NEW ANTI-INFECTIVE AGENTS IN 2003: SPECTRUM AND INDICATIONS

20th Symposium (spring 2003)

Thursday May 22nd 2003

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Streptogramins and linezolid

Prof. Dr. Dirk Vogelaers
Dpt. of Infectious diseases
linezolid - Chemistry

• First oxazolidinone antibiotic
  (S-enantiomer of N-[[3-[3-fluoro-4-(4-morpholinyl)-phenyl]-2-oxo-5-oxazolidinyl]methyl]-acetamide)

• New class (first in > 35 years)
• Fully synthetic, i.e. not derived from any natural substance, and therefore no natural resistance
linezolid – Microbiology

Initiation factors

30S + mRNA

30S Ribosome

mRNA

50S Ribosome

70S Initiation complex

Elongation cycle

Aminoglycosides, macrolides, streptogramins, tetracyclines, chloramphenicol

Elongation factors

Fusidic acid

Linezolid blocks formation of the initiation complex

Peptide product

11-1-2004
linezolid - Microbiology

- Specific anti-Gram-positive spectrum, similar to spectrum of glycopeptides,
  - all most common aerobes, i.e.
    - all *staphylococci*, incl. *Staphylococcus aureus* and all coagulase-negative staphylococci
    - all *enterococci*, incl. *Enterococcus faecalis*, *E. faecium*, and all other enterococci
    - all *streptococci*, incl. *Streptococcus pneumoniae*, *S. pyogenes*, the Viridans and all other streptococci
Activity not affected by resistance to other classes of antibiotics, hence equipotent against:
- methicillin-susceptible and -resistant staphylo-cocci (MRSA, MRSE)
- ampicillin-susceptible and -resistant enterococci (ARE) (both E. faecalis and E. faecium)
- glycopeptide-susceptible and -resistant staphylo-cocci (GISA, GRSA, GISE, GRSE)
- glycopeptide-susceptible and -resistant entero-cocci (GRE)
- penicillin-susceptible and -resistant streptococci
- erythromycin-susceptible and -resistant strepto-cocci
**linezolid - Microbiology**

- Low risk for rapid development of resistance, certainly in staphylococci:
  - extremely low spontaneous mutation frequency (10^{-11} to 10^{-9}; most infections unlikely to contain 1 mutant)
  - multiple target (= **23S rRNA**) gene copies (six in staphylococci; simultaneous mutations in multiple gene copies required for mutant to become resistant)
Different linezolid breakpoints

- **EUCAST**
  - $S \leq 4 \text{ mg/L}$
  - $R > 4 \text{ mg/L}$

- **NCCLS**
  - $S \leq 4 ; \ R \geq 8$ (staphylococci)
  - $S \leq 2 ; I = 4 ; \ R \geq 8$ (streptococci and enterococci)

*Clin Microbiol Infect* 2001; 7: 283-284
# Linezolid: In vitro activity (Belgium)

<table>
<thead>
<tr>
<th>Organism</th>
<th>MIC&lt;sub&gt;90&lt;/sub&gt; (mg/L)</th>
<th>range</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>S. aureus</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>oxa-S</td>
<td>2</td>
<td>0.25-4</td>
</tr>
<tr>
<td>MRSA</td>
<td>2</td>
<td>0.25-4</td>
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<tr>
<td>Coag.-neg staphylococcus</td>
<td></td>
<td></td>
</tr>
<tr>
<td>oxa-S</td>
<td>2</td>
<td>0.25-2</td>
</tr>
<tr>
<td>oxa-R</td>
<td>2</td>
<td>0.12-2</td>
</tr>
<tr>
<td><strong>Enterococcus faecium</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>low genta R</td>
<td>2</td>
<td>1-4</td>
</tr>
<tr>
<td>high genta R</td>
<td>2</td>
<td>1-2</td>
</tr>
<tr>
<td><strong>Enterococcus faecium</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>0.25-2</td>
</tr>
</tbody>
</table>
Linezolid: PK-PD characteristics

- 100 % bio availability $\rightarrow$ ± identical concentration-time curves after IV and oral dosing
- linezolid 600 mg IV/per os (bid)
  - $C_{\text{max}}$ 15.1 – 21.2 mg/L
  - $C_{\text{min}}$ 3.7 – 6.2 mg/L
  - AUC 138 mg/L.h
  - $t\frac{1}{2}$ 4.8 – 7.3 h
  - renal elimination 30 %
- PD parameters of activity: time above MIC (50 %) and AUC/MIC (50-100) (achieved with safety margin with serum conc curves reported; however subtherapeutic concentrations with “classic” dosing schedule resulting in therapeutic failure reported)

