Journal of Infection and Chemotherapy 28 (2022) 1023–1028

Contents lists available at ScienceDirect

Journal of Infection and Chemotherapy

journal homepage: www.elsevier.com/locate/jic

Note

Correction of thrombocytopenia caused by linezolid with scheduled sequential tedizolid use in patients with vertebral osteomyelitis by antibiotic resistant Gram-positive organisms

Takashi Ueda [a,*], Kazuhiko Nakajima [a], Kaoru Ichiki [a], Kaori Ishikawa [a], Kumiko Yamada [a,b], Toshie Tsuchida [a], Naruhito Otani [c], Yoshiko Takahashi [d], Mika Ishihara [d], Shingo Takubo [d], Kosuke Iijima [b], Hiroki Ikeuchi [e], Motoi Uchino [e], Takeshi Kimura [d], Yoshio Takesue [a,f]

[a] Department of Infection Control and Prevention, Hyogo College of Medicine, Nishinomiya, Hyogo, Japan
[b] Department of Clinical Technology, Hyogo College of Medicine, Hyogo, Japan
[c] Department of Public Health, Hyogo College of Medicine, Nishinomiya, Nishinomiya, Hyogo, Japan
[d] Department of Pharmacy, Hyogo College of Medicine Hospital, Nishinomiya, Hyogo, Japan
[e] Department of Inflammatory Bowel Disease, Hyogo College of Medicine, Nishinomiya, Hyogo, Japan
[f] Department of Clinical Infectious Diseases, Tokoname City Hospital, Tokoname, Aichi, Japan

ARTICLE INFO

Keywords:
Tedizolid
Linezolid
Thrombocytopenia
Vertebral osteomyelitis
Methicillin-resistant *Staphylococcus aureus*

ABSTRACT

Introduction: Because of thrombocytopenia, linezolid treatment tends to be stopped before the completion of therapy for complicated infections that require prolonged antimicrobial administration. In contrast, tedizolid shows a favorable hematologic profile. The primary end-point of this study was to evaluate the efficacy of switching treatment to tedizolid in patients who developed thrombocytopenia during linezolid therapy.

Methods: This retrospective study was conducted in patients with vertebral osteomyelitis (VO) caused by antibiotic-resistant Gram-positive bacteria. Treatment failure was defined as the reappearance of infection signs within 2 weeks after stopping tedizolid and discontinuation of tedizolid because of continued thrombocytopenia or other adverse effects.

Results: Eight patients with native VO (n = 3) and postoperative VO (n = 5) were included in the study. The causative organisms were MRSA in all patients except one. Platelet counts decreased from $35.2 \pm 11.5 \times 10^4/mm^3$ to $17.8 \pm 6.2 \times 10^4/mm^3$ during linezolid therapy and improved without washout period in all patients after switching to tedizolid on days 5–7 ($28.6 \pm 4.9 \times 10^4/mm^3$, p = 0.002). Tedizolid therapy was completed and treatment failure was not observed in any patient. The duration of treatment was 20.0 ± 11.2 days for linezolid and 30.3 ± 9.5 days for tedizolid (total, 50.3 ± 10.7 days). One patient died because of underlying disease, and there was no recurrence in the remaining 7 patients (median follow-up 501 days).

Conclusions: Switching therapy to tedizolid improved thrombocytopenia that occurred during linezolid therapy, and it enabled the completion of therapy for VO patients.

Oxazolidinones are a class of antibiotics that are widely used for the treatment of antibiotic-resistant Gram-positive organisms including methicillin-resistant *Staphylococcus aureus* (MSRA). These antibiotics have a novel model of action; they inhibit bacterial protein synthesis by binding to the 50S ribosomal subunit and impair mitochondrial protein synthesis [1]. The prolonged use of linezolid is associated with side effects, such as myelosuppression, lactic acidosis and peripheral neuropathies, and the inhibition of mitochondrial protein synthesis is thought to be the underlying mechanism for these effects [1].

Vertebral osteomyelitis is mainly caused by hematogenous seeding of the adjacent disc space from a distant focus or direct inoculation of micro-organisms into the spine caused by trauma or surgery [2].

