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Peripheral neuropathy during long-term suppressive therapy with tedizolid: a case series

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Background and objectives: Due to its potentially better long-term haematologic tolerance compared to linezolid, tedizolid represents an attractive option for prolonged antibiotic therapy in complicated/chronic Gram-positive infections. However, there is little information regarding the risk of peripheral neurological toxicity, representing another obstacle to the extended use of oxazolidinones. Reporting neurologic adverse events occurring during tedizolid therapy for chronic implant-associated infections.

Patients and methods: Patients experiencing tedizolid-associated neurologic adverse events were retrospectively described in a case series.

Results: Five patients (four males; age range, 65–75 years) receiving tedizolid (200 mg q24h) as long-term suppressive therapy for chronic implant-associated infection presented with peripheral neuropathy. In four cases, tedizolid was used after discontinuation of linezolid for toxicity, including one case of neuropathy. Three had at least one additional risk factor for neuropathy (including two diabetes, one of them with diabetes-related nephropathy). Neuropathic symptoms [paraesthesia (n = 2), worsening of pre-existing neuropathy (n = 2), dysesthesias (n = 1)] appeared after a median of 12.4 (IQR, 8.2–13.3) months of tedizolid treatment. Electromyoneurography (EMNG) confirmed axonal sensory polyneuropathy in all but one patient for which EMNG was still within normal ranges, but compatible with incipient neurotoxicity. Tedizolid was stopped in all patients, three patients required specific treatment for neuropathic pain. At last follow-up [2.4 (IQR, 1–2.5) years from tedizolid discontinuation], clinical recovery from neuropathy was noted in three patients. The two patients with persistent neuropathy symptoms were diabetic; one showed EMNG improvement.

Conclusions: Prolonged used of tedizolid may be associated with peripheral neurologic toxicity, which should be monitored in at-risk patients.

Introduction

Tedizolid is the second molecule in the oxazolidinone family and shares the mechanism and spectrum of activity with its predecessor, linezolid. Initially approved in 2014 for the treatment of acute bacterial skin and skin structure infections,[1] its use has since been extended to off-label indications such as bone and joint and implant-related infections.[2] Compared to linezolid, tedizolid appears to have a better safety, especially regarding haematological and neurological tolerance.[1,3] Supporting the lower toxicity of tedizolid compared to linezolid, some *in vitro* studies have shown that tedizolid may have a reduced inhibitory effect on mitochondrial protein synthesis, thereby resulting in less impairment of the mitochondrial respiratory chain, which is crucial for nervous tissue. This reduced toxicity could also be attributed to the lower dosage (200 mg q24h versus 600 mg q12h) and average molar concentration of tedizolid compared to linezolid.[4] These *in vitro* findings were further confirmed in a murine model, which showed that a 9-month therapy with tedizolid at supra-therapeutic doses did not induce mitochondrial toxicity and thus did not cause optical or peripheral neurologic toxicity.[5]

However, rare cases of tedizolid-induced optic neuritis or peripheral neuropathies have been reported.[6] We aimed to report five cases of suspected peripheral neuropathies occurring or worsening during prolonged tedizolid therapy for complicated implant-related joint and cardiovascular infections.

Patients and methods

All patients aged ≥18 years who experienced tedizolid-associated neurological adverse events in our tertiary care centre were included in a retrospective case series. Patients were identified by cross-referencing the prospective database of our reference centre for the management of complex bone and joint infection (CRIOAc Lyon) and the medical charts of our infectious disease department. Patient characteristics, tedizolid prescription modalities, neuropathy diagnosis and outcome were collected retrospectively in a standardized case report form. Imputability of adverse events was assessed by the Naranjo Adverse Drug Reaction Probability Scale.[7]

All adverse events were reported to the local pharmacovigilance centre and recorded in French national pharmacovigilance database of the French medicines agency (Agence nationale de sécurité du médicament et des produits de santé).

The study was subject to declaration with the local commission for data protection and liberties and received the approval of the Scientific and Ethical Committee of Hospices Civils de Lyon, France (reference number 25-5138). In accordance with French legislation regarding retrospective observational studies, all patients received written information about the study and their possibility to decline to participate, but the need for written informed consent was waived.

Results

Patient characteristics

Five patients with a median age of 65 (IQR, 65–72) years were included (Table 1).

All patients received tedizolid as suppressive antibiotic therapy for implant-related infections at the dose of 200 mg q24h. Of note, all patients had previously been treated with a linezolid-based regimen for a median duration of 25 days. In three cases, switch to tedizolid was prompted by linezolid toxicity, including two cases of myelotoxicity and one case of neuropathy. In this last patient, symptoms worsened under tedizolid therapy despite linezolid interruption.

Diagnostic data

Neuropathic symptoms occurred at a median of 12.4 (IQR, 8.2–13.3) months after initiation of tedizolid. Reported symptoms included paresthesias (40%), worsening of pre-existing neuropathy (40%) and dysesthesias (20%).

