Safety of Tedizolid as Suppressive Antimicrobial Therapy for Patients With Complex Implant-Associated Bone and Joint Infection due to Multidrug-Resistant Gram-Positive Pathogens: Results From the TediSAT Cohort Study

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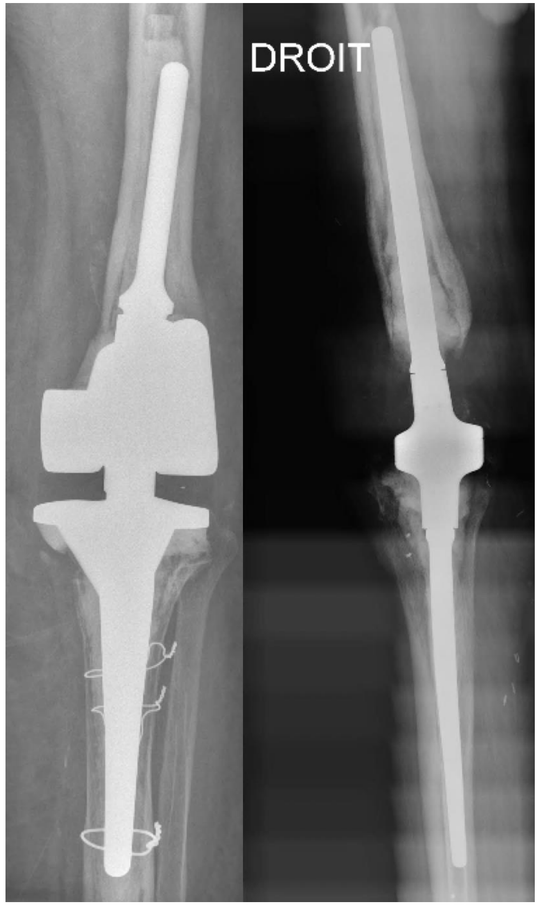
Introduction

- Bone and joint infections on implant (arthroplasty or osteosynthesis)
  - Difficult to treat, prolonged antimicrobial therapies, multiple surgeries
  - Most frequent pathogens:
    - Gram-positive cocci, including *S. aureus* and CoN staphylococci
    - **MDR gram-positive** infections are increasing worldwide
      - MDR CoN staphylococci
      - Vancomycin-resistant enterococci (VRE)



IDSA GUIDELINES

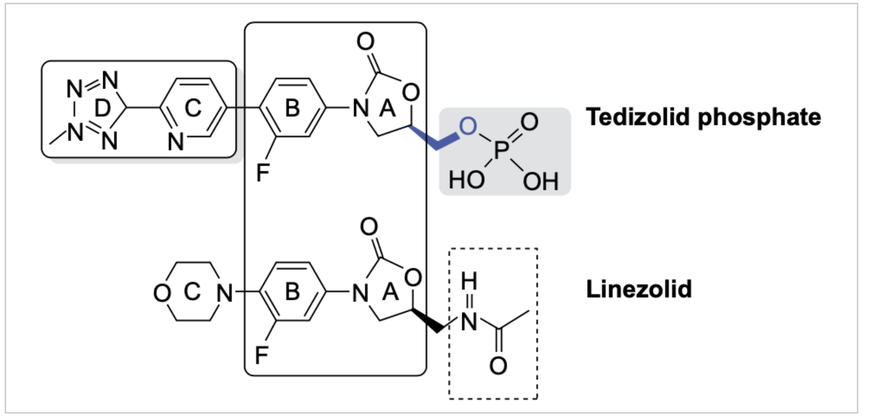
-

preserve the limb function

Titecat M. et al., Orthop Traumatol Surg Res. 2013;99(6):653-8
Osmon D et al., Clin Infect Dis. 2013 Jan;56(1)_e1-e25)
Prendki et al., Eur J Clin Microbiol Infect Dis. 2017;36(9):1577-85

Introduction

- **Linezolid (LZD)**
  - First oxazolidinone antibiotic
  - Active against these MDR Gram-positive bacteria
  - CAVEAT, known adverse events:
    - Myelotoxicity (thrombopenia)
    - Polyneuropathy
    - Drug-drug interactions (serotoninergic syndrome !)



