CHU Rennes

CENTRES DE RÉFÉRENCE POUR LES INFECTIONS OSTÉO-ARTICULAIRES COMPLEXES DU GRAND OUEST
CRIOGO

UNIVERSITÉ DE RENNES 1

Nouveaux Antibiotiques et Infections Ostéoarticulaires Quoi de neuf?

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CCA

SMIT CHU Rennes

21 octobre 2019

L’antibiotique idéal?

- J Lomas, Orthopaedics and Trauma 2019

- Activité naturelle
- Bactéricide
- Diffusion ostéoarticulaire
- Pas de résistance acquise sous traitement
- Activité planctonique > traitement empirique/D’attaque
- Activité au sein du biofilm > traitement définitif
- Tolérance parfaite
- Coût maîtrisé

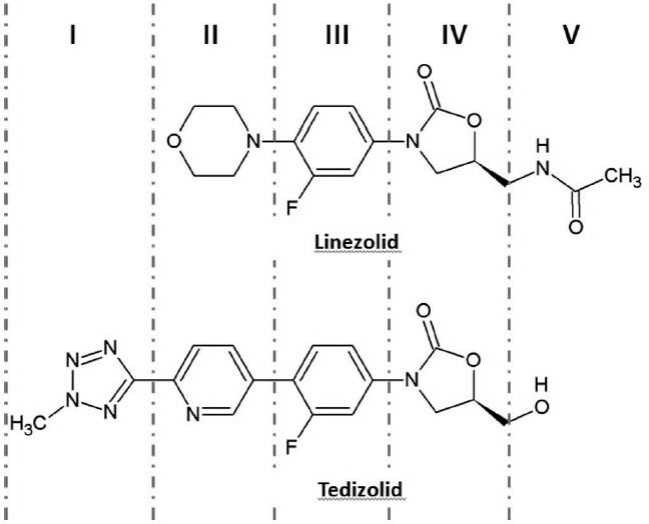
- Tedizolide
- Dalbavancine
- Ceftazidime avibactam
- Ceftolozane tazobactam

- Tedizolide
- ~~Dalbavancine~~
- ~~Ceftazidime avibactam~~
- ~~Ceftolozane tazobactam~~

- RUPTURE DE STOCK DALBAVANCINE
- NOUVELLES ASSO DE BL RESERVEES EPARGNE DES PENEMS

TEDIZOLIDE, SIVEXTRO°

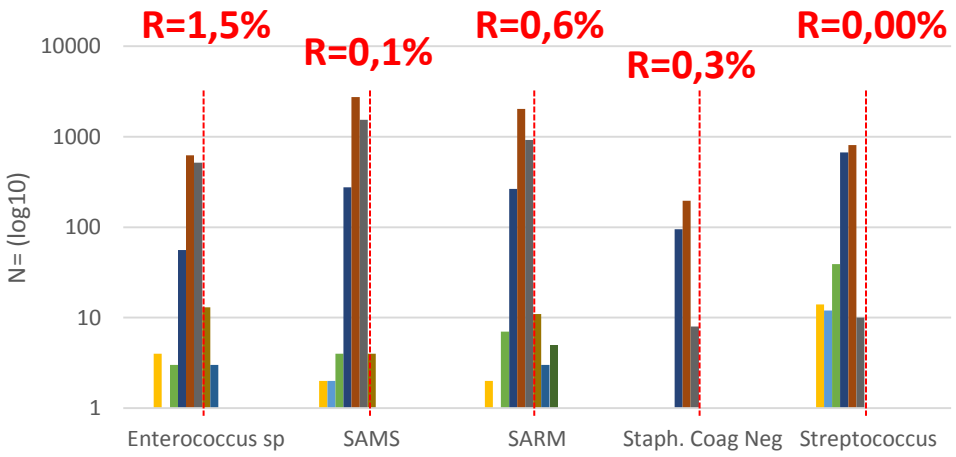
- Oxazolidinones
- Action anti Complexe d'initiation 70S (Ribosome)
- IMAO à l'origine (effet moindre que le LINEZOLIDE)