*Drugs* 2001; 61: 525-551.
*Antimicrobiol Ag Chemother* 2002; 46: 3484-3489.
Linezolid: clinical trials

• **Complicated SSTI**: linezolid 600 mg IV → po bid vs IV oxacillin and oral dicloxacillin:
  - 69.8% vs 64.9% ITT
  - 88.6% vs 85.8% clin. evaluable
  - 88.1% vs 86.1% microb. evaluable  *(AAC 2000;44:3408-13)*

• **Nosocomial pneumonia**: linezolid vs vancomycin (both + aztreonam)
  - 53.4% vs 52.1% ITT
  - 66.4% vs 68.1% clin. evaluable
  - 69.8% vs 68.4% microb. evaluable  *(CID 2001; 32:402-12)*

• **MRSA**: linezolid (IV → po) vs vancomycin
  - 73.2% vs 73.1% clin. evaluable
  - 58.9% vs 63.2% microb. evaluable  *(CID 2002; 34:1481-90)*
Linezolid: case reports or small series

• Hip prosthesis infection due to MRSA or VREF
  \((\text{CID 2002;}34:1412-14 \& \text{J Infect 2001;}43:148-57)\)

• CNS epidural catheter infection.
  \((\text{CID 2000;}30:146-51)\)

• Endovascular infections due to VREF
  \((\text{CID 2000;}30:146-51, \text{CID 2001;}32:1373-5, \text{CID 2000;}30:403-4)\)

• MRSA infections with treatment failure or intolerance for vanco
  \((\text{ICAAC Toronto 2000 abstract 2233})\)
Linezolid: handicaps

• Myelotoxicity:
  – in comparative trials low: 2.4 % in linezolid vs 1.5 % for comparator arm.
  – Higher incidence in non-comparative reports: 20-30 % of pts.

• Emergence of resistance.
  – not in a problem in infections, manageable by short term antibiotic treatment
  – mainly with protracted treatment in pts with non-removable infected prostheses/ poor underlying condition
Linezolid resistance

- E. faecalis and E. faecium in ICU: 23S rRNA mutation with probable class effect
  
  (Auckland. JAC 2002; 50:743) (MIC 64 mg/l)
  (Boo. J Hosp Infect 2003;53:312) (MIC E-test 32 mg/l)

- Nosocomial spread of linezolid resistant vancomycin-resistant E. faecium
  
  (Herrero. NEJM 2002;346)
Linezolid resistance in clinical isolates of *Staphylococcus aureus*

