2, Randomized, Double-Blind, Dose-Ranging Study Evaluating the Safety, Tolerability, Population Pharmacokinetics, and Efficacy of Oral Torezolid Phosphate in Patients with Complicated Skin and Skin Structure Infections

P. Prokocimer,1* P. Bien,1 J. Surber,2 P. Mehra,3 C. DeAnda,1 J. B. Bulitta,4 and G. R. Corey5

Trius Therapeutics, Inc., 6310 Nancy Ridge Road, Suite 105, San Diego, California 921211; SERRG, Inc., 5210 Armour Road Suite 400, Columbus, Georgia 319042; eStudy Site, 752 Medical Center Court, Suite 105, Chula Vista, California 919153; Ordway Research Institute, 150 New Scotland Avenue, Albany, New York 122084; and Duke Clinical Research Institute, 2400 Pratt Street, Durham, North Carolina 277055
Tedizolid phase II study

Phase 2, Randomized, Double-blind Study of the Safety, Tolerability, Pharmacokinetics, and Efficacy of Oral Tedizolid Phosphate (200 mg, 300 mg, 400 mg) for the Treatment of Acute Skin and Skin Structure Infections

P. Prokocimer,1* P. Bien,1 J. Surber,2 P. Lu,3 D. M. Samore,4 R. B. Snydman1

Trius Therapeutics, Inc., 6310 Nancy Ridge Drive, Suite 200, San Diego, CA 92121; 5210 Armour Road, Suite 400, Columbus, OH 43235; Chula Vista, California 91913; Ordway Research Institute, and Duke Clinical Research Institute

Intent to Treat (ITT)
All randomized patients
N=192

Modified Intent to Treat (MITT)
Patients receiving at least one dose of study drug
(200 mg N=1, 300 mg N=1, 400 mg N=2)
N=188

Clinical MITT (cMITT)
Patients with a diagnosis of cSSSI
(Includes 10 patients who discontinued study drug:
200 mg N=4, 300 mg N=3, 400 mg N=3)
N=188

Microbiological MITT (mMITT)
Patients with at least 1 Gram-positive bacterial cSSSI pathogen at baseline
N=154

Clinically Evaluable (CE)
Patients receiving minimal study therapy, have a TOC assessment, no confounding events or factors
N=164 (at TOC)

Microbiologically Evaluable (ME)
Patients in both the mMITT and CE populations
N=133 (at TOC)

FIG. 1. Populations analyzed.
# Tedizolid phase II study

## TABLE 3. Clinical cure rates with torezolid phosphate at TOC in the CE population, by lesion type and size

<table>
<thead>
<tr>
<th>Lesion type or size</th>
<th>Cure rate by torezolid phosphate dose (no. of patients cured/total no. of patients in group [%])</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>200 mg</td>
</tr>
<tr>
<td>Abscess</td>
<td>43/43 (100)</td>
</tr>
<tr>
<td>Wound</td>
<td>1/1 (100)</td>
</tr>
<tr>
<td>Cellulitis</td>
<td>11/12 (91.7)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Lesion size</th>
<th>5 &lt; 10 cm</th>
<th>10 &lt; 20 cm</th>
<th>≥20 cm</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>21/21 (100)</td>
<td>14/15 (93.3)</td>
<td>15/17 (88.2)</td>
</tr>
<tr>
<td></td>
<td>21/21 (100)</td>
<td>26/28 (92.9)</td>
<td>28/28 (100)</td>
</tr>
<tr>
<td></td>
<td>13/14 (92.9)</td>
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<td>8/9 (88.9)</td>
</tr>
</tbody>
</table>
Tedizolid phase II study