* Corresponding author. Department of Infection Control and Prevention, Hyogo College of Medicine, 1-1 Mukogawa-cho, Nishinomiya, Hyogo, 663-8501, Japan.
E-mail addresses: taka76@hyo-med.ac.jp (T. Ueda), nakajima@hyo-med.ac.jp (K. Nakajima), ichiki@hyo-med.ac.jp (K. Ichiki), i-kaori@hyo-med.ac.jp (K. Ishikawa), yamakumi@hyo-med.ac.jp (K. Yamada), tsuchida@huhs.ac.jp (T. Tsuchida), n-otani@hyo-med.ac.jp (N. Otani), yktabu@hyo-med.ac.jp (Y. Takahashi), ykkura@hyo-med.ac.jp (M. Ishihara), stakubo@hyo-med.ac.jp (S. Takubo), ko-iizima@hyo-med.ac.jp (K. Iijima), ikeuci2s@hyo-med.ac.jp (H. Ikeuchi), uchino2s@hyo-med.ac.jp (M. Uchino), t-kimura@hyo-med.ac.jp (T. Kimura), takesuey@hyo-med.ac.jp (Y. Takesue).

https://doi.org/10.1016/j.jiac.2022.04.003
Received 4 January 2022; Received in revised form 16 March 2022; Accepted 3 April 2022
Available online 25 April 2022

Linezolid has provided good efficacy in difficult-to-treat vertebral osteomyelitis from resistant Gram-positive organisms [3]. Rayner et al. [4] reported that linezolid was successful in treating patients with osteomyelitis caused by resistant Gram-positive organisms, and a reduction in hemoglobin/hematocrit and platelet counts was the most common adverse effect. Takahashi et al. [5] reported that linezolid treatment ≥14 days, creatinine clearance (<50 mL/min) and respiratory tract infection were independent risk factors for thrombocytopenia. Although 6–8 weeks of pathogen-directed antibiotic therapy may be sufficient for low-risk patients with hematogenous vertebral osteomyelitis, prolonged duration of treatment (≥8 weeks) is required for patients with MRSA. Because of the adverse effects, patients tend to discontinue linezolid before the completion of therapy [5].

Tedizolid is a novel oxazolidinone and has additional target site interactions, as reflected in its lower minimum inhibitory concentration (MIC) against Gram-positive pathogens compared with that of linezolid [6]. The absolute oral bioavailability of tedizolid after a single 200 mg dose of tedizolid was 91%; the pharmacokinetic parameters of tedizolid were similar to those of oral and intravenous administration [7]. In phase 3 clinical trial, tedizolid showed noninferior efficacy relative to that of linezolid for the management of acute bacterial skin and skin structure infection [8]. Furthermore, compared with linezolid, tedizolid was associated with lower rates of thrombocytopenia during study days 11–13 [9]. In a recent study, long-term use of tedizolid resulted in lower myelotoxicity than linezolid in osteoarticular infections and prosthetic joint infections [10]. The primary end-point of this study was to evaluate the efficacy to continue oxazolidinone therapy with switching to tedizolid in patients with vertebral osteomyelitis who developed thrombocytopenia during linezolid therapy.

This retrospective study was conducted between August 2018 and November 2021. The study was approved by the ethics committee of Hyogo College of Medicine (No. 3558). Initially, we searched for patients with infection from antibiotic-resistant Gram-positive bacteria who used tedizolid because of thrombocytopenia induced by linezolid. Among these patients, adult patients with vertebral osteomyelitis were included in the study.

Patients were diagnosed using criteria from clinical practice guidelines for the diagnosis and treatment of native vertebral osteomyelitis in adults by the Infectious Diseases Society of America [11]. Spine magnetic resonance imaging was performed in patients with suspected vertebral osteomyelitis. Patients with culture-negative pyogenic vertebral osteomyelitis were excluded. Causative organisms were determined by blood cultures or aspiration biopsy and by specimens obtained during debridement procedure. Management was carried out by an orthopedic surgeon, and debridement surgery and removal or exchange of orthopedic devices was performed when necessary. Antibiotic treatment was supervised by the antimicrobial stewardship (AS) team.

Patient comorbidities, antibiotics with activity against MRSA before use of linezolid and reasons for linezolid use, treatment duration and potential adverse events attributable to linezolid/tedizolid were recorded. Leucopenia was defined as a total leucocyte count of $<4 \times 10^9$/L. Anemia was defined as an unexplained ≥2 g/dL reduction in hemoglobin levels, and thrombocytopenia was defined as a reduction in the platelet count to ≥25% from baseline [12]. During linezolid therapy, blood data were monitored at least twice a week; when there was a tendency of decrease in platelet count, the AS team determined whether to reduce the dose of linezolid or change to other anti-MRSA drugs including tedizolid.

