2017

Thrombocytopenia with tedizolid and linezolid

Erica Yookyung Lee
University of Rhode Island

Aisling R. Caffrey
University of Rhode Island, aisling_caffrey@uri.edu

Citation/Publisher Attribution
Lee EY, Caffrey AR. 2018. Thrombocytopenia with tedizolid and linezolid. Antimicrob Agents Chemother 62:e01453-17.
http://dx.doi.org/10.1128/AAC.01453-17
Available at: http://dx.doi.org/10.1128/AAC.01453-17

Title: Thrombocytopenia with tedizolid and linezolid

Authors:

Erica Yookyung Lee[a], Aisling R. Caffrey, Ph.D., MS [a, b, c, #]

[a] University of Rhode Island College of Pharmacy, Kingston, Rhode Island; [b] Veterans Affairs Medical Center, Infectious Diseases Research Program and Center of Innovation in Long Term Services and Supports, Providence, Rhode Island; [c] Brown University School of Public Health, Providence, Rhode Island

[#]**Corresponding Author:**

Aisling R. Caffrey, PhD, MS

Assistant Professor, University of Rhode Island

7 Greenhouse Road, Kingston, RI 02881

Tel: 401-874-5320; e-mail: Aisling_Caffrey@uri.edu

Short Title: Thrombocytopenia with tedizolid and linezolid

Funding: None.

Keywords: Tedizolid, linezolid, thrombocytopenia, pharmacovigilance, drug safety

Abstract Word Count: 222

Manuscript Word Count: 1,433

Abstract

Objective: Though thrombocytopenia is a known adverse effect with linezolid, the first-in class oxazolidinone antibiotic, some have suggested a lower risk of thrombocytopenia with tedizolid, the second-in-class oxazolidinone antibiotic. We sought to evaluate adverse event reports for thrombocytopenia with tedizolid and linezolid from the Food and Drug Administration Adverse Event Reporting System (FAERS).

Methods: To assess the period since tedizolid approval, we included initial FAERS reports from July 2014 through December 2016. To evaluate historical rates with linezolid prior to tedizolid approval, we assessed AERSMine data from January 2004 through June 2014. Reporting odds ratios (ROR) and proportional reporting ratios (PRR) were calculated.

Results: Of all the reported events, 0.074% (n=1,468) were thrombocytopenia. Linezolid represented 0.02% (n=408) of all events, and tedizolid represented 0.002% (n=41). The ROR for thrombocytopenia with linezolid was 37.9 (95% confidence interval [CI] 20.78-69.17) and with tedizolid was 34.0 (95% CI 4.67- 247.30). The PRR for thrombocytopenia with linezolid was 36.9 (95% CI 20.56-66.28) and with tedizolid was 33.2 (95% CI 4.79- 230.10). From 2004 through June 2014, the linezolid ROR was 12.1 (95% CI 11.19-12.96) and PRR was 11.1 (95% CI 10.38-11.87).

Conclusion: We observed a significantly increased risk of thrombocytopenia of similar magnitude with both linezolid and tedizolid. Thrombocytopenia with tedizolid should be assessed with real-world comparative safety studies as more patients are treated with tedizolid.

Introduction

Linezolid is an oxazolidinone antibiotic that was approved by the Food and Drug Administration (FDA) in April 2000. Tedizolid, a second-in-class oxazolidinone antibiotic, was approved in June 2014. Linezolid's FDA approved indications include vancomycin-resistant *Enterococcus faecium* infections, nosocomial pneumonia, complicated skin and skin structure infections, including diabetic foot infections without concomitant osteomyelitis, uncomplicated skin and skin structure infections, and community-acquired pneumonia (1). Tedizolid's FDA approved indications include acute bacterial skin and skin structure infections (ABSSSI) (2).

As tedizolid has only been on the market for 3 years, adverse events during real-world use are still being discovered and studied. Though thrombocytopenia is a known side effect with linezolid as noted in the Warnings and Precautions section of the label, the package insert for tedizolid does not include such a warning (3, 4). In a pooled analysis of two phase 3, double-blind, randomized, comparator-controlled trials in patients with ABSSSI, rates of thrombocytopenia were found to be lower with tedizolid as compared with linezolid (5). Subsequently, review articles have cited this finding, suggesting a lower risk of thrombocytopenia with tedizolid (6, 7). Therefore, we sought to determine whether rates of thrombocytopenia adverse event reporting were lower with tedizolid than with linezolid.