Activité naturelle

- CMI 0,5mg/L
- Sauf le groupe S anginosus 0,25mg/L

Echelle logarythmique



http://mic.eucast.org

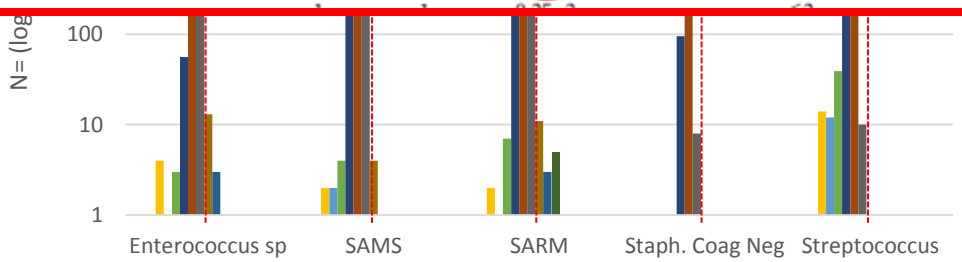
Activité naturelle

- CMI 0,5mg/L
- Sauf le groupe S anginosus 0,25mg/L

Table 1. *In vitro* activity of tedizolid comparator antimicrobial agents against *Staphylococcus aureus*, coagulase-negative staphylococci, *Enterococcus* spp., *Corynebacterium* spp. and *Propionibacterium* spp. involved in documented prosthetic joint infections between 2013 and 2016

Species (number of isolates)/Antibacterial agent	MIC (μg ml^{-1})			2017 EUCAST susceptibility breakpoint	% of susceptible isolates
	MIC_{50}	MIC_{90}	Range		
Staphylococcus aureus (*n*=104)					
Tedizolid	0.12	0.25	0.06–1	≤0.5	99
Linezolid	1	2	0.5–4	≤4	100

Ract JMM 2017



http://mic.eucast.org

Effet bactéricide du Tedizolide?

- Non
- Bactériostatique comme le Linezolide
- Effet inhérent au mécanisme d'action (blocage réplication)
- Effet post antibiotique (Locke CID2007, Bayer AAC2016)

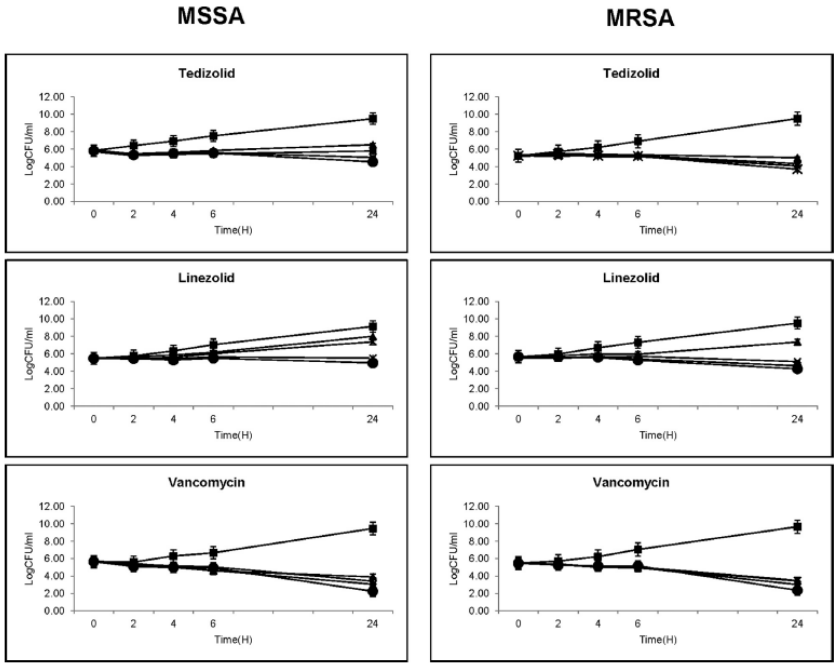


FIG 1 Tedizolid, linezolid, and vancomycin *in vitro* MSSA (Xen29) and MRSA (Xen30) time-kill curves. Symbols: ■, control; ▲, 1× MIC; X, 2× MIC; *, 5× MIC; ●, 10× MIC.