### Table 1. Susceptibilities of MRSA isolates

<table>
<thead>
<tr>
<th>Isolate number</th>
<th>Number of days post-empyema drainage</th>
<th>Site of isolate</th>
<th>BSAC linezolid disc zone diameter (mm)</th>
<th>Etest MIC of linezolid (mg/L)</th>
<th>NCCLS MIC of linezolid (mg/L)</th>
<th>NCCLS MIC of erythromycin (mg/L)</th>
<th>NCCLS MIC of vancomycin (mg/L)</th>
<th>NCCLS MIC of teicoplanin (mg/L)</th>
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<tbody>
<tr>
<td>1</td>
<td>17</td>
<td>axilla</td>
<td>28</td>
<td>1.0</td>
<td>2.0</td>
<td>&gt;64.0</td>
<td>1.0</td>
<td>0.5</td>
</tr>
<tr>
<td>2</td>
<td>20</td>
<td>sputum</td>
<td>&gt;18</td>
<td>1.0</td>
<td>2.0</td>
<td>&gt;64.0</td>
<td>1.0</td>
<td>0.25</td>
</tr>
<tr>
<td>3</td>
<td>20</td>
<td>empyema fluid</td>
<td>&gt;18</td>
<td>2.0</td>
<td>2.0</td>
<td>&gt;64.0</td>
<td>1.0</td>
<td>0.25</td>
</tr>
<tr>
<td>4</td>
<td>20</td>
<td>drain site swab</td>
<td>&gt;18</td>
<td>1.0</td>
<td>2.0</td>
<td>&gt;64.0</td>
<td>1.0</td>
<td>0.25</td>
</tr>
<tr>
<td>5</td>
<td>23</td>
<td>sputum</td>
<td>&gt;18</td>
<td>1.0</td>
<td>2.0</td>
<td>&gt;64.0</td>
<td>0.5</td>
<td>0.25</td>
</tr>
<tr>
<td>6</td>
<td>24</td>
<td>sputum</td>
<td>&gt;18</td>
<td>1.0</td>
<td>2.0</td>
<td>&gt;64.0</td>
<td>1.0</td>
<td>0.25</td>
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<tr>
<td>7</td>
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<td>empyema fluid</td>
<td>&gt;18</td>
<td>1.0</td>
<td>2.0</td>
<td>&gt;64.0</td>
<td>1.0</td>
<td>0.25</td>
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<tr>
<td>8</td>
<td>40</td>
<td>drain site swab</td>
<td>&gt;18</td>
<td>2.0</td>
<td>2.0</td>
<td>&gt;64.0</td>
<td>1.0</td>
<td>0.25</td>
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<tr>
<td>9</td>
<td>48</td>
<td>drain site swab</td>
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<td>2.0</td>
<td>&gt;64.0</td>
<td>1.0</td>
<td>0.25</td>
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<tr>
<td>10</td>
<td>63</td>
<td>drain site swab</td>
<td>30</td>
<td>2.0</td>
<td>2.0</td>
<td>&gt;64.0</td>
<td>1.0</td>
<td>0.25</td>
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<td>14</td>
<td>32.0</td>
<td>32.0</td>
<td>0.5</td>
<td>0.5</td>
<td>0.25</td>
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<tr>
<td>11</td>
<td>71</td>
<td>empyema fluid</td>
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<td>2.0</td>
<td>&gt;64.0</td>
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<td></td>
<td>12</td>
<td>32.0</td>
<td>16.0</td>
<td>0.5</td>
<td>1.0</td>
<td>0.25</td>
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</tbody>
</table>
Linezolid resistance in S. aureus

- Report of 2 cases of MRSA endocarditis failing to respond to IV linezolid, but successfully treated with TMP/SMX + genta and vanco + rifa resp.
  
  *(Ruiz. CID 2002; 35:1018)*

- Persistent MRSA bacteremia in pt. with low linezolid levels

  *(Sperber. CID 2002;36)*
Table 1. Linezolid blood levels achieved at various dosages in a patient treated with linezolid every 12 hours.

<table>
<thead>
<tr>
<th>Level</th>
<th>600 mg po</th>
<th>600 mg iv</th>
<th>900 mg iv</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peak(^a)</td>
<td>1.73 (21.20 ± 5.78)</td>
<td>3.15 (15.10 ± 2.52)</td>
<td>9.14</td>
</tr>
<tr>
<td>Trough(^b)</td>
<td>0.10 (6.15 ± 2.94)</td>
<td>Trace (3.68 ± 2.36)</td>
<td>1.8</td>
</tr>
</tbody>
</table>

**NOTE.** High-pressure liquid chromatography assay was performed at the National Jewish Medical and Research Center, Denver, Colorado.

\(^a\) Sample was obtained immediately after completion of administration of intravenous dose and 2 h after administration of oral dose.

\(^b\) Sample was obtained just prior to administration of dose.
Hematologic Effects of Linezolid: Summary of Clinical Experience

FIG. 1. Patients with at least one substantially low PLTC, hemoglobin value, or neutrophil count in linezolid and comparator groups—cumulative percentage over time.

ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Aug. 2002, p. 2723
Mechanisms for linezolid-induced anemia and thrombocytopenia

LINEZOLID - BELGIUM

Reimbursement limited to:

a) Hospitalized pts with

- severe infections with MRSA, MRSE, VRE, ampicillin-resistant enterococci
- severe side effects due to glycopeptides in GP-sensitive Gram positive infection
- documented resistance or reduced susceptibility to GP + sensitivity to linezolid

b) Ambulatory pts: oral sequential therapy following in hospital treatment with either IV linezolid or glycopeptide

- Motivated application + renewal per 20 days of treatment.
Streptogramins

Quinupristin

Dalbopristin
Quinupristin/dalfopristin (Q/D)

- 30:70 mixture of quinupristin (Q) + dalfopristin (D), semisynthetic derivatives of streptogramin groups B and A resp.
- Individual components primarily bacteriostatic.
- Combination often bactericidal, more potent + potentially active even if resistance to 1 component (Synercid)
- Synergy through conformational change in the bacterial ribosome after D binding

(Cocito. JAC 1997; 39 (suppl A: 7-13)
Quinupristin/dalfopristin.