- **Tedizolid (TZD)**
  - Second of this antibiotic class, 200 mg bd PO, only validates for cSSSI
  - No renal or hepatic adjustement
  - Less active on mitochondrial protein synthesis —> Less side effects ?
  - Longest TZD duration study : 12 weeks (Senneville *et al.*, PJI), case reports (NTM)

Douros A et al., Expert Opin Drug Metab Toxicol. 2015;11(12):1849-59
Senneville E et al., Antibiotics (Basel). 2020;10(1)
Matin A et al., Int J Antimicrob Agents. 2017;49(4):488-92
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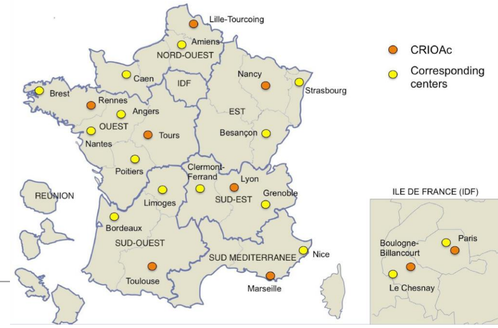
Ferrandez et al., Drug Des Devel Ther. 2016 Dec 22;11:65-82

Introduction

Aim of this study: to evaluate the safety of TZD as Suppressive Antimicrobial Therapy (SAT)

TediSAT cohort study

Method



- A prospective monocentric cohort study was conducted between January 2017 and December 2020
- At **CRIOAc Lyon** (Centre de Référence des Infections Ostéo-Articulaires complexes) = BJI referral Centre for Auvergne-Rhône-Alpes region (≈ 8Mio inhabitants)
- **PJI** or **osteosynthesis-associated** infections with TZD as SAT
- Each case was discussed in multidisciplinary meetings (orthopaedic and plastic surgeons, microbiologist, ID specialist) —> TZD = only oral option
- No exclusion criteria
- <u>Objectives</u>:
  - To evaluate the tolerance of TZD as SAT
  - To evaluate the efficacy of TZD as SAT

Results - Baseline characteristics

- **17 patients**
- Male: 13 (76%)
- Median age: **73 years** (IQR: 69-81)
- Mean BMI: 28.1 ± 5.1 kg/m^2
- Mean ASA score: 2.2 ± 0.6

- **Infection type**, n (%)
  - **Knee PJI**: 10 (59%)
  - **Hip PJI**: 5 (29%)
  - Shoulder PJI: 1
  - Femoral intramedullary nail: 1

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- **Pathogens**, n:
  - **CoN staphylococci**: 16 (76.2%)
  - *Corynebacterium striatum*: 2
  - Vancomycin-resistant *E. faecium*: 1
  - Co-infection with Gram-negative bacteria: 3

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- **Surgical procedure type**, n (%)
  - **DAIR**: 13 (76%)
  - Arthrodesis: 1
  - One-stage prosthesis exchange: 1
  - One-stage nail exchange: 1
  - No surgical procedure: 1

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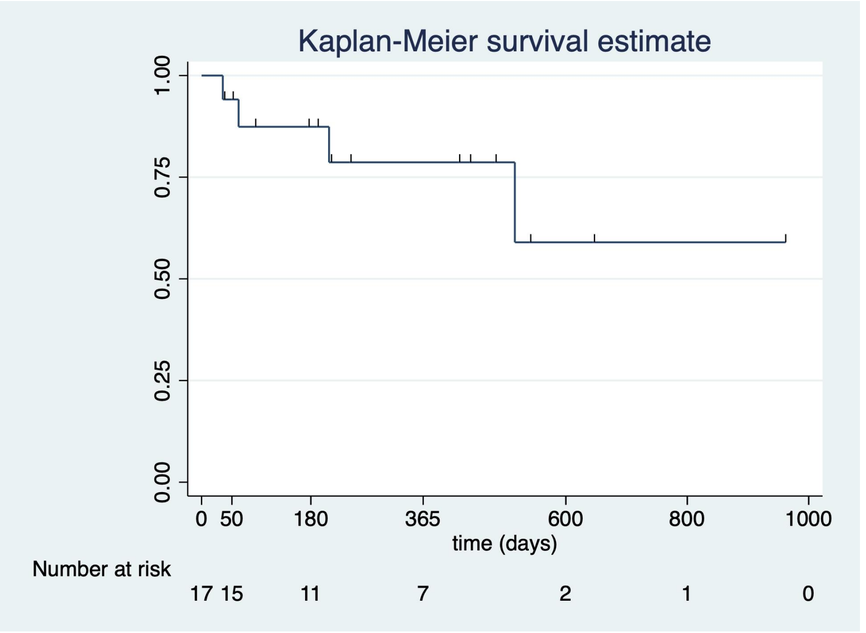
  - LZD in 13 patients:
    - **9/13 experienced severe adverse event**:
      - Myelotoxicity: 8
      - Gastro-intestinal intolerance: 1

Results - TZD duration and failures

- **<u>Median duration of TZD: 6 months</u>** (IQR: 2-15, range 1-31)
  - 2 patients had a short follow-up (included at the end of the study)
  - 2 failures at 1 and 2 months

- Failure of SAT:
  - n=4 (23.5%)
    - Sinus tract: n=3 (at 1, 6, and 16 months)
    - New infection: n=1 (at 2 months of TZD)
  - NB: 2 cases with intermittent drainage due to small sinus tract: decision to continue SAT given the benefits
    → not considered as failures



