Société belge d'infectiologie et de microbiologie clinique

Belgische vereniging voor infectiologie en klinische microbiologie

NEW ANTI-INFECTIVE AGENTS IN 2003 : SPECTRUM AND INDICATIONS

20th Symposium (spring 2003)

Thursday May 22nd 2003

Streptogramins and linezolid

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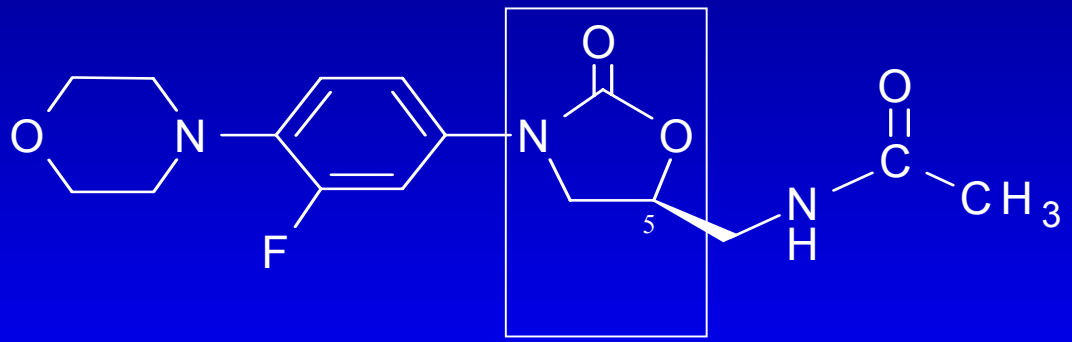
linezolid - Chemistry