Methods

We reviewed adverse event reports from the FDA Adverse Event Reporting System (FAERS) for the time period of July 2014 through December 2016 (8). Follow-up reports and reports missing all three categories of event date, sex, and age were excluded. A broad search term for thrombocytopenia was used and subsequent listings of adverse events were reviewed for inclusion. To evaluate adverse events reports for thrombocytopenia with linezolid before tedizolid was approved, we used AERSMine with a restricted time period of January 2004

through June 2014 (9). Using a case-non-case design, reporting odds ratios (ROR) and proportional reporting ratios (PRR), and corresponding 95% confidence intervals (CI) were calculated with OpenEpi (10-12).

Results

There were 1,995,573 adverse events that fit the defined criteria from July 2014 through December 2016 (Table 1). Of these adverse events, 0.07% (n=1,468) were thrombocytopenia. Among all adverse events, 0.02% (n=408) were from linezolid and 0.002% (n=41) were from tedizolid. Thrombocytopenia represented 2.70% (n=11) of the adverse events for linezolid and 2.44% (n=1) for tedizolid. The ROR for thrombocytopenia with linezolid was 37.9 (95% CI 20.78-69.17) and with tedizolid was 34.0 (95% CI 4.67- 247.30). The PRR for thrombocytopenia with linezolid was 36.9 (95% CI 20.56-66.28) and with tedizolid was 33.2 (95% CI 4.79- 230.10).

In the analysis of thrombocytopenia with linezolid prior to the approval of tedizolid using AERSmine from 2004 through June 2014, there were 5,818,659 adverse events that were reported. Of these adverse events, 0.79% (n=45,701) were thrombocytopenia and among all adverse events 0.16% (n=9,267) included linezolid. There were 795 cases of thrombocytopenia reported with linezolid, resulting in a ROR of 12.1 (95% CI 11.19-12.96) and PRR of 11.1 (95% CI 10.38-11.87).

Discussion

Based on our analysis of adverse event reports from the real-world clinical use of linezolid and tedizolid, both antibiotics were associated with a significantly increased risk of thrombocytopenia and this risk was of similar magnitude. Since it is recognized that adverse event reporting to FAERS is higher in the years following drug approval, we assessed two time periods, the period since tedizolid approval, and a ten year period prior to the approval of tedizolid (13). In the

tedizolid post-approval period, the risk of thrombocytopenia was over 30 times higher with both tedizolid and linezolid as compared with adverse event reports from other medications. In the period prior to tedizolid approval, the risk of thrombocytopenia was 12 times higher with linezolid (5, 14).

Our study assessed thrombocytopenia from adverse events terms (Medical Dictionary for Regulatory Activities, MedDRA), however clinical trials have used various platelet count thresholds to define this adverse event (8). A “substantially low platelet count” has been defined as <75% of the lower limit of normal or baseline, where the lower limit of normal (LLN) is 150,000 cells/mm^3, resulting in a platelet count of 112,500 cells/mm^3 (3, 5, 15). However, a lower threshold of less than 100,000 cells/mm^3 is considered clinically relevant and has been used to operationally define thrombocytopenia (5, 14).

Rates of thrombocyotopenia from previous clinical trials, though numerically higher with linezolid, were not statistically significantly higher compared with tedizolid. Both trials assessed the efficacy and safety of 6-day oral and/or intravenous tedizolid in acute bacterial skin and skin structure infections versus 10-day oral and/or intravenous linezolid therapy (ESTABLISH-1 and ESTABLISH-2, NCT01170221 and NCT01421511 as registered at ClinicalTrials.gov) (15, 16). In the safety analysis set from ESTABLISH-1, substantially low platelet counts (<75% of the LLN/baseline) were observed in 2.3% of patients in the tedizolid group (n=331) and 4.9% of patients in the linezolid group (n=335) (15). It was noted that half of the patients with thrombocytopenia (11/22) also had hepatitis C. Though there were more patients in the linezolid group with hepatitis C (tedizolid 101/329, 30.7%; linezolid 116/327, 35.5%; p=0.19), the distribution of hepatitis C plus thrombocytopenia by treatment group was not presented.

ESTABLISH-2 only presented platelet counts less than the LLN (<150,000 cells/mm^3) instead of less than 75% of the LLN/baseline (<112,500 cells/mm^3) as reported from ESTABLISH-1. Therefore, event rates were higher in ESTABLISH-2 but still not significantly different (tedizolid 27/314, 9%; linezolid 41/305, 13%; p=0.07). Again, hepatitis C was slightly more common in the linezolid group (tedizolid 65/322, 20%; linezolid 80/321, 25%; p=0.15), however the distribution of hepatitis C plus thrombocytopenia by treatment group was not presented.