Treatment success was defined as no clinical evidence of infection and no need for antibiotics or surgical treatment until two weeks after the end of tedizolid therapy. Oral antibiotics with activity against causative organisms could be used following tedizolid therapy. Treatment failure was defined as reappearance of infection signs within 2 weeks after stopping tedizolid, discontinuation of tedizolid because of continued thrombocytopenia or other adverse effects, no improvement despite active treatment with tedizolid, need for suppressive antibiotic therapy to control infection or death related to infection [11]. We also conducted a follow-up study to determine any relapses after discharge.

Statistical analyses were performed using SPSS ver. 24 (SPSS Inc., Chicago, IL, USA). The level of significance was set at $p < 0.05$.

During the study period, 19 patients were treated with tedizolid, and 11 of these patients (57.9%) were treated with tedizolid because of thrombocytopenia caused by linezolid. The infection types were as follows: vertebral osteomyelitis in eight patients, and pyogenic knee arthritis, bronchial pneumonia and septic pulmonary embolism in one patient each. Finally, eight patients with native vertebral osteomyelitis (n = 3) and postoperative vertebral osteomyelitis (n = 5) were included in the study. Information on patient background and antibiotic use is summarized in Tables 1 and 2. The causative organisms were MRSA in seven patients and *Enterococcus faecium* in one patient. The MIC of linezolid was 2 μg/mL for MRSA in the seven patients and ≤2 μg/mL for *E. faecium*. The MIC of tedizolid was not available. The organisms were isolated from blood cultures in six patients and from specimens taken intraoperatively in four patients (two patients had both blood culture and specimens available for analyses). No patient was diagnosed by aspiration biopsy. No anti-MRSA drug or other type of antibiotics was used during tedizolid therapy. Surgical intervention was indicated in four patients. The debridement procedure was conducted within one week after the diagnosis of vertebral osteomyelitis in three patients and after one week in one patient. This intervention was not performed after the use of tedizolid. Secondary bacteremia was observed in six patients. Adjacent tissue expansion of infection was confirmed in four patients (epidural abscess [n = 3] and iliopsoas abscess [n = 2]).

The dosage of linezolid was 600 mg twice daily; in one patient (patient No. 1), the dosage was reduced to 400 mg twice daily because of thrombocytopenia (platelet count 13.6×10^4 cells/mm^3 at the start of linezolid therapy to 10.2×10^4 cells/mm^3 on day 13). Tedizolid was administered orally at 200 mg once daily in all patients. There was no washout period, and an immediate switch from linezolid to tedizolid was performed for all patients. No patient received concomitant treatment of drugs that interacted with oxazolidinones during linezolid and tedizolid therapy, such as mono-amino oxidase inhibitors, selective serotonin reuptake inhibitors, opioids and anticonvulsant drugs. The number of days from debridement to linezolid therapy, complications of disseminated intravascular coagulation syndrome, and history of drugs administered are shown in Supplementary Table 1.

Platelet count decreased from $35.2 \pm 11.5 \times 10^4$/mm^3 to $17.8 \pm 6.2 \times 10^4$/mm^3 during linezolid therapy (reduction rate compared with baseline: median 48.8%, ranging from 43.4% to 55.6%). Thrombocytopenia continued in four of eight patients on days 3–4 after changing to tedizolid and improved in all patients on days 5–7 ($28.6 \pm 4.9 \times 10^4$/mm^3 vs. the platelet count at the end of linezolid therapy, p = 0.002). The improved platelet count was sustained throughout tedizolid therapy ($32.2 \pm 4.3 \times 10^4$/mm^3 at the end of therapy) (Fig. 1). Thrombocytopenia continued in four of eight patients on days 3–4 of tedizolid therapy (patient No. 4, 6, 7 and 8), but increased on days 5–7, indicating that thrombocytopenia had recovered in all patients and tedizolid treatment was complete. There was no significant difference in the duration of linezolid therapy, linezolid dose, or eGFR at the start and end of linezolid therapy between patients who did or did not thrombocytopenia continued on days 3–4 of tedizolid therapy (median duration of linezolid therapy: 22 days vs 16 days, p = 0.468, median linezolid daily per kg dose: 22.0 mg/kg/day vs 15.7 mg/kg/day, p = 0.149, median eGFR at the start of linezolid therapy: 93.0 mL/min/1.73 m^2 vs 77.0 mL/min/1.73 m^2, p = 0.564, median eGFR at the end of linezolid therapy: 91.5 mL/min/1.73 m^2 vs 75.5 mL/min/1.73 m^2, p = 0.623). No adverse reactions such as leucopenia or anemia were observed during either the linezolid or tedizolid treatment period. Although patient No. 8 developed nausea on the sixth day of tedizolid administration, tedizolid could be continued with the use of metoclopramide.