Bayer, AAC2016

Diffusion ostéoarticulaire

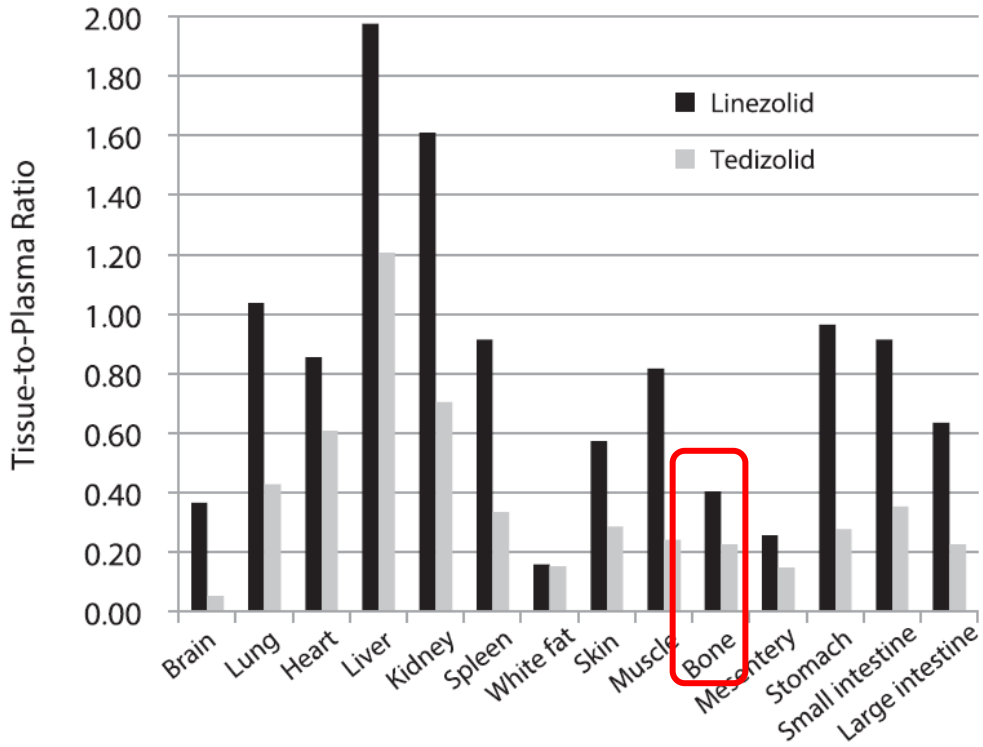


Fig. 1. Mean tissue-to-plasma concentration ratios at 6 hours after a single intravenous dose of tedizolid phosphate (13.3 mg/kg, molar equivalent to 10 mg/kg tedizolid) or linezolid (10 mg/kg) in rats.

Ong
DRUG METAB DISPOS,
2014

Réserves : modèles animaux (rats), effet d'un dose unique alors qu'accumulation intracellulaire rapportée des oxazolidinones

Résistance acquise

- Problème du LINEZOLIDE
- Acquisition plasmidique du gène *cfr*
- Méthylation ribosomale > résistance au LINEZOLIDE

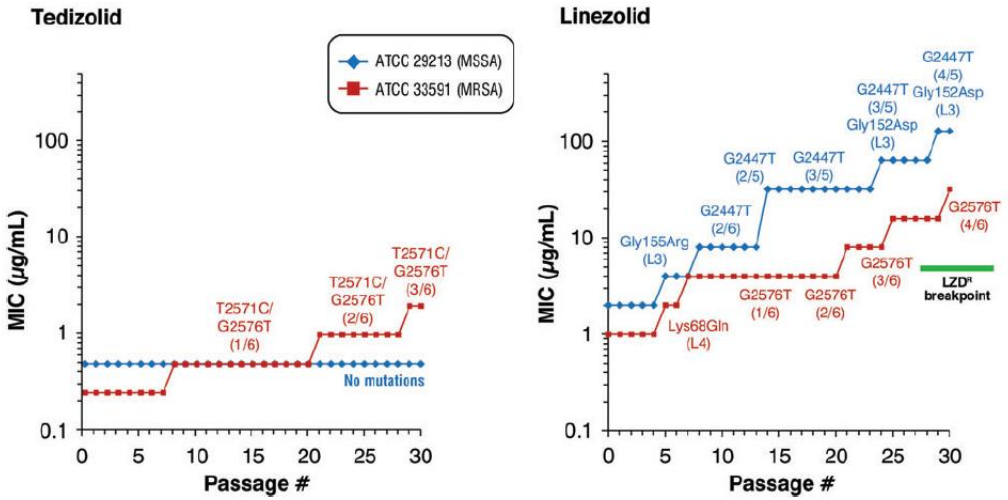


Figure 2. Serial passage of *Staphylococcus aureus* in tedizolid or linezolid. Adapted from Locke et al [38], with permission from American Society for Microbiology. Total mutant population minimum inhibitory concentration values are plotted for each serial passage of ATCC 29213 and ATCC 33591 with tedizolid and linezolid. Underlying mutations in 23S rRNA genes and ribosomal proteins L3 and L4 are shown corresponding to the stepwise minimum inhibitory concentration values at which they were identified by analysis of individual colonies. Fractional 23S rRNA values indicate the number of mutant alleles out of the total number of 23S alleles detected by polymerase chain reaction. The *Escherichia coli* numbering system is used for 23S rRNA gene mutations and the *S. aureus* numbering system is used for L3 and L4 residue mutations. Abbreviations: ATCC, American Type Culture Collection; LZD^R, linezolid resistant; MIC, minimum inhibitory concentration; MRSA, methicillin-resistant *S. aureus*; MSSA, methicillin-susceptible *S. aureus*.

