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Time Course Distributions of Laboratory Indices: A Strategy for Evaluating Laboratory Data from Clinical Trials

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ABSTRACT

Background: The traditional approach for assessing drug safety is to compute the baseline to end of treatment change in a laboratory measure. This strategy may miss important time-dependent value trends in patient subsets during or after treatment. We describe a strategy for evaluating time trends in laboratory parameters and applied the approach to platelet (plt) count analyses during linezolid (lzd) therapy.

Methods: Plt counts obtained before, during and after treatment were available from 2789 patients enrolled in 7 Phase III trials comparing linezolid to comparator antibiotics. Box plots (25th to 75th percentiles) and whiskers (5th to 95th percentiles) of platelet counts were superimposed on scattergrams (< 5th and >95th percentiles) and normalized to start of treatment for each group. Additional plots were further developed to investigate patients with substantially low values defined as < 75% of the lower limit of normal or < 75% of baseline if abnormal at baseline.

Results: The median plt count rose from baseline but remained within normal limits during treatment; this trend was similar in comparator patients. Twenty-seven (1.9%) patients on lzd had at least one substantially low value compared to 11 (0.8%) in the comparator group. These patients were more likely to have had a low baseline plt count, regardless of treatment group. The mean (SD) time to first occurrence of a substantially low plt count was 12.0 ± 6.2 days for the lzd patients and 11.3 ±10.1 for the comparator group.

Conclusions: Examination of the time course of laboratory values with boxplots allows for detection of trends and development of risk assessment models for laboratory indices. This comparative method also allows for the identification and tracking of outlier performance.

INTRODUCTION

The 1996 FDA guidance on conducting a clinical safety review for a new drug suggests standard analyses and exploration of laboratory data. Since much of the laboratory data are continuous in nature, common practice is to compare mean or median changes from baseline across treatment groups. This approach may miss important time-dependent trends in laboratory safety indices in patient subsets. An additional strategy for evaluating time trends was applied to platelet count analyses during linezolid therapy, and allowed for indentification and tracking of outlier patients. Linezolid is an oxazolidinone, a novel chemical class of synthetic antimicrobial agents, which demonstrates in vitro and vivo activity against gram-positive organisms.

METHODS

Patients

- 2789 patients enrolled in 7 Phase III linezolid comparator-controlled trials in community-acquired pneumonia (30%), hospital-acquired pneumonia (10%), skin and soft tissue infections (32% uncomplicated and 26% complicated), bacteremia (0.5%), urinary tract infections (0.5%), and other infections (1%). Patients were included only if they received at least one dose of linezolid or comparator (ceftriaxone, cefpodoxime, clarithromycin, dicloxacillin, oxacillin, or vancomycin)

Study Procedures

- Linezolid dosage regimen: 400 or 600 mg BID
- Platelet counts: obtained before, during and after treatment
- Population time plots: median laboratory assay values by study day were generated for the populations of interest
  - boxplots (25th to 75th percentiles) and whiskers (5th to 95th percentiles) were superimposed on scattergrams (< 5th and >95th percentiles)
  - additional plots were developed to investigate patients with substantially low platelet counts defined as <75% of the lower limit of normal or < 75% of baseline if abnormal at baseline based on normal reference ranges at the central laboratory

RESULTS

Linezolid versus Comparator

- Median platelet counts for linezolid patients rose from baseline but remained within the normal limits throughout the treatment and follow-up periods; this trend was similar to comparator patients as seen in **Figures 1-4.**
- The boxes also rose during treatment and remained above the lower limit of normal (LLN) throughout the treatment and follow-up periods for both groups.
- This rise in platelet counts is expected with acute infectious disease process since platelets act as an acute phase reactant.
- There was a slight decrease in median platelet counts in linezolid treated patients who were treated more than 2 weeks as seen in **Figure 1** and **Figure 3**.

RESULTS

FIGURE 1. Platelet counts for all linezolid patients – boxplots & scattergrams.

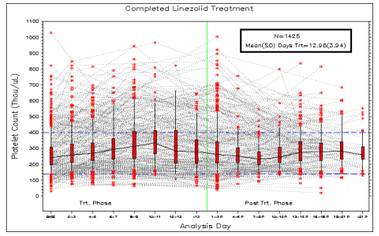


FIGURE 2. Platelet counts for all comparator patients – boxplots & scattergrams.

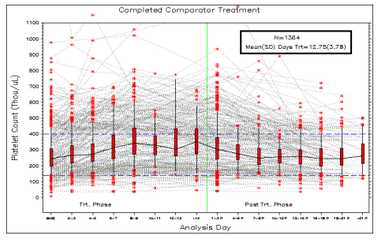


FIGURE 3. Platelet counts for all linezolid patients – boxplots.