Clinical response was obtained with linezolid therapy in all patients, and response was sustained even after the change to tedizolid

Table 1
Baseline demographics of patients included in the study.

No	Gender	Age (years)	Body weight (kg)	eGFR[a] (mL/min/1.73m^2)	Underlying disease	Classification of vertebral osteomyelitis	Isolated Gram-positive cocci	Location of infected vertebrae	Secondary bacteremia	Complication of vertebral osteomyelitis
1	Male	60	76.8	75	Mitral regurgitation, heart failure, rheumatoid arthritis	Hematogenous	MRSA	Lumbar 4/5	Yes	Spinal epidural abscess, iliopsoas muscle abscess
2	Male	52	76.5	99	None	SSI after the surgery for spinal canal stenosis	MRSA	Thoracic 7	Yes	Spinal epidural abscess
3	Male	77	76.1	56	Nephrosclerosis	SSI after the surgery for spinal scoliosis	MRSA	Lumbar 1/2	Yes	Spinal epidural abscess
4	Male	77	54.0	127	Benign prostatic hyperplasia	SSI after the surgery for spinal canal stenosis	MRSA	Lumbar 3/4	Yes	Iliopsoas muscle abscess
5	Female	83	41.4	79	Multiple myositis	Hematogenous	MRSA	Lumbar 5, sacrum 1	Yes	None
6	Male	74	62.3	59	Hypertension	SSI after the surgery for herniated lumbar disk	MRSA	Lumbar 3/4	No	None
7	Male	68	55.0	157	Cronkhite–Canada syndrome	SSI after the surgery for spinal canal stenosis	MRSA	Lumbar 4/5	No	None
8	Female	89	39.2	57	Severe aortic stenosis, chronic kidney disease	Hematogenous	*Enterococcus faecium*	Lumbar 1/2	Yes	None

MRSA, methicillin-resistant *Staphylococcus aureus*.
[a] eGFR at the start of linezolid therapy.

(Supplementary Fig. 1). All eight patients (100%) met the definition of treatment success two weeks after the end of tedizolid therapy. The duration of treatment was 20.0 ± 11.2 days for linezolid and 30.3 ± 9.5 days for tedizolid, and the total duration of oxazolidinone antibiotics was 50.3 ± 10.7 days (over 6 weeks) in all patients (Table 2). In seven patients with vertebral osteomyelitis by MRSA, sequential oral step-down therapy was performed (16–70 days) (Table 2). Oral medication that showed antibacterial activity against the isolate was not available in one patient with vertebral osteomyelitis by *E. faecium*. One patient died of underlying disease (acute decompensated heart failure). The other seven patients had no recurrence of vertebral osteomyelitis (median follow-up 501 days).

Switching therapy to tedizolid in patients with thrombocytopenia induced by linezolid provided good efficacy for vertebral osteomyelitis in eight patients. In addition, the oral bioavailability of tedizolid was 91% [7], and thus good efficacy was obtained in this study. The thrombocytopenia in this study was thought to be linezolid-induced myelotoxicity, since no other concomitant drugs were discontinued and the thrombocytopenia improved after linezolid discontinuation. There was no need for any washout period after linezolid-induced myelotoxicity, and early recovery of thrombocytopenia within 7 days was confirmed with the immediate start of tedizolid. In addition, no subsequent new toxicity occurred despite the prolonged use of tedizolid in all patients. Yuste et al. [13] performed a 26-day washout period without linezolid before introducing tedizolid in a patient with linezolid-induced thrombocytopenia. However, Khatchatourian et al. [14] reported rapid correction after the immediate switch to tedizolid in two of three cases with linezolid-induced myelotoxicity.

In our institution, glycopeptides or daptomycin [15] are used as first-line therapy for patients with vertebral osteomyelitis by MRSA, and linezolid is alternatively used as second-line therapy. If mild to moderate thrombocytopenia is observed from linezolid therapy, the dose is decreased in patients with impaired renal function [16] or planned switch therapy with tedizolid is scheduled. At least six weeks of antimicrobial therapy was suggested by the AS team. The duration of treatment with additional oral antibiotics was 16–70 days at the discretion of the attending physician in the outpatient setting.

