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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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BACKGROUND

Tedizolid (TZD) is an oxazolidinone antibiotic that: (i) is recommended at the dose of 200 once daily in patients with skin and soft tissue infection; (ii) seems to have a better long-term hematological and neurological safety profile in comparison with linezolid; (iii) remains active on multidrug-resistant (MDR) Gram-positive pathogens. Consequently, it might represent an option as suppressive antimicrobial treatment (SAT) in patients with complex implant-associated bone and joint infection (BJI) due to MDR Gram-positive pathogens.

METHODS

A prospective monocentric cohort study was conducted between 2017 and 2020 at our referral center for the management of complex BJI (CRIOAc) in Lyon, France (http://www.crioac-lyon.fr).

Clinical situation of every adult patient referred to our reference center with peri-prosthetic joint infection (PJI) or osteosynthesis-associated infection was discussed during multidisciplinary meetings (infectious disease specialist, microbiologist, orthopedic and plastic surgeons). In all cases, use of tedizolid was validated as the last oral treatment option for SAT. There were no exclusion criteria.

The primary objective of this study was to evaluate the safety of TZD as SAT. Any adverse event (AE), any reason for discontinuation, and standard biological data, were prospectively collected. Failure of SAT was defined as the presence of clinical signs suggestive of uncontrolled infection and the need for a new surgical procedure.

CONCLUSION

Tedizolid seems to be a safe option as SAT in patients with complex implant-associated BJI due MDR Gram-positive pathogens.

RESULTS

Seventeen patients received TZD orally at 200 mg once daily as SAT for late complex BJI, with a median duration of TZD treatment of six months (range: 1-31, interquartile range: IQR: 2-15). Patients were predominantly male (n=13, 76%), with a median age of 73 years (IQR: 69-81), a mean body mass index of 28.1 ± 5.1 kg/m2 (range: 19.5-36.7) and a mean ASA score of 2.2 ± 0.6 (range: 1-3). Knee PJI were the most frequent infections (n=10, 59%), followed by hip (n=5, 29%), and shoulder PJI (n=1, 6%). There was one femoral intramedullary nail infection (6%).

Pathogens were mainly MDR coagulase-negative staphylococci (n=16, 80%), followed by C*orynebacterium striatum* (n=2), vancomycin-resistant *Enterococcus faecium* (VRE, n=1) and/or methicillin-sensitive *S. aureus* (n=1). Co-infections with Gram-negative pathogens (*Pseudomonas aeruginosa*, *Serratia marcescens* and *Proteus mirabilis*) were observed in 3 patients.

An empirical intravenous (IV) antibiotic therapy followed each surgical procedure (mainly debridement and implant retention (n=13, 76.5%)), with subsequent adjustment based on bacterial susceptibility. Median duration of this primary IV treatment was 47 days (IQR: 35-79; range 5-168), followed by LZD in 13 (76.5%) patients. Antibiotic treatment was then changed to tedizolid in these 13 patients, including nine (75.0%) who experienced linezolid-induced serious AE: myelotoxicity in eight (66.7%) patients and severe gastro-intestinal intolerance in one patient. These events were reversible after transition to TDZ. In four other patients, TZD was introduced in first intention for SAT after discussion during multidisciplinary meeting.

The only reason for discontinuation of TZD was failure of conservative strategy in four patients (23.5%), mostly (n=3, 17%) due to persistence of infection with sinus tract. Two patients presented a small and intermittent sinus tract: it was considered beneficial to continue TZD and they were not considered as failure. One patient presented a new infection of his arthroplasty, with a new Gram-negative pathogen (*Citrobacter koseri*). A serious AE or discontinuation of TZD due to an AE were not reported in any patient. There was no clinically significant drug-drug interaction despite co-administration with serotoninergic agents: tricyclic antidepressants (n = 2) and tramadol (n = 4).

At 12 months after surgery, there was no difference from baseline in platelet (*P*=0.55), white blood cells (*P*=0.75) and neutrophils counts (*P*=0.93) (FIGURE 1). Hemoglobin level increased during the first year of treatment (mean difference of 2.95 ± 3.55 g/dL from baseline, but it was not statistically significant (*P*=0.051). Anemia was observed in two patients, in whom an alternate etiology was already known (chronic leukemia and esophageal varices). One case of thrombocytopenia, already observed before introduction of TZD in a cirrhotic patient (80 G/L [160-400]), remained stable during treatment course of 12 months. A transient mild neutropenia (1.4 G/L) was observed in one patient. No neurological AE were observed.

Median duration of follow-up was eight months (IQR: 5-17). One patient died during the study period, with death not considered associated with TZD, AE or to uncontrolled infection.

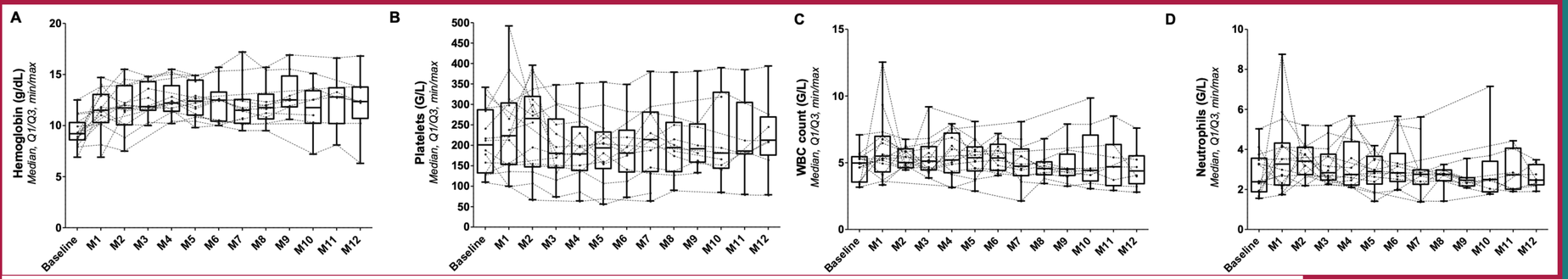

FIGURE 1: Evolution of hemoglobin, platelets count, white blood cell (WBC) count and neutrophil count during the first 12 months of SAT with tedizolid.