Locke, CID2007

Resistance acquise

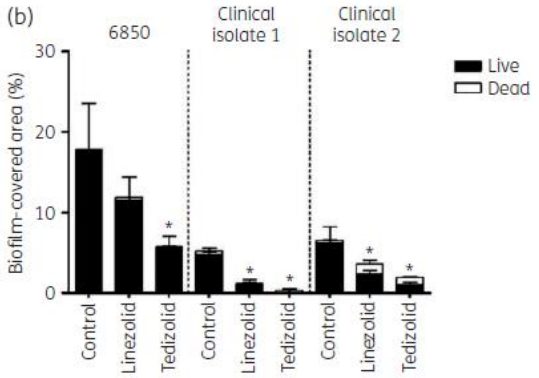
Table 3. In Vitro Activity of Tedizolid and Linezolid Against Linezolid-Resistant Clinical Isolates

Organism (number tested)	Antimicrobial Agent	MIC (μg/mL)		
		50%	90%	Range
S. aureus (17)	Tedizolid	0.25	2	0.12–8
	Linezolid	2	16	1–64
S. epidermidis (19)	Tedizolid	4	8	2–>32
	Linezolid	32	>128	16–>128
E. faecalis (16)	Tedizolid	4	4	2–4
	Linezolid	32	32	8–32
E. faecium (36)	Tedizolid	2	4	0.5–8
	Linezolid	32	64	4 –>128

Activité planctonique *versus* bactérie quiescente (biofilm)

(a)

bMIC (mg/L)	Linezolid	Tedizolid
6850 reference strain	1	0.25
Clinical isolate 1	1	0.25
Clinical isolate 2	2	0.5



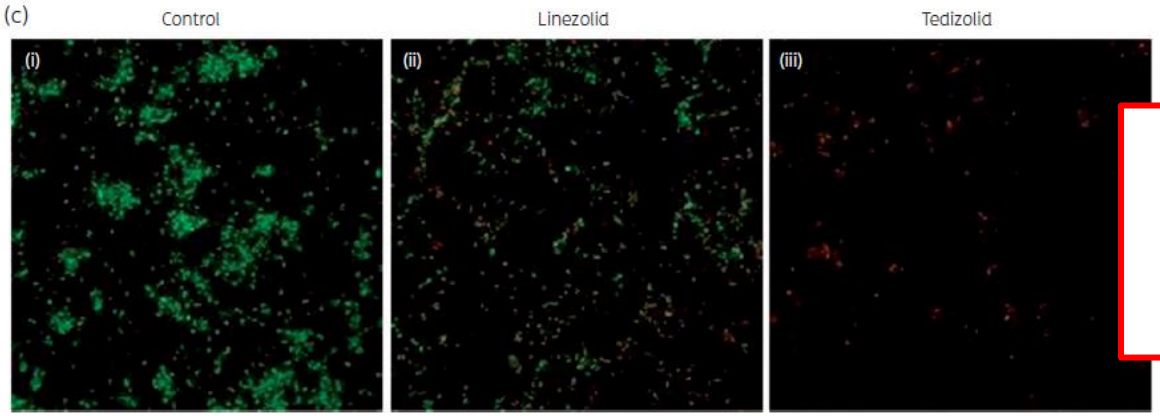


Figure 2. Ability of linezolid and tedizolid to prevent biofilm formation. (a) bMICs of linezolid and tedizolid for the *S. aureus* 6850 reference strain and two BJI clinical isolates determined using the Antibiofilmogram® method. (b) Proportion of *S. aureus* viable cells determined using CLSM after treatment with linezolid or tedizolid at bMICs compared with untreated cells. (c) CLSM showing biofilm-embedded viable (green) and dead (red) *S. aureus* 6850 without treatment (i), after treatment with linezolid (ii) and after treatment with tedizolid (iii). This figure appears in colour in the online version of *JAC* and in black and white in the print version of *JAC*.

Prévient *in vitro* la formation du biofilm

Abad
JAC 2019

Biofilm (suite)

Faible activité bactérienne au sein d'un biofilm déjà formé (*in vitro*)