A significant difference in thrombocytopenia was not observed until data from ESTABLISH-1 and ESTABLISH-2 were pooled. A significant difference between groups was observed using two definitions of thrombocytopenia (<150,000 cells/mm^3, <100,000 cells/mm^3) during study days 11-13 days but not during study days 7-9 (5). A limitation of this pooled analysis was that tedizolid therapy ended on day 6, while linezolid therapy ended on day 10. Additionally, this was a pooled analysis of clinical trial data, which does not confer the same benefits as a meta-analysis of randomized data (17). In the real-world clinical setting, duration of exposure will be important to consider as comparative safety is assessed, particularly if duration for either or both antibiotics is shorter than the duration used in clinical trials.

A possible explanation for the observed differences in thrombocytopenia form clinical trials may relate to the difference in metabolism and excretion with these two antibiotics (18). The majority of tedizolid is metabolized through the liver (82%), and less so through the kidneys (18%), while 30% of linezolid is excreted through urine (3, 4). Studies suggest that for linezolid, the risk of thrombocytopenia might arise from its increased exposure in renal insufficient patients (19-21). Due to linezolid's metabolite accumulation, renal dysfunction may become more severe resulting in higher metabolite levels than those with normal kidney function. Tedizolid is predominantly eliminated through the fecal route as tedizolid sulfate (18). The involvement of metabolites in thrombocytopenia however, is still unclear (20).

There are some limitations with our study. The true incidence of adverse events with tedizolid and linezolid are not known. Due the nature of FAERS reporting, which is not mandatory in all cases, incidence cannot be estimated. Additionally, FAERS data is subject to different sources of bias such as over reporting, underreporting, and missing information (13). Further limitations include the use of MedDRA terms for defining thrombocytopenia, since platelet counts/changes were not available, and reports with other adverse event terms which did not specifically mention thrombocytopenia were not included. As there was only one report of thrombocytopenia with tedizolid, the confidence intervals of the ROR and PRR were large and though statistically significant, the magnitude of the lower end of the confidence interval did vary between linezolid (~20 times higher risk) and tedizolid (~4 times higher risk). Lastly, FDA FAERS data was not available for the first several years after linezolid approval (April 2000 through December 2003), and therefore this initial time period could not be assessed for linezolid.

Conclusions

Though several publications have suggested a lower risk of thrombocytopenia with tedizolid, using FDA FAERS data, we observed a significantly increased risk of thrombocytopenia of similar magnitude with both linezolid and tedizolid. The incidence of thrombocytopenia in linezolid clinical trials was low, affecting only 2.2% of patients (22). Much higher rates were observed in real-world studies in the two years following drug approval, which ranged from 19-32%, with 47-48% of patients experiencing greater than a 30% reduction in platelet count (14, 23). Based on this previous experience, thrombocytopenia with tedizolid should be monitored and event rates should be assessed with real-world comparative safety studies as more patients are treated with tedizolid.

Acknowledgements

The views expressed are those of the authors and do not necessarily reflect the position or policy of the United States Department of Veterans Affairs.

Conflicts of Interest

Erica YooKyung Lee has no conflicts to disclose. Aisling Caffrey has received research funding from Pfizer, Merck (Cubist), and The Medicines Company.

References

1. First antibiotic in new class of drugs fights resistant infections. FDA Consum. 2000 Jul-Aug;34(4):4
2. Hall RG, Michaels HN. Profile of tedizolid phosphate and its potential in the treatment of acute bacterial skin and skin structure infections. *Infection and Drug Resistance*. 2015;8:75-82. doi:10.2147/IDR.S56691.
3. Pfizer, Inc. 2013. Zyvox package insert. Pfizer Inc., New York, NY.
4. Cubist Pharmaceuticals. 2014. Sivextro (tedizolid phosphate) package insert. Cubist Pharmaceuticals US, Lexington, MA.
5. 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(12):7198–7204.
6. Durkin MJ, Corey GR. New developments in the management of severe skin and deep skin structure infections – focus on tedizolid. *Therapeutics and Clinical Risk Management*. 2015;11:857-862
7. Rybak JM, Roberts K. Tedizolid Phosphate: a Next-Generation Oxazolidinone. *Infectious Diseases and Therapy*. 2015;4(1):1-14.
8. U.S. Food and Drug Administration. FDA adverse event reporting system (FAERS). U.S. Food and Drug Administration, Silver Spring (MD); 2017 http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/default.htm (Accessed February 21, 2017)
9. Sarangdhar M, Tabar S, Schmidt C, Kushwaha A, Shah K, Dahlquist JE, Jegga AG, Aronow BJ. Data mining differential clinical outcomes associated with drug regimens using adverse event reporting data. Nat Biotechnol. 2016 Jul 12;34(7):697-700.

