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Pharmacokinetics and pharmacogenetics of high-dosage tedizolid for disseminated nocardiosis in a lung transplant patient

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Introduction

Nocardiosis is an uncommon Gram-positive bacterial infection caused by aerobic actinomycetes in the genus *Nocardia*, usually occurring in individuals with a weakened immune system (diabetes, malignancies, HIV/AIDS, transplantation, immunosuppressive drugs), but immunocompetent hosts are also widely involved.[1] Nocardiosis has a wide range of clinical manifestations, with pulmonary nocardiosis being the most frequent. Due to the lack of prospective controlled trials, graded recommendations for the treatment of nocardiosis have not yet been proposed.[2]

In fact, trimethoprim/sulfamethoxazole is mainly regarded as a first-line therapy, and combination regimens are required in severe infections.[3] Alternative agents to trimethoprim/sulfamethoxazole are essential in allergic patients or those developing adverse effects or when isolates are resistant to trimethoprim/sulfamethoxazole. Given that clinical isolates of *Nocardia* spp. are often resistant to multiple antimicrobial agents and treatment duration is usually longer than 6 months, the therapeutic management of this infection remains challenging. In spite of the broad use of trimethoprim/sulfamethoxazole, different regimens have been used with antimicrobial drugs active against Gram-positive bacteria.[4] Among these approaches, one possible antimicrobial class of choice are the oxazolidinones. *Nocardia* spp. is almost always susceptible to linezolid, whose use in long-term treatment is limited by the risk of drug-related toxicities. Tedizolid, an oxazolidinone-class antibiotic approved only for the treatment of acute bacterial skin and skin structure infections, has been increasingly used in recent years as off-label indication for infection requiring prolonged treatment. Safety profile, pharmacokinetic (PK) properties and high tissue penetration make it a potential alternative to linezolid in pulmonary infections.[5] There are few data on the role of tedizolid in nocardiosis and, to the best of our knowledge, no data are available so far about the use of therapeutic drug monitoring (TDM) or pharmacogenomics.[6,7]

We report here the first case of disseminated nocardiosis, appropriately treated with TDM-guided higher dosage of tedizolid.

Case report

A 21-year-old female was admitted to the hospital for fever, fatigue and dyspnoea 2 months after bilateral lung transplantation for cystic fibrosis. At admission, a painless skin nodule associated with subcutaneous abscess and erythematous infiltration of a thoracotomy scar was found in the left submammary fold. Her immunosuppressive regimen consisted of tacrolimus, mycophenolate mofetil and low-dose steroids, with ongoing post-transplant prophylaxis with trimethoprim/sulfamethoxazole. A chest CT scan was performed, showing multiple-nodule pneumonia. *Nocardia farcinica* was isolated both from percutaneous drainage of cutaneous abscess and bronchoalveolar lavage, and diagnosis of disseminated nocardiosis was made. Waiting for susceptibility results, combination IV treatment with trimethoprim/sulfamethoxazole, amikacin and ertapenem was started, then switched to linezolid, amikacin and tigecycline according to antimicrobial susceptibility. After 2 weeks, the patient was discharged and oral therapy with linezolid at standard dosage was continued. Two months after linelozid introduction, she developed myelotoxicity, likely linezolid related (anaemia, thrombocytopenia). Therefore, therapy was initially switched to tedizolid 200 mg once daily with tedizolid of plasma samples.

The tedizolid trough plasma concentration (C_{min}) was measured by a validated UPLC tandem MS method (KIT-SYSTEM® Antibiotics, CoQua Lab, Turin, Italy) after 7 days of treatment, and it was undetectable (<0.04 mg/L). On Day 14, C_{min} and C_{max} were 0.07 and 0.89 mg/L, respectively, considerably lower than the previously described values in adults at steady state (~1.8–2.6 mg/L for C_{max}).[8,9] Therefore, with confirmed tedizolid underexposure, the daily dose was increased to 300 mg once daily. After 14 days of such treatment, C_{min} and C_{max} increased non-linearly to 0.41 mg/L and 3.83 mg/L, respectively. Subsequent drug plasma concentrations were as follows

Table 1. PK parameters of 300 mg once-daily tedizolid for disseminated nocardiosis

	Day 7	Day 14	Day 28	Day 35	Day 49
C_{min} (ng/mL)	Undetectable	65	406	137	273
C_{max} (ng/mL)	Undetectable	890	3831	2034	3881
Estimated AUC_{0-24} (mg/L h)	Undetectable	11.5	50.9	26.1	49.9

(Table 1): 0.137 mg/L and 2.034 mg/L (C_{min} and C_{max}, respectively) after 3 weeks, and 0.273 mg/L and 3.881 mg/L after 5 weeks, approaching the reported concentration ranges for C_{max}. In all TDM evaluations, the half-life was around 6 h, similar to the data previously observed in adolescents.[10]

According to the low values of C_{min} and C_{max} with standard dosage of tedizolid, we decided to investigate the pharmacogenetic variants possibly associated with lower concentrations of tedizolid. The method used for pharmacogenetic analysis was allelic discrimination through real-time PCR (TaqMan probes). Because tedizolid is a substrate of ABCB1 and ABCG2 (efflux pumps), the following genotypes were described in this patient: *ABCB1* 3435 CT, *ABCB1* 1236 CT, *ABCB1* 2677 TT, *ABCG2* 421 CC and *ABCG2* 1194+928 TC. Considering the analysed genetic variants, the drug underexposure could be partially related to the genetic influence on tedizolid transport (possible increased elimination).

On the other hand, reaching a similar or higher C_{max} than previously reported values in adults was considered pivotal because, after fAUC/MIC, the fC_{max}/MIC ratio was described as the second PK/pharmacodynamic predictor of success in the animal models.[8,11] Thereafter, no further dose changes were adopted. The patient received a 4 month course of tedizolid with a marked improvement of the pulmonary lesions on imaging, without recurrence of infection. Additionally, surgical treatment of the skin abscesses was performed with complete resolution. The drug was well tolerated, without developing gastrointestinal disorders and myelotoxicity.

In conclusion, we report that a higher tedizolid dosage, TDM-guided, is safe even for long-term treatment in disseminated nocardiosis after lung transplant, thus representing a valid alternative to linelozid in this setting. Furthermore, the evaluation of pharmacogenetics, especially for efflux pumps and tedizolid transporters, described a possible increased elimination of the drug, that could partially explain the low plasma concentrations. TDM and pharmacogenetics may be needed to manage and individualize antibiotic therapy especially in special populations, such as transplant patients, with difficult-to-treat infections and prolonged treatments.

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Transparency declarations

None to declare.

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