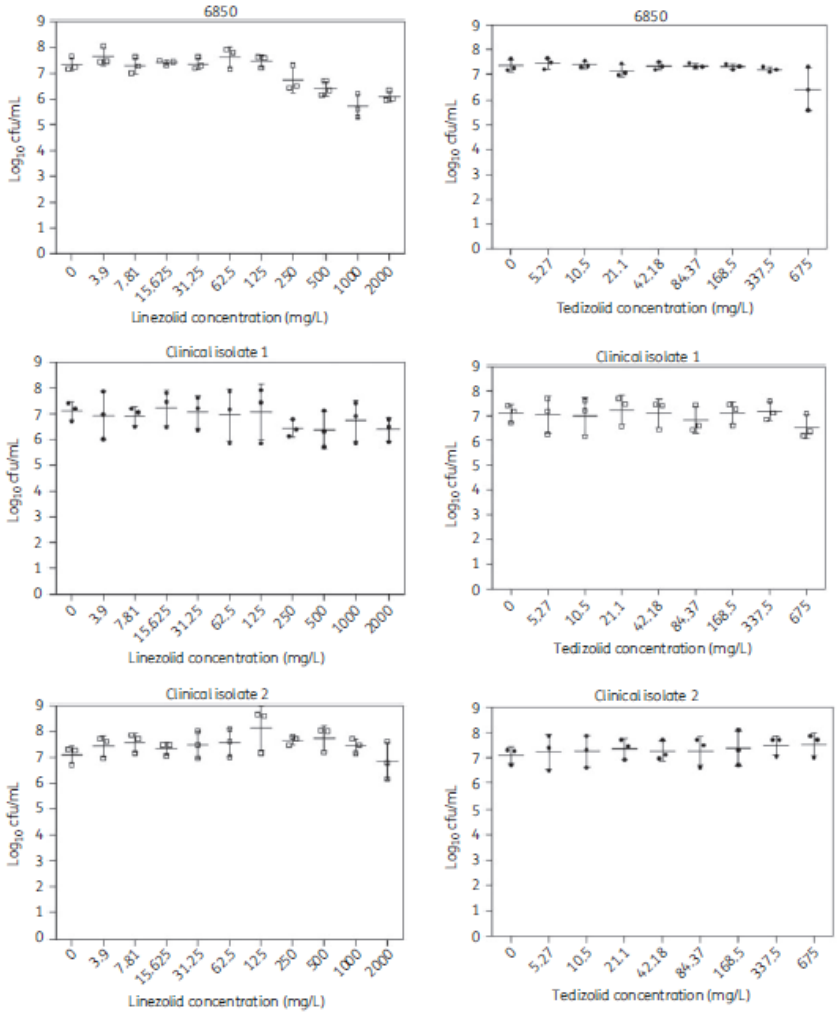


Figure 3. Determination of the MBECs of linezolid and tedizolid for *S. aureus* reference strain 6850 and two BJI clinical isolates.

MBECs
Minimum
Biofilm
Eradication
Concentration

Seuil >90% des bactéries au sein du biofilm

Seuil :
>2000mg/L (LINE)
> 675mg/L (TEDI)

Abad
JAC 2019

