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Severe Optic Neuropathy Induced by Very Prolonged Tedizolid as Suppressive Therapy: Description of a Case Report and Implication for Better Assessment

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The long-term tolerability of linezolid is low because of mitochondrial toxicity, whereas tedizolid may represent a better option for suppressive therapy. We report a first presumed case of tedizolid-associated optic neuropathy after a very prolonged (18-month) intake and believe that screening for optic neuropathy should be considered for patients undergoing tedizolid suppression.

Keywords. optic neuropathy; oxazolidinones; suppressive therapy; tedizolid; vascular graft infections.

Oxazolidinones class has become a main option for empirical or documented treatment of gram-positive cocci infections, with many advantages including broad-spectrum, large-tissue diffusion, absence of dose-adaptation needs to renal or hepatocellular function, and excellent oral bioavailability. The antimicrobial activity is effected by inhibition of the 50S ribosomal subunit protein synthesis; however, because of structural similarities between mitochondrial and prokaryotic ribosomes, oxazolidinones may also induce clinically relevant impairment in mitochondrial protein synthesis [1]. Linezolid (LNZ), the reference oxazolidinone, has precisely been approved for the treatment of community/nosocomial-acquired pneumonia and acute bacterial skin and skin structure infections, which usually does not exceed a few days. Nonetheless, this drug presents poor long-term tolerability related to dose- and duration-dependent mitochondrial toxicity, including lactic acidosis, bone marrow suppression, and peripheral and optic neuropathy; therefore, its off label prolonged prescription (>14 days) is limited to select patients only [2–4].

In contrast, tedizolid (TDZ), second-in-class oxazolidinone, has proven efficacy in prospective trials of short-course therapy [5, 6], with a better global safety profile than LNZ, notably reduced myelotoxicity [7]. Of note, no case of optic neuritis or neuropathy has been described after TDZ therapy of up to 6 months, mostly required for vascular graft or prosthetic joint infections [8–10]. Nonetheless, data relating to longer term therapeutic use of TDZ are scarce, with only a few reports available in the current literature on tolerance outcomes [11–13]. Rare studies have also evaluated TDZ as antimycobacterial protracted therapy (1–20 months' duration), with none reporting any ophthalmological side effect; however, most patients still received this treatment for less than 6 months [14–17]. Studies using rat models have indicated that 9 months' TDZ administration at supra therapeutic dosage does not induce mitochondrial toxicity nor optic/peripheral neuropathy development [18, 19]. In vitro, TDZ has been shown to be 4- to 16-fold more potent than LNZ against most gram-positive pathogens and as a more effective mitochondrial protein synthesis inhibitor owing to additional target sites interactions [19]. However, the reduced mitochondriopathic effect could be explained by the lower dosage regimen and intake spacing (200 mg daily), allowing mitochondrial recovery at therapeutic dose, along with higher plasma-binding protein, decreased central nervous system and bone diffusion, and reduced accumulation phenomenon [13, 19, 20].

Altogether, it appears that TDZ may be generally safer than LNZ for prolonged use, but the outcomes for very long term use are poorly understood. To the best of our knowledge, we describe here the first presumed case of optic neuropathy induced by 18 months of TDZ administration as suppressive therapy in a nonoperable 60-year-old man after 3 years of management for vascular prosthesis infection. Durable blindness severely affected the patient's quality of life, leading to the decision of active medical support interruption, which resulted in death.

CASE PRESENTATION

A 57-year-old man with a history of aorto-bi-iliac prosthesis implantation for aneurysm 2 years before presentation, with coronaropathy and active smoking (40 pack-years) consulted in 2019 for afebrile back pain. Computed tomography (CT) revealed a large abscess sheathing the right iliac branch

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prosthesis, and the patient was referred to a tertiary center for complete prosthesis removal and reconstruction by pericardial patch and omentoplasty. Postoperatively, he received piperacillin–tazobactam, daptomycin, and caspofungin because sample cultures revealed *Escherichia coli* and anaerobes. Unfortunately, evolution was unfavorable, with relapsing massive digestive bleeding resulting from an anastomotic leak from the inferior mesenteric artery insertion, despite 2 additional surgical interventions with anastomotic repair. Of note, a suffering jejunal loop sticking to the periprosthetic aneurismal bag could not be resected because of patient hemodynamic instability. Finally, in situ aorto right iliac endoprosthesis implantation plus surgical femorofemoral bridge was performed, then antimicrobial therapy was upgraded with meropenem and Mycamine. Postoperative CT revealed increased airy components inside the aneurysmal bag, but the patient did not present with digestive bleeding anymore. Thus, medical staff decided against any additional surgery and initiated suppressive therapy with intravenous ertapenem and oral fluconazole, which was continued at home for 8 months.