Results - Tolerance and adverse events

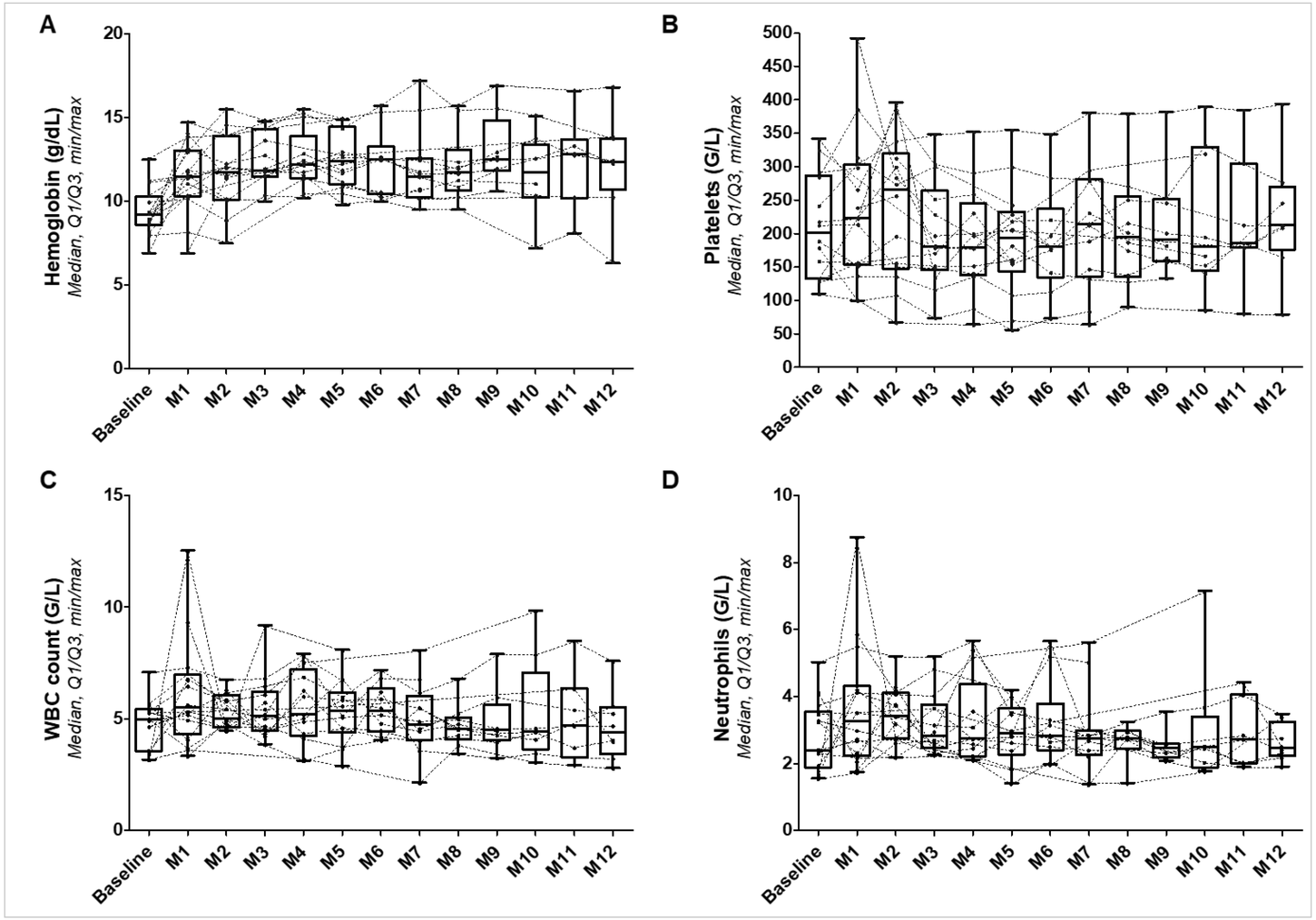
- All AEs related to LZD (n=9) were reversed on TZD
- No AE leading to TZD interruption, including gastro-intestinal or neurological AE
- No drug-drug interaction despite concomitant prescription of:
  - Tramadol (n=4)
  - Tricyclic antidepressant (n=2)

- 1 death, however not related to the initial chronic infection.

Results - Hematological tolerance

- No difference at 12 months in:
  - Platelet count (p=0.55)
  - WBC count (p=0.75)
  - Neutrophil count (p=0.93)

- Increase at 12 months in Hb (+2.95 g/dL (±3.55), p=0.051)



Discussion

- Strengths/Limitations

+ Longest treatment and follow-up duration without AE leading to TZD discontinuation

+ Similar efficacy of SAT with TZD compared to other studies

- Limited patient number

- Expensive treatment (≈200€/day in France, ≈400$/day in the USA), and not available in every country (Switzerland!)

Conclusion

Tedizolid seems to be a safe and well-tolerated SAT for complex implant-associated BJIs, when no other oral alternatives are available

Aknowledgements

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Thank you for your attention