Tolérance du Tedizolide

- LE défaut du Linezolide ++++
- Toxicité temps dépendante (>21-28j) et dose-dpte
- Hématotoxicité (mécanisme??)
- Toxicité mitochondriale (acidose lactique, neurotoxicité)
- Effet IMAO

Tolérance du Tedizolide

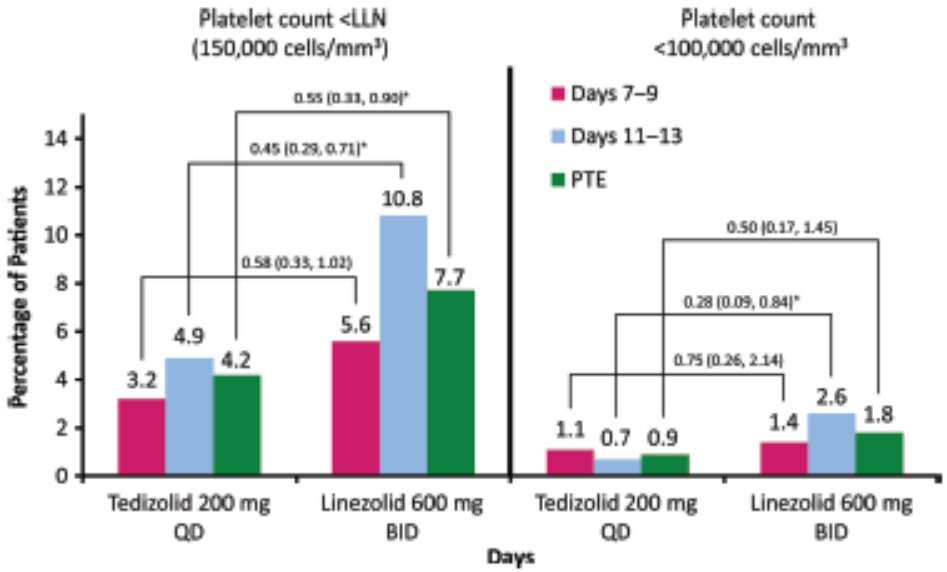
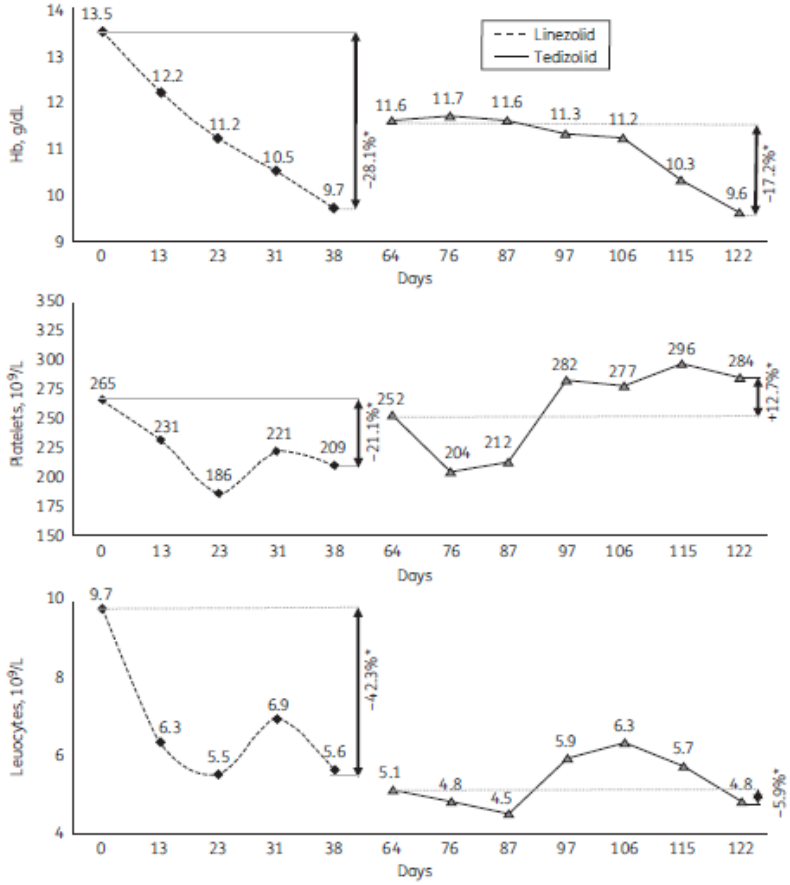