- NCCLS criteria for susceptibility:
  
  | S | < 1 µg/ml |
  | I | 2         |
  | R | > 4 µg/ml |

- ± all S aureus strains (both MRSA and MSSA) and CNS strains susceptible

- Resistance rare (35/3052 S aureus isolates in Europe in 1997-98 surveillance (SENTRY))
  
  (Schmitz et al. Diagn Microb Infec Dis 2002; 43:783-92)

- Potential of clonal spread of resistant strains
  
  (Schmitz et al. JAC 1999;44:847)
Quinupristin/dalfopristin

- Q/D almost always inactive against *E. faecalis* (intrinsic efflux pump to dalfopristin)
  
  *(Singh. AAC 2002;46:1845-50)*

- 94 % of vancomycin-R *E. faecium* (1st isolates) Q/D-S

  *(Eliopoulos. AAC 1998;42:1088-92)*

- In vitro clinda-S *S. aureus* killed by Q/D whereas erythro/clinda-R strains only inhibited

  *(Fuchs. AAC 2000;44:2880-2)*

- Constitutive MLS-B resistance (MLS-B phenotype) no obvious effect on outcome

  *(Drew. JAC 2000;46:775-84)*
Clinical outcomes VREF

- 19 bloodstream and 5 localized infections VREF: 83% cured or improved  
  \( (CID \ 2000;30;790-7) \)

- VREF emergency use protocol:
  - 55.3% clin succes all pts.
  - 73.6% clin. evaluable pts.
  - 65.4% overall succes (clin & bact. succes)  
  \( (JAC \ 1999;44:251-61) \)

- Second VREF emergency (396 pts.)
  - 51% clin response
  - 68.8% clin evaluable pts.
  - 65.6% overall succes  
  \( (CID \ 2001;33:1816-23) \)
Clinical outcomes in randomized comparisons

- Complicated SSTI vs oxacillin/cefazoline or vanco (7.5mg/kg q12h)
  - 68.2% vs 70.7% clin evaluable
  - 66.6% vs 77.7% pathogen-eradication
  (JAC 1999; 44:263-73)

- Nosocomial pneumonia vs Vanco (7.5mg/kg q8h)
  (both + aztreonam, imipenem or tobramycin): clinical succes rates
  - 43.3% vs 45.3% all treated + bact. assessable pts.
  - 66.7% vs 58.1% MSSA
  - 30.9% vs 44.4% MRSA
  (Am J Resp CCM 2000;161:753-62)
Safety issues

- Significant interactions CYP 3A4
- Common venous intolerance when administrated through peripheral vein.
- Incompatibility with saline -> dextrose 5%
- 7-10% myalgias and/or arthralgias
- Increases in conjugated bilirubin levels to >5 times in 5.5% of pts.
Positioning of Q/D

- vanco-resistant E. faecium: problem bug (mainly in ICU) in US (hence accelerated FDA approval on the basis of clearing of VREF bacteremia)
- similar outcomes in other types of Gram pos infection (nosoc. pneumonia, SSTI) and hence with current resistance patterns no added value
Synercid: availability

- European registration.
- No price or reimbursement in Belgium.
- No compassionate use program from Aventis, Belgium.
- Recently sold to KING (in principle only distribution in US); unclear whether product will remain available in Europe in near-future; looking for distribution partners in Europe.
- Acquisition cost: 500 mg: 45.42 (Austria)-60.5 (Netherlands)-63.16 Euro (Germany); hence daily cost at 7.5 mg/kg bid or tid (70 kg) in range of 100-150 Euro.
- Can be ordered from large retailers or hospitals in France (57,93 Euro/500 mg) (comm. Aventis, Belgium)
Positioning of linezolid

- documented GP-resistant infection (currently very rare in Belgium)
- major intolerance to GP
- short-term followup treatment of initial GP treatment of beta-lactam resistant gram pos infections, allowing for more rapid discharge
- warning for toxicity + risk for selection of resistance in difficult to treat infections (foreign bodies); no significant trials in osteomyelitis/ foreign body infections