Multivariable analysis indicated that end stage renal disease, MRSA infection and undrained paravertebral/psoas abscesses were independent baseline risk factors for recurrence in vertebral osteomyelitis [2]. Although 6–8 weeks of pathogen-directed antibiotic therapy may be sufficient for patients with hematogenous vertebral osteomyelitis without these risk factors, prolonged duration (≥8 weeks) of treatment is recommended for patients with any of these factors. With this definition, seven of the eight patients in this study were classified as high-risk VO.

This study has several limitations. First, the patients were evaluated retrospectively in this study. Second, patients with postoperative and hematogenous vertebral osteomyelitis were included in this study, and the treatment policy might be different between these patient groups. Third, we did not demonstrate the clinical efficacy of the sequential therapy with oxazolidinones as first-line therapy for vertebral ostemomyelitis. If further studies confirm the efficacy of oxazolidinones as an initial therapy, sequential therapy with tedizolid would be indicated in a higher number of patients with vertebral osteomyelitis. Finally, only one of eight patients showed a platelet count of less than $10 \times 10^4/mm^3$ during linezolid therapy, and the usefulness of tedizolid to recover severe thrombocytopenia was not addressed in this study.

In conclusion, switching of therapy from linezolid to tedizolid without a washout period improved thrombocytopenia caused by linezolid, and oxazolidinone therapy was completed in all patients with vertebral osteomyelitis by antibiotic-resistant Gram-positive organisms (primarily MRSA).

Funding

This research received no external funding.

Authorship statement

All authors meet the ICMJE authorship criteria.

Table 2
Administered anti-MRSA drug for the treatment of vertebral osteomyelitis.

No	Antibiotics with anti-MRSA activity before the administration of linezolid	Debridement	Reasons for the use of linezolid	linezolid			Tedizolid			Total duration of oxazolidinones (day)	Oral antibiotics after tedizolid therapy		Treatment success	Recurrence (days of Follow-up)
				Dose (/day)	Route of administration	Duration of therapy (day)	Dose (/day)	Route of administration	Duration of therapy (day)		Oral antibiotics	Duration of therapy (days)		
1	Daptomycin	No	Treatment failure	600mg × 2 →400mg × 2	IV	16	200mg × 1	PO	30	46	Rifampicin; sulfamethoxazole-trimethoprime	30	Yes	No (69[a])
2	Teicoplanin, daptomycin	No	Treatment failure	600mg × 2	IV → PO	7	200mg × 1	PO	36	43	Rifampicin; sulfamethoxazole-trimethoprime	28	Yes	No (598)
3	Daptomycin	Yes	Treatment failure	600mg × 2	IV → PO	21	200mg × 1	PO	21	42	Rifampicin; minocycline	28	Yes	No (286)
4	Daptomycin	Yes	Daptomycin resistant (MIC: 2μg/mL)	600mg × 2	IV → PO	43	200mg × 1	PO	25	68	Rifampicin; , levofloxacin	56	Yes	No (501)
5	Teicoplanin, daptomycin	No	Side effects (CPK elevation)	600mg × 2	PO	15	200mg × 1	PO	27	42	Sulfamethoxazole-trimethoprime, minocycline	16	Yes	No (212)
6	daptomycin	Yes	Side effects (CPK elevation and skin eruption)	600mg × 2	IV → PO	15	200mg × 1	PO	28	43	Rifampicin; minocycline	70	Yes	No (853)
7	Vancomycin, daptomycin	Yes	Side effects (CPK elevation)	600mg × 2	IV → PO	29	200mg × 1	PO	24	53	Rifampicin; sulfamethoxazole-trimethoprime	30	Yes	No (429)
8	teicoplanin	No	Side effects (skin eruption)	600mg × 2	IV → PO	14	200mg × 1	PO	51	65	None	None	Yes	No (536)

MRSA, methicillin-resistant *Staphylococcus aureus*; IV, intravenous injection, PO, oral administration; CPK, creatine phosphokinase; MIC, minimum inhibitory concentration.
[a] Died from the underlying disease.