FIG 1 Incidence of platelet counts of <150,000 and <100,000 cells/mm³ at the visit on study days 7 to 9, at end of therapy (EOT) on study days 11 to 13, and at posttherapy evaluation (PTE) (7 to 14 days after EOT visit). BID, twice daily; LLN, lower limit of normal; PTE, posttherapy evaluation; QD, once daily. Treatment differences (shown over the connecting lines) reflect relative risk (RR) (95% CI). *, $P < 0.05$ (Fisher's exact test).

Yuste JAC 2017

Tolérance du Tedizolide



- Contexte mycobactérie
- Toxicité linezolide
- Wash aout 26 jours
- Introduction tedizolide

Yuste JAC 2017

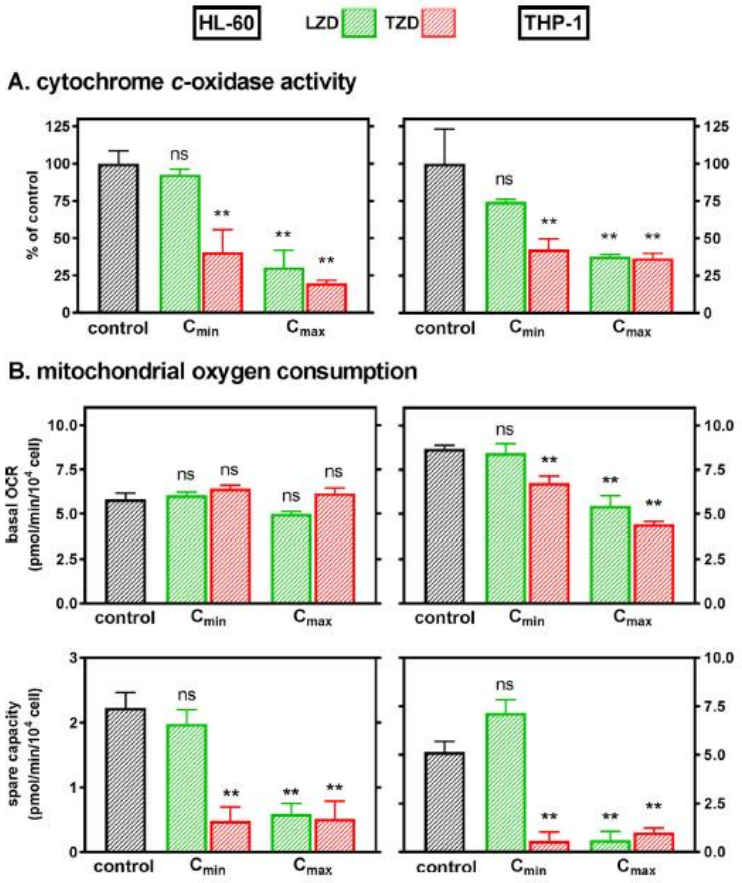
Tolérance du Tedizolide

- Données de pharmacovigilance FDA 2014-2016
- 1468 cas de thrombopénie médicamenteuse
- 408 (0,02%) sous Linezolide
- 41 (0,002%) sous Tedizolide
- Respectivement 2,44% et 2,77% des EI de chaque molécule
- Reporting OR estimé :
  - ROR Linezolide = 37,9 (IC95 20,78-69,17)
  - ROR Tedizolide = 34.0 (IC95 4,67-247,30)
- ROR Linezolide préTedizolide = 12,1 (IC95 11,19-12,96) lié à une sous déclaration initiale classique en pharmacovigilance

Comments CID2018, auteur?

Tolérance du Tedizolide

- Moindre effet sur la toxicité mitochondriale
- Effet surtout rapporté en post commercialisation pour le Linezolide
- Milosevic AAC 2018 (recherche fondamentale)



Coût?

- Oral (forme IV existe)
- Prise Unique (200mg/j)
- 165e pour 6cp soit 1155e environ pour 42j
- Coût de la surveillance biologique (pas de recommandation propre de surveillance)

Table 2. Comparison of pharmacokinetic properties between linezolid and tedizolid phosphate after oral administration.[29,36,54]

	Linezolid 600 mg twice daily oral	Tedizolid phosphate 200 mg once daily oral
Oral bioavailability (%)	100	91
C_{max} (mg/L)	12.2	1.8
Elimination half-life (h)	3.8	11
$AUC_{0-\infty}$ (mg/L × h)	78.1	21.6
Protein binding (%)	30	70–90
Volume of distribution (L)	42.9	117
Elimination	As metabolites 50% urine/9% feces As parental compound 30% in urine	As metabolites 20% urine/80% feces

Douros, Expert Opin. Drug Metab. Toxicol. 2015

Efficacité dans les IOA???

- Très peu de données
- Case report Scheng, Infect Dis Baltimor 2017

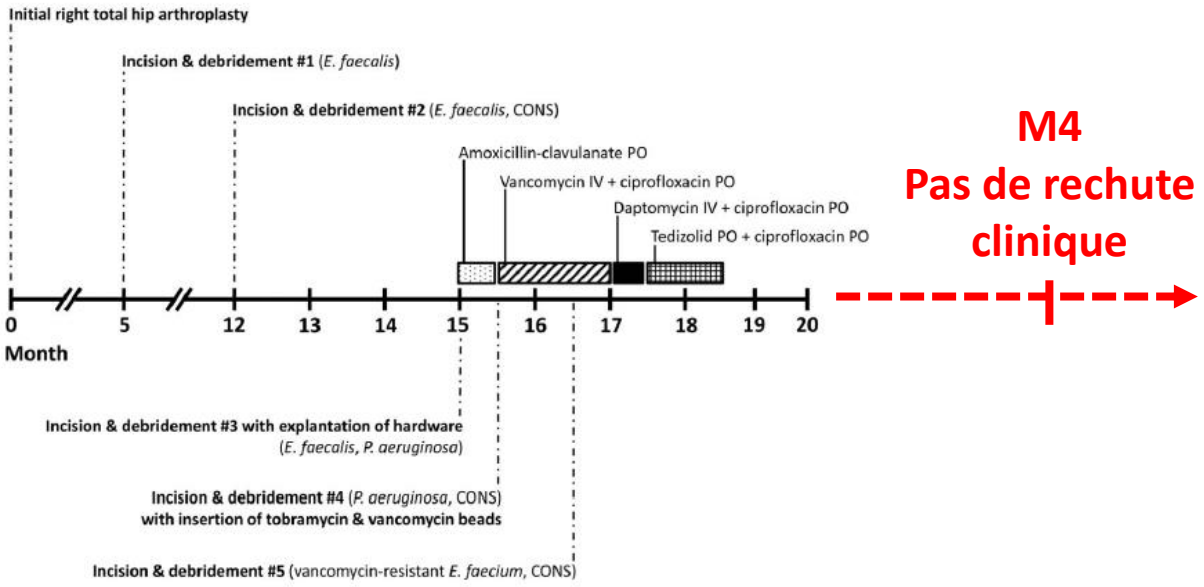


Figure 1.
Case timeline, including surgeries, operative cultures, and antimicrobial therapy.
CONS: coagulase-negative staphylococci