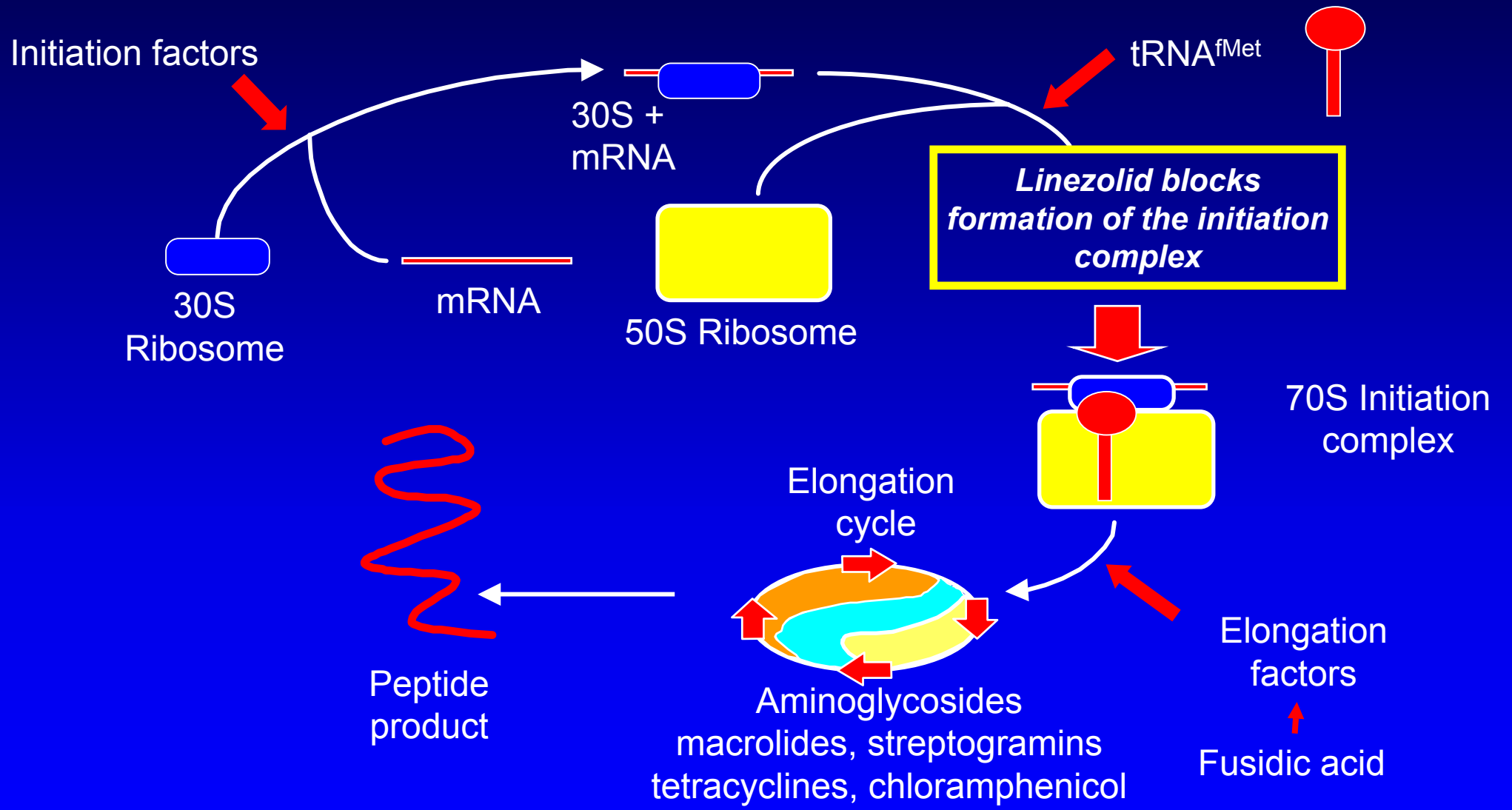
- First oxazolidinone antibiotic

  (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



Norrby R. *Exp Opin Pharmacother* 2001

linezolid - Microbiology

- Specific anti-Gram-positive spectrum, similar to spectrum of glycopeptides,
  - all most common aerobes, i.e.
    - allstaphylococci,incl.*Staphylococcus aureus* and all coagulase-negative staphylococci
    - all enterococci, incl. *Enterococcus faecalis*, *E. faecium*, and all other enterococci
    - all streptococci, incl. *Streptococcus pneu-moniae*, *S. pyogenes*, the Viridans and all other streptococci

linezolid - Microbiology

- 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 ≤ 4 mg/L
  - R > 4 mg/L
- **NCCLS**
  - S ≤ 4 ; R ≥ 8 (staphylococci)
  - S ≤ 2 ; I = 4 ; R ≥ 8 (streptococci and enterococci)

J Antimicrobiol Chemother 2001; 48: 445-448.
Clin Microbiol Infect 2001; 7: 283-284

Linezolid: In vitro activity (Belgium)

	MIC_{90} (mg/L)	range
S. aureus		
oxa-S	2	0.25-4
MRSA	2	0.25-4
Coag.-neg staphylococcus		
oxa-S	2	0.25-2
oxa-R	2	0.12-2

	MIC_{90} (mg/L)	range
S. pneumoniae	1	0.25-2
Streptococcus sp.	2	0.25-2
Enterococcus faecalis		
low genta R	2	1-4
high genta R	2	1-2
Enterococcus faecium	2	0.25-2

ICAAC 2001: Abstract E-1424.

Linezolid: PK-PD characteristics

- 100 % bio availability→ ± identical concentration-time curves after IV and oral dosing
- linezolid 600 mg IV/per os (bid)

Cmax	15.1 – 21.2 mg/L
Cmin	3.7 – 6.2 mg/L
AUC	138 mg/L.h
t ½	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**
  (CID 2002;34:1412-14 & J Infect 2001;43:148-57)

- **CNS epidural catheter infection.**
  (CID 2000;30:146-51)

- **Endovascular infections due to VREF**
  (*CID 2000;30:146-51, CID 2001;32:1373-5,*
  CID 2000;30:403-4)

- **MRSA infections with treatment failure or intolerance for vanco**
  (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, managable 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

  (Johnson. Eur J Clin Microb Inf Dis 2002;21:751)

  (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

Isolate number	Number of days post-empyema drainage	Site of isolate	BSAC linezolid disc zone diameter (mm)	Etest MIC of linezolid (mg/L)	NCCLS MIC of linezolid (mg/L)	NCCLS MIC of erythromycin (mg/L)	NCCLS MIC of vancomycin (mg/L)	NCCLS MIC of teicoplanin (mg/L)
1	17	axilla	28	1.0	2.0	>64.0	1.0	0.5
2	20	sputum	>18	1.0	2.0	>64.0	1.0	0.25
3	20	empyema fluid	>18	2.0	2.0	>64.0	1.0	0.25
4	20	drain site swab	>18	1.0	2.0	>64.0	1.0	0.25
5	23	sputum	>18	1.0	2.0	>64.0	0.5	0.25
6	24	sputum	>18	1.0	2.0	>64.0	1.0	0.25
7	25	empyema fluid	>18	1.0	2.0	>64.0	1.0	0.25
8	40	drain site swab	>18	2.0	2.0	>64.0	1.0	0.25
9	48	drain site swab	>18	1.0	2.0	>64.0	1.0	0.25
10	63	drain site swab	30	2.0	2.0	>64.0	1.0	0.25
			14	32.0	32.0	0.5	0.5	0.25
11	71	empyema fluid	30	1.0	2.0	>64.0	1.0	0.125
			14	8.0	8.0	0.25	1.0	0.25
			12	32.0	16.0	0.5	1.0	0.25