All patients underwent electromyoneurography (EMNG). Results are presented in Table 1. Of note, for the patient with a history of linezolid-induced neuropathy, EMNG testing was performed during tedizolid treatment but 2 weeks only after discontinuation of linezolid.

Considering drug exposure and symptom history, and confounding factors, tedizolid imputability in the occurrence of neuropathy was considered as possible for three patients, probable for one, and doubtful for another when assessed using the Naranjo Adverse Drug Reaction Probability Scale.

Outcomes

At the first follow-up visit conducted 14 (IQR, 12–20) days after tedizolid discontinuation, four out of five patients reported stable symptoms, while one had achieved clinical resolution. At the last follow-up visit conducted 2.4 (IQR, 1–2.5) years after tedizolid discontinuation, two additional patients had achieved clinical recovery from neuropathy. The remaining two patients continued to experience peripheral neuropathy symptoms, one of whom required specific therapy (patient with pre-existing diabetic neuropathy). The other patient underwent a follow-up EMNG test seven months after the initial test, showing improvement compared with the previous results.

Discussion

Suppressive antimicrobial therapy is an emerging strategy for complex device-associated infections at high risk of relapse, especially when the surgical management has likely been insufficient for infection control. Candidate antimicrobials for such prolonged therapy must be chosen based on their long-term tolerability profile, which has not been investigated in approval studies. Experience of prolonged treatment with recently labelled molecules is limited, and the cumulative risk of toxicity may be increased especially in patients with chronic infections and comorbidities. In this context, we report the first case series of patients with EMNG-documented neurological toxicity occurring during prolonged (>6 months) therapy with tedizolid. Some limitations should be address: (i) the comorbidities, especially diabetes, could have act as a favourable substrate and a confounding factor in some cases; (ii) observance could not be retrospectively assessed and no therapeutic drug monitoring was available, preventing any real exposure evaluation; and (iii) all patients developed neuropathy after previous exposure to linezolid, preventing us to formally attributed neuropathy to tedizolid rather than a cumulative toxicity of oxazolidinones. Finally, our databases do not allow us to determine how many patients received tedizolid for

Table 1. Characteristics of the five patients with neuropathy occurring during prolonged course of tedizolid therapy

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Baseline characteristics					
Sex, age (years)	Male, 72	Male, 65	Male, 65	Female, 65	Male, 75
Charlson's comorbidity index	6	3	7	5	4
Other cause of neuropathy	—	Diabetes; other neurotoxic drug (statin)	Diabetes; chronic renal failure	—	Immune-mediated disease
Index infection	Prosthetic joint infections	Prosthetic joint infections	Cardiovascular implants	Implant-associated osteomyelitis	Prosthetic joint infections
Implicated pathogen	MRSE; MSSA	MRSE	MRSE; *S. marcescens; C. glabrata*	*K. pneumoniae ESBL+*; *MRSE*	*MRSA*
Tedizolid therapy					
Previous therapy before tedizolid (duration of linezolid therapy, days)	Ciprofloxacin + linezolid (26)	Linezolid (15)	Levofloxacin + linezolid (25) + daptomycin + caspofungin	Piperacillin/ tazobactam + linezolid (44)	Linezolid (25)
Concomitant therapy with tedizolid	No	No	Levofloxacin + caspofungin	Piperacillin/ tazobactam + ciprofloxacin	No
Neuropathy description					
Time between tedizolid initiation and symptom onset or worsening (months)	13.3	2.7	12.4	8.2	25.0
Symptoms	Paraesthesia	Worsening pre-existing neuropathy	Worsening pre-existing neuropathy	Dysestesia	Paraesthesia
Localization	Hands (bilateral)	Lower limbs	Feet (bilateral)	Feet (bilateral)	Upper and lower limbs
Time between symptom onset and EMNG (days)	92	36	81	162	42
EMNG results	Severe sensory axonal polyneuropathy in upper and lower limbs	Axonal, sensory, length-dependent polyneuropathy	Axonal, sensory, length-dependent polyneuropathy	Normal (upper limits of the normal range)	Chronic axonal, sensory and motor peripheral polyneuropathy, predominantly in the lower limbs
Naranjo Adverse Drug Reaction Probability Scale	6 (Probable)	3 (Possible)	0 (Doubtful)	3 (Possible)	3 (Possible)
Tedizolid discontinuation					
Tedizolid total duration (months)	20	2.9	16.5	8.6	25.1
Antimicrobial switch	Dalbavancin	Dalbavancin	Dalbavancin	No antibiotic	Dalbavancin
Time between discontinuation of tedizolid and first follow-up visit (days)	14	11	12	97	20
Persistence of symptoms at first follow-up visit	Yes, stable	Yes, stable	Yes, stable	Yes, stable	No, resolved
Need for neuropathy treatment	Yes	Yes	Yes	No	No
Last follow-up					

Continued

Table 1. *Continued*

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Time since discontinuation of tedizolid (years)	2.6	2.5	0.9	1	2.4
Persistence of symptoms	No, resolved	Yes, improved	Yes, stable	No, resolved	No, resolved
Need for neuropathy treatment	—	No	Yes	—	—
EMNG control	No	Yes, improved	No	No	Yes, improved

EMNG, electromyoneurography; MRSE, *Methicillin-resistant Staphylococcus epidermidis*; MSSA, *Methicillin-susceptible Staphylococcus aureus*; MRSA, *Methicillin-resistant Staphylococcus aureus*; ESBL, *extended-spectrum beta-lactamase.*

suppressive purposes. Consequently, we are unable to calculate the incidence of its neurological side effects.