Prudence

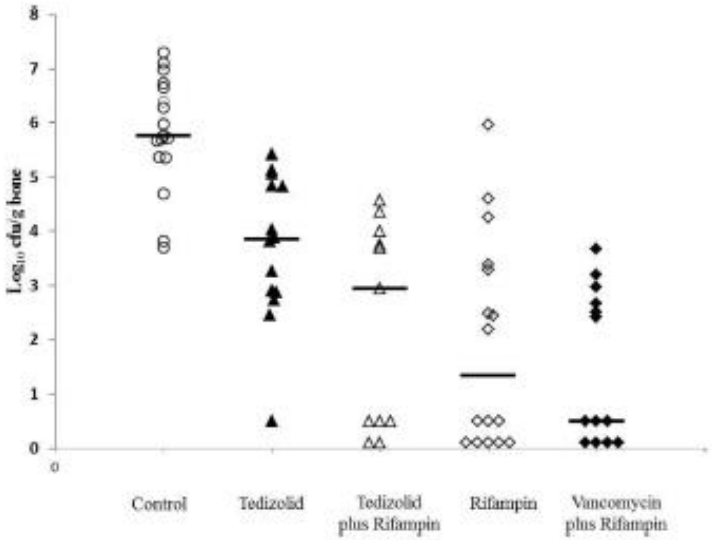
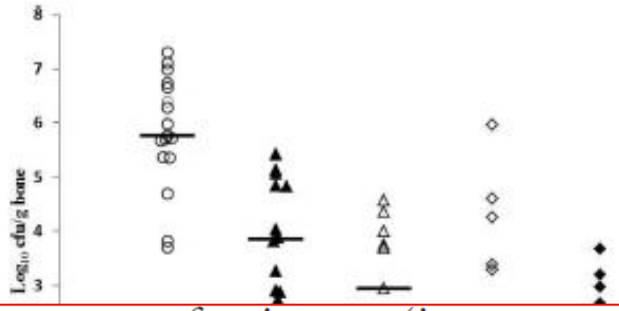


FIG 1 Results of quantitative bone culture. The median value (bars) and individual results (individual symbols) are shown for each study group. Differences between the control group and each treatment group were statistically significant ($P \leq 0.0001$).

- Modèle de rat
- osteomyelite tibia avec matériel
- SAMS
- Tedizolide 30mg/kg

Park AAC 2016

Prudence



Emergence of resistance. Emergence of resistance (i.e., a post-treatment rifampin MIC of >4 μg/ml) was detected in 10 animals (63%) in the rifampin group, 8 animals (73%) in the tedizolid plus rifampin group, and 1 animal (8%) in the vancomycin plus rifampin group. The differences between the rifampin monotherapy and vancomycin plus rifampin groups ($P = 0.006$) and between the tedizolid plus rifampin and vancomycin plus rifampin groups ($P = 0.002$) were statistically significant, but there was no difference between the rifampin monotherapy and tedizolid plus rifampin groups ($P = 0.69$). The findings remained significant, in spite of adjustment for multiple comparisons. There was no emergence of resistance to tedizolid or vancomycin in the respective treatment groups.

- Mo
- ost
- SAI
- Tedizolide 30mg/kg

Park AAC 2016

1eres études en cours

Efficacy and Tolerance of 4 Weeks of Tedizolid in Prosthetic Joint Infections Treated With Implant Removal (PROTEDI)

The safety and scientific validity of this study is the responsibility of the study sponsor and investigators. Listing a study does not mean it has been evaluated by the U.S. Federal Government. Know the risks and potential benefits of clinical studies and talk to your health care provider before participating. Read our disclaimer for details.

ClinicalTrials.gov Identifier: NCT03746327

Recruitment Status : Not yet recruiting
First Posted : November 19, 2018
Last Update Posted : July 11, 2019

See **Contacts and Locations**

Sponsor:
Fundacion Clinic per a la Recerca Biomédica

Information provided by (Responsible Party):
Anna Cruceta, Fundacion Clinic per a la Recerca Biomédica

Tedizolid Prolonged Treatment for Prosthetic Joint Infections (TEDIZOAM)

The safety and scientific validity of this study is the responsibility of the study sponsor and investigators. Listing a study does not mean it has been evaluated by the U.S. Federal Government. Read our disclaimer for details.

ClinicalTrials.gov Identifier: NCT03378427

Recruitment Status : Active, not recruiting
First Posted : December 19, 2017
Last Update Posted : September 11, 2019

Sponsor:
Tourcoing Hospital

Collaborator:
Eric SENNEVILLE M.D. Ph.D.

Information provided by (Responsible Party):
Tourcoing Hospital

Résumé

	TEDIZOLIDE	LINEZOLIDE
Activité naturelle	↑	-
Bactéricide	=	Non
Diffusion ostéoarticulaire	=	15-30%
Barrière de résistance	↑	Gene *cfr*
Activité planctonique	=	Oui
Activité au sein du biofilm	Prévient seulement	Faible
Tolérance parfaite	Identique ou moindre?	+++
Coût	↑	faible

merci