10. Dean AG, Sullivan KM, Soe MM. OpenEpi: Open Source Epidemiologic Statistics for Public Health, Version. www.OpenEpi.com, updated 2013/04/06, accessed 2017/04/18.
11. van Puijenbroek EP, Bate A, Leufkens HG, Lindquist M, Orre R, Egberts AC. A comparison of measures of disproportionality for signal detection in spontaneous reporting systems for adverse drug reactions.*Pharmacoepidemiol Drug Saf.* 2002;11:3-10
12. Evans SJ, Waller PC, Davis S. Use of proportional reporting ratios (PRRs) for signal generation from spontaneous adverse drug reaction reports. *Pharmacoepidemiol Drug Saf.*2001;10:483-486.
13. Strom BL. Overview of automated databases in pharmacoepidemiology. In: Strom BL, Kimmel SE, Hennessy S, editors. Textbook of pharmacoepidemiology. 2nd ed. Chichester, UK: John Wiley & Sons, Ltd; 2013. p. 118-122.
14. Attassi K, Hershberger E, Alam R, Zervos MJ. Thrombocytopenia associated with linezolid therapy. Clin Infect Dis. 2002 Mar 1;34(5):695-8.
15. Prokocimer P, De Anda C, Fang E, et al. Tedizolid phosphate vs linezolid for treatment of acute bacterial skin and skin structure infections: the ESTABLISH-1 randomized trial. JAMA. 2013; 309 (6): 559-569.
16. Moran GJ, Fang E, Corey GR, et al. Tedizolid for 6 days versus linezolid for 10 days for acute bacterial skin and skin-structure infections (ESTABLISH-2): a randomized, double-blind, phase 3, non-inferiority trial. *Lancet Infect Dis.* 2014; 14 (8): 696-705.
17. Bravata DM, Olkin I. Simple pooling versus combining in meta-analysis. Eval Health Prof. 2001 Jun;24(2):218-30.
18. Ong V, Flanagan S, Fang E, Dreskin HJ, Locke JB, Bartizal K, Prokocimer P. Absorption, distribution, metabolism, and excretion of the novel antibacterial prodrug tedizolid phosphate. Drug Metab Dispos. 2014 Aug;42(8):1275-84.

19. Matsumoto K, Takeshita A, Ikawa K, Shigemi A, Yaji K, Shimodozono Y, Morikawa N, Takeda Y, Yamada K. 2010. Higher linezolid exposure and higher frequency of thrombocytopenia in patients with renal dysfunction. Int. J. Antimicrob. Agents 36:179–181.
20. Nukui Y, Hatakeyama S, Okamoto K, Yamamoto T, Hisaka A, Suzuki H, Yata N, Yotsuyanagi H, Moriya K. 2013. High plasma linezolid concentration and impaired renal function affect development of linezolid-induced thrombocytopenia. J. Antimicrob. Chemother. 68:2128–2133.
21. Brier ME, Stalker DJ, Aronoff GR, Batts DH, Ryan KK, O'Grady M, Hopkins NK, Jungbluth GL. 2003. Pharmacokinetics of linezolid in subjects with renal dysfunction. Antimicrob. Agents Chemother.47:2775–2780.
22. Gerson SL, Kaplan SL, Bruss JB, Le V, Arellano FM, Hafkin B, Kuter DJ. Hematologic effects of linezolid: summary of clinical experience. Antimicrob Agents Chemother. 2002 Aug;46(8):2723-6.
23. Orrick JJ, Johns T, Janelle J, Ramphal R. Thrombocytopenia secondary to linezolid administration: what is the risk? Clin Infect Dis. 2002 Aug 1;35(3):348-9.

Table 1. Thrombocytopenia from adverse event reports

	All adverse events	Thrombocytopenia	Reporting odds ratio (95% confidence interval)	Proportional reporting ratio (95% confidence interval)
All medications, 07/2014-12/2016	1,995,573	1,468 (0.07%)	--	--
Linezolid	408	11 (2.70%)	37.9 (20.78-69.17)	36.9 (20.56-66.28)
Tedizolid	41	1 (2.44%)	34.0 (4.67-247.30)	33.2 (4.79-230.10)
All medications, 01/2004-06/2014	5,772,958	45,701 (0.79%)	--	--
Linezolid	9,267	795 (8.58%)	12.1 (11.19-12.96)	11.1 (10.38-11.87)