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)

→ **Suppressive Antimicrobial Therapy** (SAT) is adequate to preserve the limb function

IDSA GUIDELINES

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 adjustment
  - Less active on mitochondrial protein synthesis —> Less side effects ?
  - Longest TZD duration study : 12 weeks (Senneville *et al.*, PJI), case reports (NTM)
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
- Objectives:
  - 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/m²
- 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
Results - Baseline characteristics

- **17 patients**
  - Male: 13 (76%)
  - Median age: **73 years** (IQR: 69-81)
  - Mean BMI: 28.1 ± 5.1 kg/m²
  - Mean ASA score: 2.2 ± 0.6

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

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

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

- Initial antimicrobial therapy
  - IV: median duration 47 days (IQR: 35-79; range 5-168), followed by:
    - LZD in 13 patients:
      - 9/13 experienced severe adverse event:
        - Myelotoxicity: 8
        - Gastrointestinal intolerance: 1
Results - Initial antimicrobial therapy

• **Initial antimicrobial therapy**
  • IV: median duration 47 days (IQR: 35-79; range 5-168), followed by:
  • LZD in 13 patients:
    • **9/13 experienced severe adverse event:**
      • Myelotoxicity: 8
      • Gastro-intestinal intolerance: 1
Results - TZD duration and failures

- **Median duration of TZD: 6 months** (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.
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Thank you for your attention