The patient moved for family reasons and attended follow-up at our infectious disease department in May 2020. Because he mentioned intravenous injection weariness and intolerance to subcutaneous administration, many antibiotic simplifications were attempted but all failed from side effects (clindamycin–co-trimoxazole association causing hepatitis) or bacteremia/fungemia recurrences, notably with vancomycin-susceptible *Enterococcus faecium* and fluconazole-resistant *Candida glabrata* (doxycycline 100 mg orally twice daily or ceftriaxone 2 g intravenously daily monotherapy). Then, duodeno-prosthetic fistula concerning the third portion of the duodenum was revealed via CT imaging; hence, surgical duodenal disconnection and periprosthetic collection debridement were performed in December 2020. Meropenem, oral TDZ 200 mg daily, and caspofungin were administered postoperatively. The decision to use TDZ as the primary therapy was supported by experiences of the team with poor tolerance outcomes of prolonged linezolid (myelosuppression) or daptomycin (eosinophilic pneumonia). Unfortunately, a routine CT scan examination showed periprosthetic collection reconstitution fusing to the median laparotomy scar via a new fistulous route, although blood cultures remained sterile. Treatment was continued for 6 months; thereafter, a new regimen of antibiotic simplification was attempted (meropenem switch by intravenous amikacin 3 times a week) but led to resurgence of bacteremia with *Pseudomonas aeruginosa* resistant to all non-novel beta-lactams. Then, ceftazidime–avibactam, TDZ, and caspofungin was initiated and maintained as suppressive therapy because any additional surgery was unreasonable. The medical team reevaluated the situation every 3 months and confirmed treatment maintenance as patient quality of life and autonomy were preserved.

After an 8-month course of this triple antimicrobial therapy, the patient reported symptoms of painful feet and legs. Peripheral neuropathy was suspected but could not be confirmed because of electromyogram intolerance. Platelet, red blood cell, and white cell counts were unmodified (respective minimal value: hemoglobin, 9.7 g/dL; platelet count, 336×10^9/L, white blood cell count, 8.1×10^9/L), as was serum creatinine level (1.27 mg/dL). Lactic acid levels were normal (1.3 mmol/L). Ophthalmologic evaluation revealed bilateral corticonuclear cataracts, whereas both macular and optic nerve optical coherence tomography results were normal and stable at the 3-month follow-up. The best-corrected visual acuity was 20/25 and 20/20 for the left and right eyes, respectively. Because clinical TDZ-induced neurotoxicity had not been described previously, its implication on painful symptoms was considered uncertain, and treatment was continued according to patient's preference. Symptoms remained stable thereafter.

Nine months later, while the patient was still treated with ceftazidime–avibactam, TDZ, and caspofungin, he underwent bilateral phacoemulsification for progressive cataract, which led to decreased vision (20/50 and 20/200 in right and left eyes, respectively). A vision test performed 1 month postoperatively revealed no improvement (<20/200 bilaterally). The P100 wave was not identified on pattern reversal and was normal on flash visual-evoked potentials, whereas automated perimetry of the 30 central degrees and macular optical coherence tomography were highly suggestive of bilateral severe optic neuropathy related to mitochondrial dysfunction (Figure 1). The patient reported following a normal diet, especially concerning vitamin B1 intake. At this time, he was also being treated for ischemic heart disease by ramipril, bisoprolol, eplerenone, clopidogrel, and lansoprazole. Investigations did not find any other potential drug in past or daily patient therapy that are known to cause optic neuritis manifestations (eg, quinolones, amiodarone, phosphodiesterase type 5 inhibitors, antimycobacterial and antitumoral drugs). According to the Naranjo adverse drug reaction probability scale [21], there was a probable relationship (total score = 5) between this adverse drug event and TDZ therapy. TDZ was suspected as the causal agent because of its mitochondria-mediated effect and was immediately ceased and replaced with dalbavancin 1500 mg administered every 2 weeks. Two months after the drug interruption, there was no improvement and the patient remained legally blind (<20/200 in both eyes), with subsequent loss of autonomy and impaired vision-related quality of life. Bleeding from the laparotomy median scar occurred, requiring iterative red cell transfusions, whereas CT failed to identify the source of bleeding. The medico-surgical team decided to withdraw antimicrobial therapy and transfusions. He was started on exclusive palliative management and died a few days later.