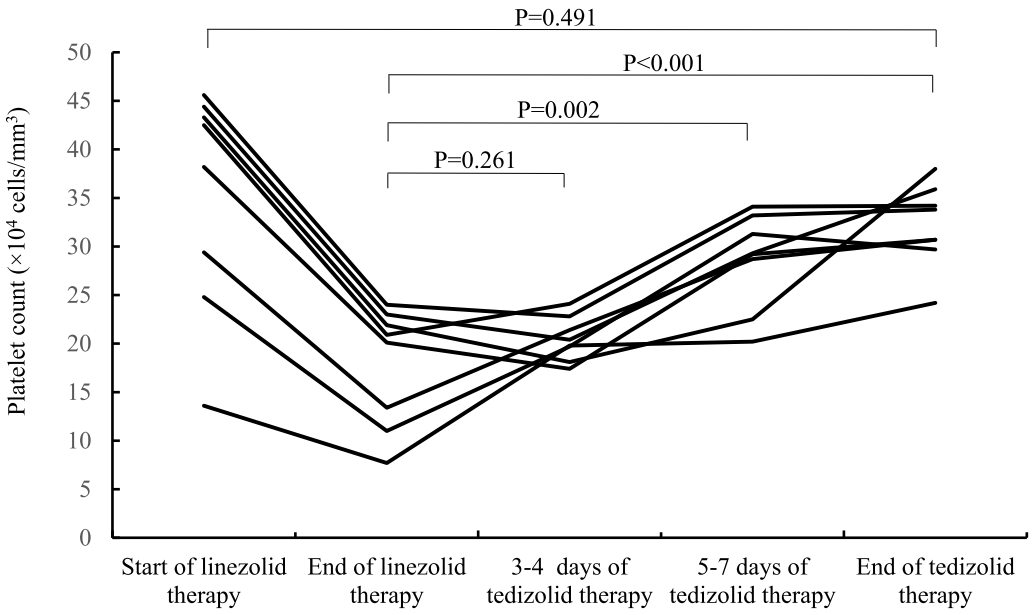

Fig. 1. Changes in platelet counts during linezolid and tedizolid administration. Platelet counts were 35.2 ± 11.5 × 10^4 cells/mm^3 at the start of linezolid therapy, 17.8 ± 6.2 × 10^4 cells/mm^3 at the end of linezolid therapy, 20.5 ± 2.3 × 10^4 cells/mm^3 on days 3–4 of tedizolid therapy, 28.6 ± 4.9 × 10^4 cells/mm^3 on days 5–7 of tedizolid therapy and 32.2 ± 4.3 × 10^4 cells/mm^3 at the end of tedizolid therapy.

Authors' contributions

Takashi Ueda was involved in study conception; data collection, analysis and interpretation; creation of new software used in the work; and manuscript writing and revision. Yoshio Takesue was involved in the design of the study and drafting of the manuscript. Kazuhiko Nakajima, Kaoru Ichiki, Kaori Ishikawa, Kumiko Yamada, Toshie Tsuchida, Naruhito Otani, Yoshiko Takahashi, Mika Ishihara, Shingo Takubo, Kosuke Iijima, Hiroki Ikeuchi, Motoi Uchino and Takeshi Kimura contributed to data collection and interpretation. All authors provided substantial input to the drafting and review of the manuscript, and all authors approved the final version prior to publication.

Declaration of competing interest

Y. Takesue received grant support from Shionogi & Co., Ltd. and payment for lectures from Astellas Pharma Inc. and MSD Japan. The other authors have no conflict of interest to declare.

Acknowledgements

We thank Gabrielle White Wolf, PhD, from Edanz (https://jp.edanz.com/ac) for editing a draft of this manuscript.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jiac.2022.04.003.

References

[1] Leach KL, Swaney SM, Colca JR, McDonald WG, Blinn JR, Thomasco LM, et al. The site of action of oxazolidinone antibiotics in living bacteria and in human mitochondria. Mol Cell 2007;26:393–402. https://doi.org/10.1016/j.molcel.2007.04.005.

[2] Park KH, Cho OH, Lee JH, Park JS, Ryu KN, Park SY, et al. Optimal duration of antibiotic therapy in patients with hematogenous vertebral osteomyelitis at low risk and high risk of recurrence. Clin Infect Dis 2016;62:1262–9. https://doi.org/10.1093/cid/ciw098.

[3] Senneville E, Legout L, Valette M, Yazdanpanah Y, Beltrand E, Caillaux M. Effectiveness and tolerability of prolonged linezolid treatment for chronic osteomyelitis: a retrospective study. Clin Therapeut 2006;28:1155–63. https://doi.org/10.1016/j.clinthera.2006.08.001.