The safety of prolonged use of tedizolid in off-label clinical contexts has rarely been reported, especially in treatments exceeding six months.[6] In a prospective multicentre observational study published in 2020, Senneville *et al.* evaluated the tolerability of tedizolid in patients treated for prosthetic joint infection.[8] A total of 33 patients received tedizolid for a median duration of 8.8 ± 2.8 weeks (range 6–12 weeks), in combination therapy in 54.5% of cases (mainly with rifampicin, 48.5%). A total of 20 patients experienced at least one adverse event during treatment with tedizolid (with no significant differences between monotherapy and combination therapy groups), but no optical or peripheral neurological toxicities were reported. In 2023, Miller *et al.*[9] reported excellent neurological safety outcomes in an open-label non-comparative trial involving 37 patients treated with tedizolid for bone and joint infections, excluding patients with a history of peripheral or optical neuropathy and/or with uncontrolled comorbidities. Again, no adverse events were reported. However, the median duration of treatment was 12 weeks. We previously published our experience with suppressive antimicrobial therapy with tedizolid (median 6 months, IQR 2–15) in the 2021 'TediSAT' study.[10] Among the 17 included patients, eight (47%) were treated for more than 6 months (median treatment duration 15.5 months, IQR 13.7–18), with no adverse events.

No tedizolid-induced optic or peripheral neuropathy was reported in the six large-scale randomized clinical trials designed for the approval of tedizolid, in which tedizolid was prescribed for short periods (mostly 6 days, up to 21 days). A total of nine cases of tedizolid-induced neuropathy have been reported in prospective and retrospective studies published after tedizolid market approval, and recently reviewed.[6] Using a large pharmacovigilance analysis, no significant difference in the incidence of optic or peripheral neuropathy was observed between patients treated with tedizolid (n = 7/271, 2.6%) and linezolid (n = 488/11,259, 4.3%), with no information regarding treatment durations.[11]

These observations raise the question of a potential cumulative toxicity, as observed for linezolid. Indeed, the median duration of tedizolid therapy in our series was more than 12 months, largely exceeding the exposure reported in previous studies. However, the median delay in the onset of tedizolid-associated neuropathy in the FDA pharmacovigilance report was 21 days[11] and may be impacted by pre-exposure to linezolid.

Of note, some reports suggest that even slight symptoms of peripheral neuropathy may precede more severe forms, including optic neuropathy. For example, Coustilleres *et al.*[12] described a case of probable tedizolid toxicity during chronic suppressive therapy in a patient with a vascular prosthesis infection. After 8 months of treatment, the patient developed symptoms consistent with peripheral polyneuropathy. Therapy was continued and the patient developed bilateral optic neuritis with no other apparent cause, leading to presume tedizolid toxicity after 10 months of treatment. Similarly, York *et al.*[13] report a case of visual impairment following paraesthesia.

Taken all together, these data suggest that neurological adverse events should be monitored during chronic suppressive therapy with tedizolid, as they may worsen after many months or even years of therapy. Pre-existing neuropathy has not been pointed out as a determinant of oxazolidinone neuropathy but can imped the monitoring of neurological toxicity occurrence under treatment. In our view, pre-existing neuropathy does not represent a contraindication for tedizolid use, but prescribers must be particularly vigilant in this situation, and discuss the implementation of (i) therapeutic drug monitoring that has been suggested to reduce the risk of linezolid-induced toxicity while limiting overexposure[14]; and (ii) systematic EMNG evaluation at baseline and under treatment. However, in the specific case of patient experiencing linezolid-induced neuropathy, switch to tedizolid cannot be recommended in the current state of knowledge, considering the time-dependent nature of linezolid-induced neuropathy, also suspected for tedizolid, and the absence of data regarding the cumulative toxicity of both oxazolidinones.

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Transparency declarations

None to declare.

Author contributions

F.V. and T.F. designed and supervised the study. All authors participated to data collection: C.J., S.R., E.B., P.C., A.C. and F.A. for clinical data, S.G., T.B. and J.C. for pharmacological and pharmacovigilance data, and CDC for microbiological data. T.B. and J.B. centralized and computed the data. C.J., S.R., E.B., P.C., A.C., F.A., T.F. and F.V. provided medical care to the participants. T.B. and F.V. performed the descriptive analysis and drafted the article. All authors read, revised and approved the final version of the manuscript.

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