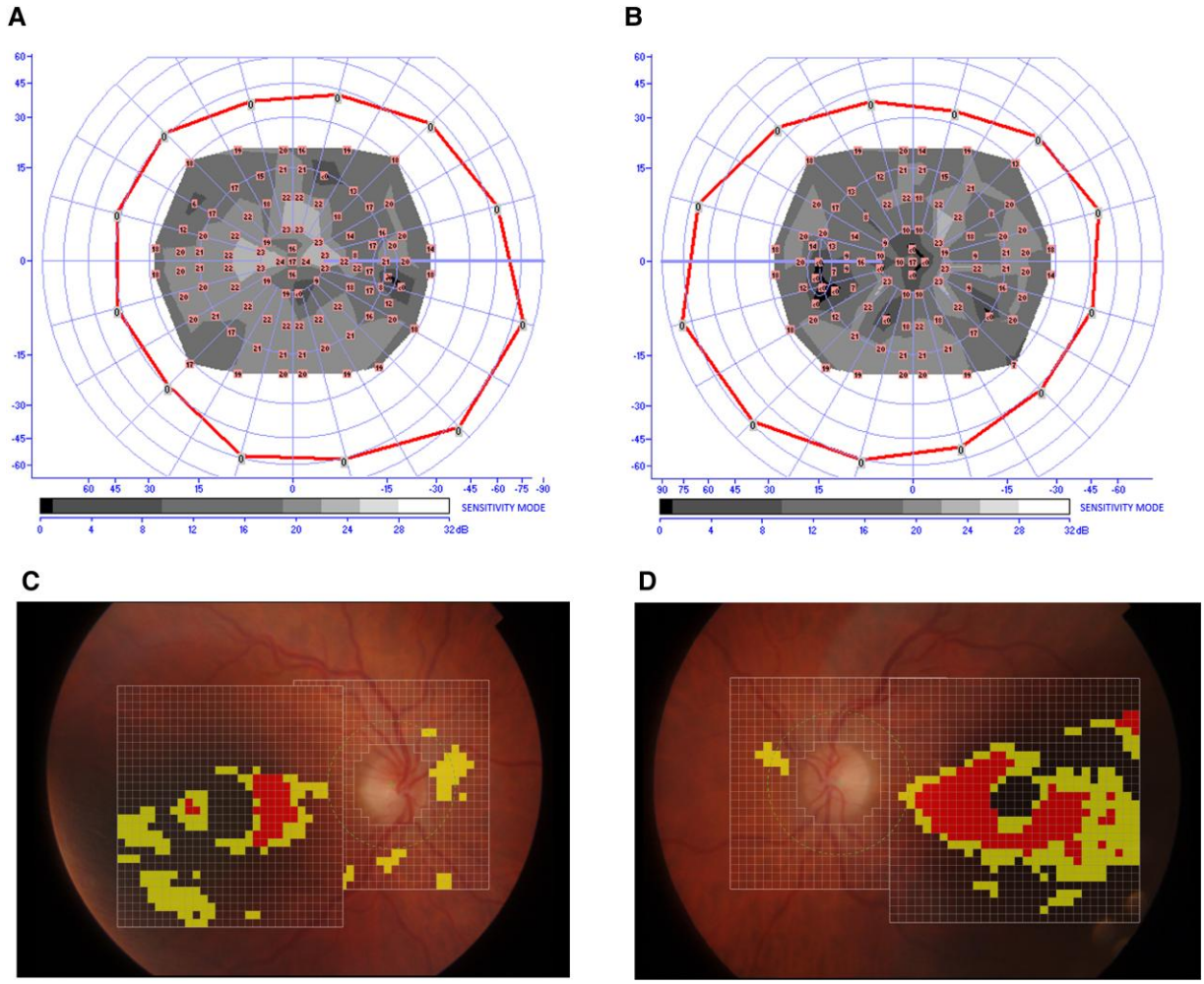

Figure 1. Ophthalmological examination revealing signs of bilateral optic neuropathy-related to mitochondrial dysfunction. Right (*A*)/left (*B*) eye automated perimetry of the 30 central degrees (Metrovision): cecocentral scotoma with reduced foveal threshold to 17 decibels in both eyes. Right (*C*)/left (*D*) macular and papillary optical coherence tomography: bilateral severe thinning of the ganglion cell inner layer in the papillomacular bundle with additional temporal thinning in the left eye.