**TABLE 3.** Clinical cure rates with torezolid phosphate at TOC in the CE population, by lesion type and size

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</tr>
<tr>
<td>Wound</td>
<td>1/1 (100)</td>
</tr>
<tr>
<td>Cellulitis</td>
<td>11/12 (91.7)</td>
</tr>
<tr>
<td></td>
<td>300 mg</td>
</tr>
<tr>
<td>Abscess</td>
<td>36/38 (94.7)</td>
</tr>
<tr>
<td>Wound</td>
<td>3/4 (75)</td>
</tr>
<tr>
<td>Cellulitis</td>
<td>12/12 (100)</td>
</tr>
<tr>
<td></td>
<td>400 mg</td>
</tr>
<tr>
<td>Abscess</td>
<td>39/42 (92.9)</td>
</tr>
<tr>
<td>Wound</td>
<td>5/5 (100)</td>
</tr>
<tr>
<td>Cellulitis</td>
<td>7/7 (100)</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Lesion size</td>
<td></td>
</tr>
<tr>
<td>5 &lt; 10 cm</td>
<td>21/21 (100)</td>
</tr>
<tr>
<td>10 &lt; 20 cm</td>
<td>21/21 (100)</td>
</tr>
<tr>
<td>≥20 cm</td>
<td>13/14 (92.9)</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
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<tr>
<td></td>
<td>26/28 (92.9)</td>
</tr>
<tr>
<td></td>
<td>11/11 (100)</td>
</tr>
<tr>
<td></td>
<td>15/17 (88.2)</td>
</tr>
<tr>
<td></td>
<td>28/28 (100)</td>
</tr>
<tr>
<td></td>
<td>8/9 (88.9)</td>
</tr>
</tbody>
</table>

**this IS the effective dose!**
Tedizolid phase III studies: why two non-inferiority trials?

1. For most indications, both FDA and EMA usually require **two independent studies** demonstrating efficacy and safety

- **It is preferred that two major (pivotal) studies of efficacy are performed for each clinical indication sought**… (EMA)

- **… Two adequate and well-controlled trials generally are recommended to provide evidence of effectiveness** … (FDA)

---

- General Considerations for Clinical Trials (EMEA - March 1998 -- CPMP/ICH/291/95)

- Evaluation of medicinal products indicated for treatment of bacterial infections - Adopted guideline (EMA - 2011 -- CPMP/EWP/558/95 rev 2)

- Guidance for Industry: Acute Bacterial Skin and Skin Structure Infections: Developing Drugs for Treatment (FDA - CDER -- October 2013)
Tedizolid phase III studies: why two non-inferiority trials?

2. Appropriate comparators should be utilized and adequate numbers of subjects included to achieve the study objectives

- Comparisons may be made with placebo, no treatment, active controls or of different doses of the drug under investigation
- The choice of the comparator depends, among other things, on the objective of the trial

- The regimen selected [for comparison] should be considered one of the best available treatments based on one or more of previous studies, medical opinion, indication specific treatment guidelines… and anticipated prevalence of resistance to the comparative agent at the investigative sites … (EMA)

- For ABSSSI, there were no placebo-controlled trials reported in the historical literature… (FDA)

---

Do we need antibiotics for ABSSSIs?
Some say that antibiotics are not needed for "minor skin infections"...

Skin Abscess

This interactive feature addresses the approach to a clinical issue. A case vignette is followed by specific options, neither of which can be considered correct or incorrect. In short essays, experts in the field then argue for each of the options. Readers can participate in forming community opinion by choosing one of the options and, if they like, providing their reasons.

CASE VIGNETTE

A Woman with an Abscess
MaryAnn B. Wilbur, M.D., M.P.H.

- one area of fluctuance (2 cm diameter, with tenderness, on the left anterior thigh…
- Erythema up to 2 cm beyond the edges of the fluctuance.
- No spontaneous drainage and no associated lymphadenopathy.

TREATMENT OPTION 1
Incision and Drainage Alone
Robert S. Daum, M.D

TREATMENT OPTION 2
Incision and Drainage Followed by Trimethoprim–Sulfamethoxazole Therapy
Howard S. Gold, M.D.
Evidence-based medicine…

**The New England Journal of Medicine**

**Original Article**

Trimethoprim–Sulfamethoxazole versus Placebo for Uncomplicated Skin Abscess

David A. Talan, M.D., William R. Mower, M.D., Ph.D.,
Anusha Krishnadasan, Ph.D., Fredrick M. Abrahamian, D.O.,
Frank Lovecchio, D.O., M.P.H., David J. Karras, M.D., Mark H.
Richard E. Rothman, M.D., Ph.D., Rebecca Hoagland, M.D.,
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**Background**

U.S. emergency department visits for cutaneous abscess have increased with the emergence of methicillin-resistant *Staphylococcus aureus* (MRSA). The role of antibiotics for patients with a drained abscess is unclear.

**Conclusions**

In settings in which MRSA was prevalent, trimethoprim–sulfamethoxazole treatment resulted in a higher cure rate among patients with a drained cutaneous abscess than placebo. (Funded by the National Institute of Allergy and Infectious Diseases; ClinicalTrials.gov number, NCT00729937.)

we do need antibiotics…