[4] Rayner CR, Baddour LM, Birmingham MC, Norden C, Meagher AK, Schentag JJ. Linezolid in the treatment of osteomyelitis: results of compassionate use experience. Infection 2004;32:8–14. https://doi.org/10.1007/s15010-004-3029-9.

[5] Takahashi Y, Takesue Y, Nakajima K, Ichiki K, Tsuchida T, Tatsumi S, et al. Risk factors associated with the development of thrombocytopenia in patients who received linezolid therapy. J Infect Chemother 2011;17:382–7. https://doi.org/10.1007/s10156-010-0182-1.

[6] Locke JB, Finn J, Hilgers M, Morales G, Rahawi S, G C K, et al. Structure-activity relationships of diverse oxazolidinones for linezolid-resistant Staphylococcus aureus strains possessing the cfr methyltransferase gene or ribosomal mutations. Antimicrob Agents Chemother 2010;54:5337–43. https://doi.org/10.1128/AAC.00663-10.

[7] Flanagan S, Fang E, Muñoz KA, Minassian SL, Prokocimer PG. Single-and multiple-dose pharmacokinetics and absolute bioavailability of tedizolid. Pharmacotherapy 2014;34:891–900.

[8] Mikamo H, Takesue Y, Iwamoto Y, Tanigawa T, Kato M, Tanimura Y, et al. Efficacy, safety and pharmacokinetics of tedizolid versus linezolid in patients with skin and soft tissue infections in Japan - results of a randomised, multicentre phase 3 study. J Infect Chemother 2018;24:434–42. https://doi.org/10.1016/j.jiac.2018.01.010.

[9] Lodise TP, Fang E, Minassian SL, Prokocimer PG. Platelet profile in patients with acute bacterial skin and skin structure infections receiving tedizolid or linezolid: findings from the Phase 3 ESTABLISH clinical trials. Antimicrob Agents Chemother 2014;58:7198–204. https://doi.org/10.1128/AAC.03509-14.

[10] Benavent E, Morata L, Escrihuela-Vidal F, Reynaga EA, Soldevila L, Albiach L, et al. Long-term use of tedizolid in osteoarticular infections: benefits among oxazolidinone drugs. Antibiotics (Basel) 2021;10:53. https://doi.org/10.3390/antibiotics10010053.

[11] Berbari EF, Kanj SS, Kowalski TJ, Darouiche RO, Widmer AF, Schmitt SK, et al. Infectious Diseases Society of America. 2015 Infectious Diseases Society of America (IDSA) clinical practice guidelines for the diagnosis and treatment of native vertebral osteomyelitis in adults. Clin Infect Dis 2015;61:e26–46. https://doi.org/10.1093/cid/civ482.

[12] Legout L, Valette M, Dezeque H, Nguyen S, Lemaire X, Loïez C, et al. Tolerability of prolonged linezolid therapy in bone and joint infection: protective effect of rifampicin on the occurrence of anaemia? J Antimicrob Chemother 2010;65:2224–30. https://doi.org/10.1093/jac/dkq28.

[13] Yuste JR, Bertó J, Del Pozo JL, et al. Prolonged use of tedizolid in a pulmonary non-tuberculous mycobacterial infection after linezolid-induced toxicity. J Antimicrob Chemother 2017;72:625–8. https://doi.org/10.1093/jac/dkw484.

[14] Khatchatourian L, Bourgeois AL, Asseray N, Biron C, Lefebvre M, Navas D, et al. Correction of myelotoxicity after switch of linezolid to tedizolid for prolonged

treatments. J Antimicrob Chemother 2017;72:2135–6. https://doi.org/10.1093/jac/dkx097.

[15] Telles JP, Cieslinski J, Tuon FF. Daptomycin to bone and joint infections and prosthesis joint infections: a systematic review. Braz J Infect Dis 2019;23:191–6. https://doi.org/10.1016/j.bjid.2019.05.006.

[16] Ide T, Takesue Y, Ikawa K, Morikawa N, Ueda T, Takahashi Y, et al. Population pharmacokinetics/pharmacodynamics of linezolid in sepsis patients with and without continuous renal replacement therapy. Int J Antimicrob Agents 2018;51:745–51. https://doi.org/10.1016/j.ijantimicag.2018.01.021.