DISCUSSION

To the best of our knowledge, this is the first described case of presumed optic neuropathy following TDZ therapy. Aortic prosthesis infections are severe conditions with challenging management, high relapse, and mortality rate [22], especially when surgical graft explantation cannot be performed [23]. In this singular case, each attempt of suppressive treatment spectrum reduction failed because of relapsing bacteremia during the patient's 3-year survival, necessitating continuation of broad-spectrum therapy including TDZ.

The patient in the present case had severe comorbidities, risk factors for optic neuritis such as smoking, and previous or concomitant multiple drug expositions; thus, it could be argued that the etiology was multifactorial. Nonetheless, the highly suggestive pattern of mitochondrial dysfunction-related event strongly suggests TDZ involvement. We did not find any reported case of optic neuropathy after exposition of echinocandin or cephalosporin class drugs or patient's cardiovascular medications in the literature and the French pharmacovigilance database. Moreover, patients undergoing suppressive antibiotic therapy are frequently severely ill and under polypharmacy [23, 24]; thus, the present case is not isolated and TDZ-associated optic neuropathy could recur in other situations. In this description, the late but rapid worsening of visual acuity is intriguing, and the delay between visual loss and drug interruption might have contributed to the absence of improvement 3 months after TDZ discontinuation. In most cases (>90%), LNZ-induced optic neuropathy manifestations improve a few weeks or months after drug interruption, whereas peripheral neuropathy (associated in 50% of cases) is irreversible in more than 2 of 3 cases [4, 25].

The premarketing safety summary of TDZ relates to 6 days treatment duration only [5–7], and very few ophthalmological

side effects of short- or long-therapy have been reported so far, mostly dry eye, pruritus, hyperemia, and transient blurred vision or light bursts that contrast with findings of normal ophthalmological examination [9, 10, 26]. Despite the well-known potential of oxazolidinones to cause mitochondrial toxicity, there are no clear guidelines specifying the need for ophthalmologic monitoring during prolonged therapy. LNZ-induced optic neuropathy occurs in 1.3%–13.2% of treated patients, depending on the duration of exposure, and in most cases after 1–10 months' intake [2–4, 25, 27, 28], with later onsets being rare. It could be speculated that TDZ-associated optic neuropathy might be only deferred compared with LNZ and may occur at a similar frequency for longer intake durations. Thus, we believe that visual modification occurring during TDZ therapy should be investigated and ophthalmologic follow-up may be considered for patients taking TDZ for more than 6 months.

The tolerance profiles of new drugs deserve further investigations when prescribed as suppressive therapy, because their safety profiles may differ to a great extent compared with on-label use. It is interesting to note that ceftazidime-avibactam and caspofungin were well tolerated for the entire duration (11 and 20 months, respectively), as tolerance reports are lacking for very prolonged administration of these drugs. Finally, little is known about monitoring TDZ plasma concentration and/or dose reduction benefit for the prevention of toxicity. Some data suggest that monitoring LNZ antimycobacterial therapy could be helpful for reducing mitochondrial toxicity and improve long-term tolerance [29, 30]. Thus, pharmacological studies might be useful for TDZ suppressive therapy.

CONCLUSION

Optic neuropathy may occur after prolonged TDZ therapy. More safety data are needed for very long duration prescription, peculiarly for suppressive therapy.

Notes

Author contributions. F.C., E.M.T., S.O., M.O.N.P, and M.L.L.L. were in charge of the patient. M.L.L.L. provided iconography. F.C., R.K.K., and M.L.L.L. wrote the original draft. E.M.T., S.O., M.O., and N.P. reviewed and edited the manuscript.

Consent for publication. Oral consent for publication was obtained while the patient was alive. His 2 daughters have given consent for publication; written consent is available on request.

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