Wilson. JAC (2003) 51, 186-8

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)

Clinical Infectious Diseases 2003:36 (1 March)

Table 1. Linezolid blood levels achieved at various dosages in a patient treated with linezolid every 12 hours.

	Level achieved (expected, mean ± SD), μg/mL, by dosage		
Level	600 mg po	600 mg iv	900 mg iv
Peak[a]	1.73 (21.20 ± 5.78)	3.15 (15.10 ± 2.52)	9.14
Trough[b]	0.10 (6.15 ± 2.94)	Trace (3.68 ± 2.36)	1.8

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

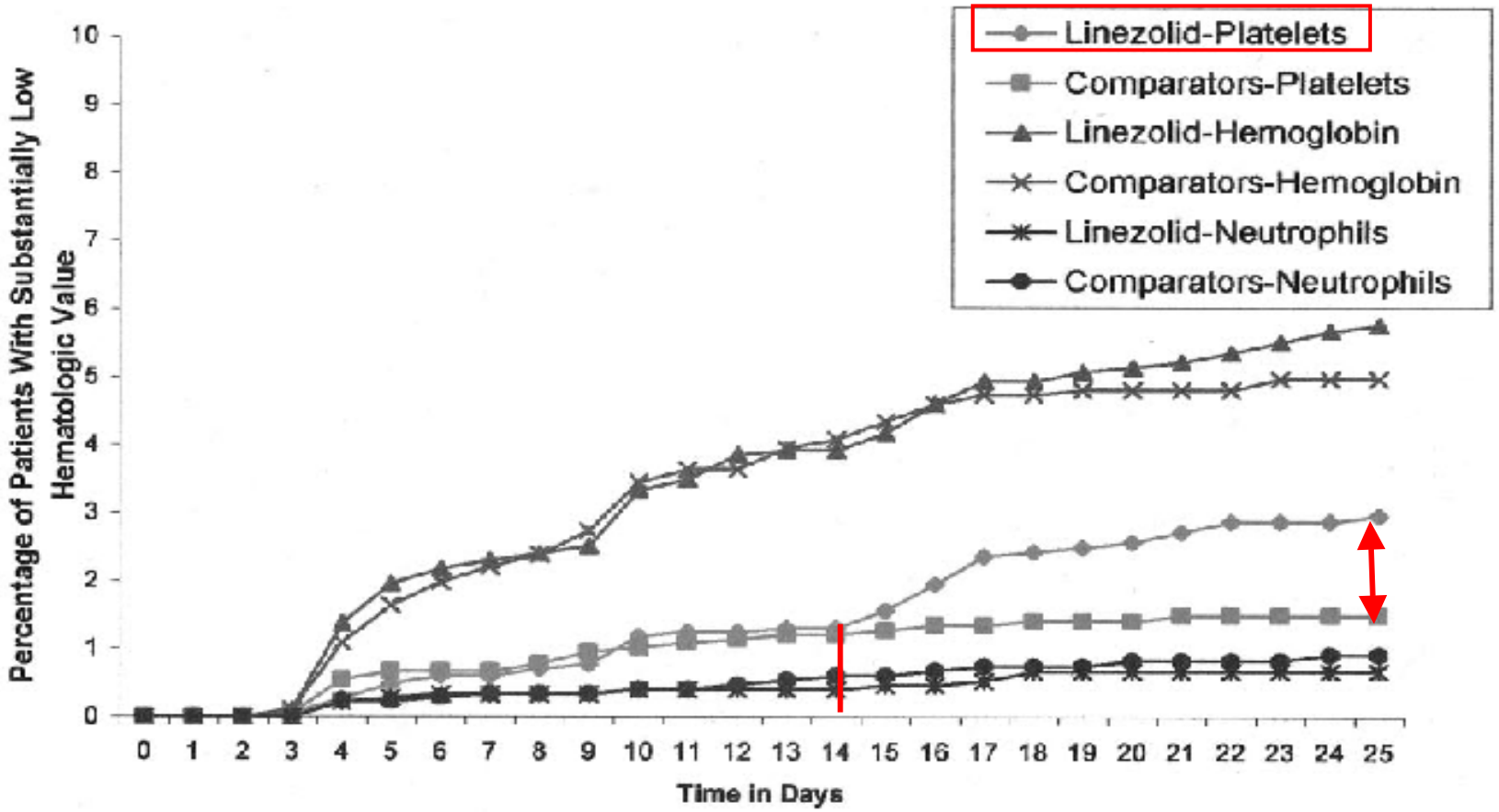
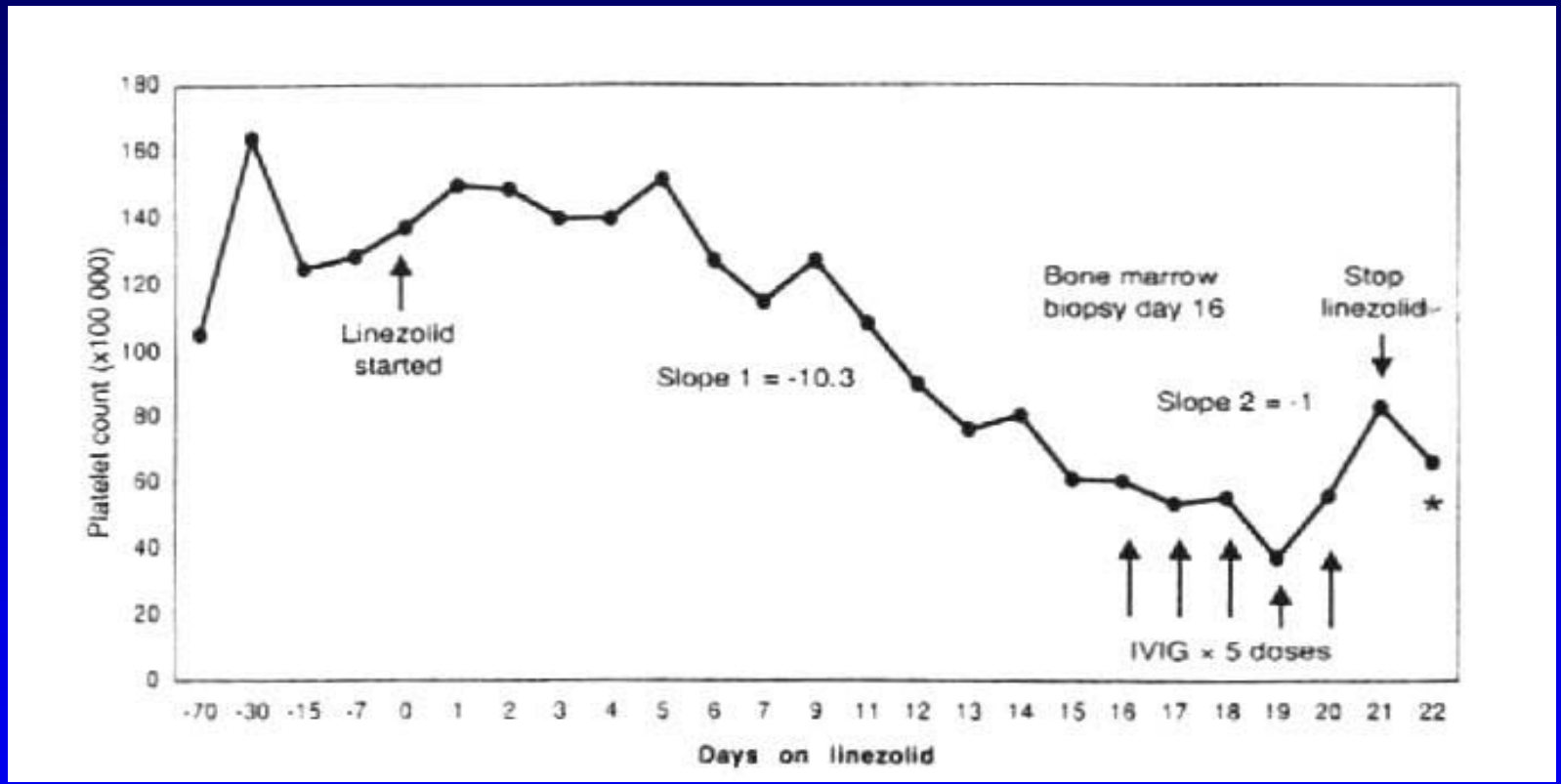


FIG. 1. Patients with at least one substantially low PLTC, hemoglobin value, or neutrophil count in linezolid and comparator groups—cumulative percentage over time.

ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Aug. 2002, p. 2723

Mechanisms for linezolid-induced anemia and thrombocytopenia



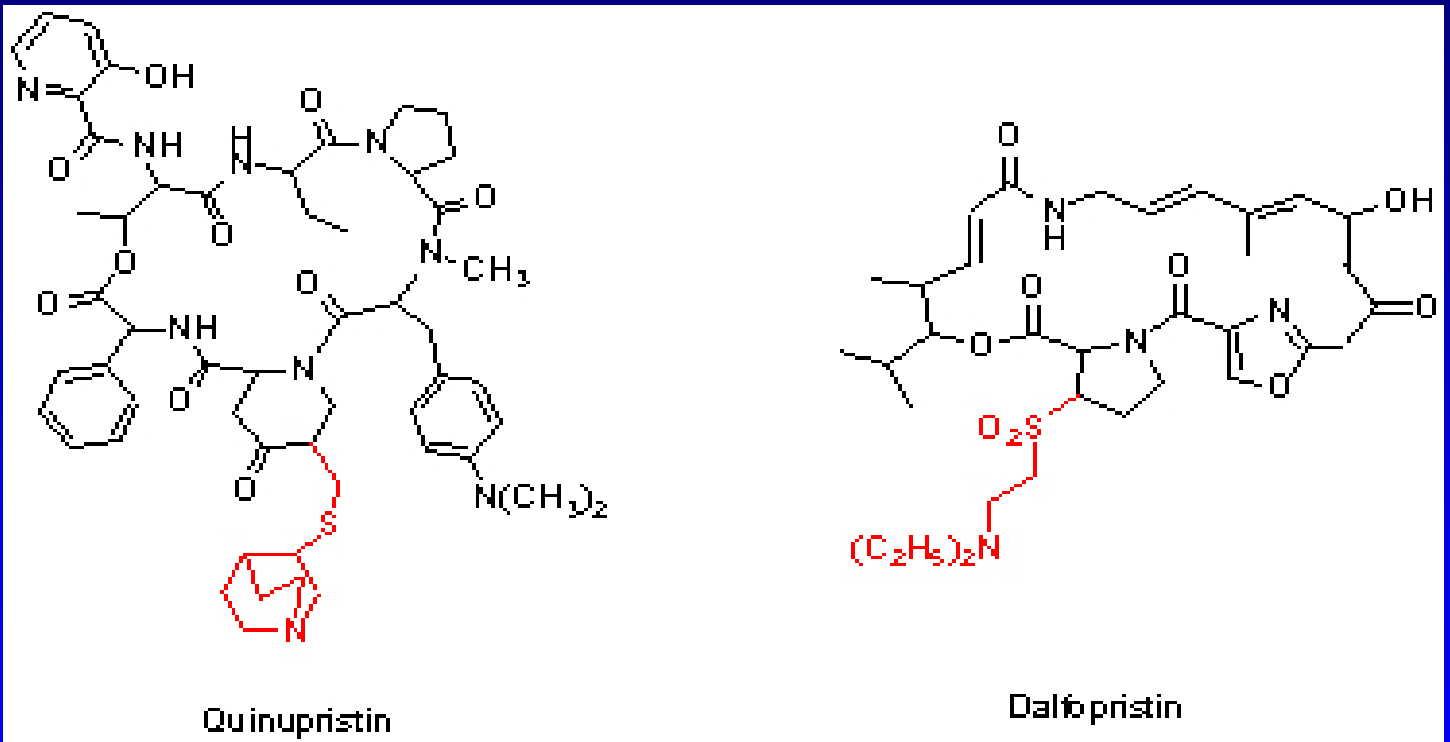
Bernstein, Ann Pharmacother 2003:37(4):517

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/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