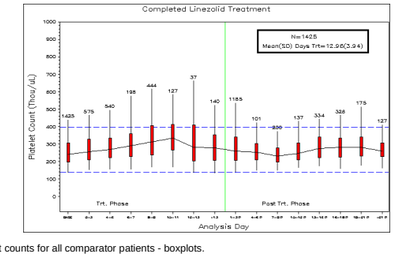
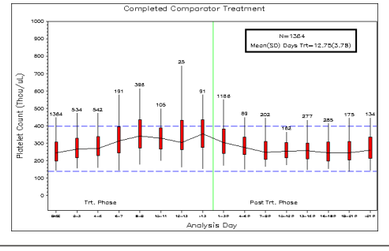


FIGURE 4. Platelet counts for all comparator patients - boxplots.



RESULTS (continued)

Patients With Substantially Abnormal Values

- Twenty-seven linezolid patients and 11 comparator patients who developed at least 1 substantially low platelet count during the study period were included in the analyses **(Figures 5-6).** The mean (SD) duration of therapy for these patients was 15.4 ± 4.5 days and 12.2 ± 3.0 days, respectively.
- The mean duration therapy for patients in both groups who developed at least 1 substantially low platelet count was longer than for patients in the overall population (13.0 ± 3.9 days; 12.8 ± 3.8 days).
- The median platelet count for linezolid patients who developed at least 1 substantially abnormally low platelet count was near the LLN, dropping below the LLN at EOT and rising back into the normal range at follow-up. The median platelet count for comparator patients remained below the LLN for most of the study period. (Note: no scattergrams were generated if there were fewer than 10 patients at any given time point since all of the patients would by definition lie between the 5th and 95th percentiles).
- A scattergram of platelet counts for linezolid patients with at least 1 substantially low value is provided in **Figure 7**. Several patients had platelet counts at baseline less than 100,000 cells/uL, but these values remained stable throughout the study period.

FIGURE 5. Platelet counts for linezolid patients with substantially abnormal values – boxplots & scattergrams.

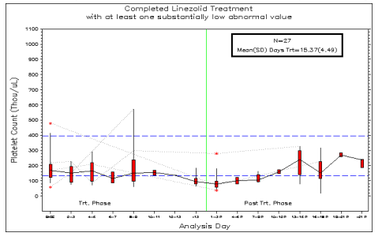


FIGURE 6. Platelet counts for linezolid patients with substantially abnormal values – boxplots & scattergrams.

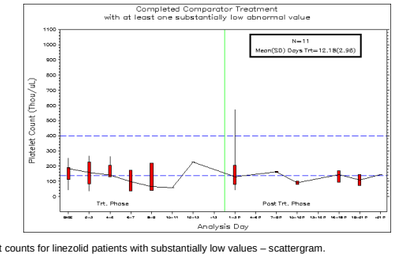
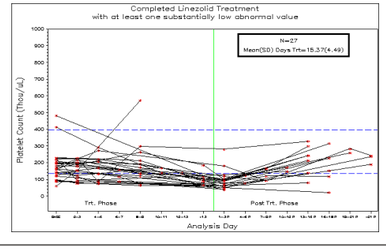


FIGURE 7. Platelet counts for linezolid patients with substantially low values – scattergram.



RESULTS (continued)

Study Discontinuations

- In order to be certain that discontinued patients were not influencing the population time plots, they were analyzed separately.
- The median platelet count for linezolid patients who discontinued during the study period was similar to that seen in the overall population throughout the study period **(Figure 8)**. Median count for comparator patients who discontinued were similar to linezolid patients who discontinued.
- A total of 295 linezolid patients and 281 comparator patients who were discontinued during the study period had available duration of therapy information; linezolid patients are shown in **Figure 9**. The mean (SD) duration of therapy for these patients was 5.4 ± 3.9 days and 5.6 ± 4.0 days, respectively. The median platelet counts over time did not decline and remained within the normal range throughout the study period, regardless of increasing duration of therapy.

FIGURE 8. Platelet counts for linezolid patients who discontinued linezolid treatment – boxplots.

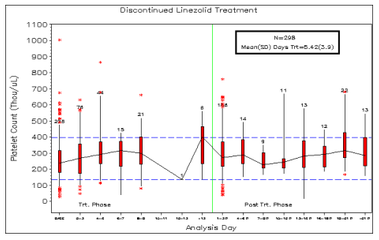
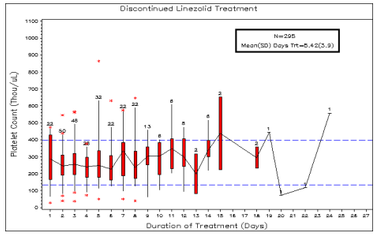


FIGURE 9. Platelet counts versus duration of treatment for linezolid patients – boxplots.



CONCLUSION

- **Overall, boxplots and whiskers of platelet counts superimposed on scattergrams provided a unique method of evaluating time-dependent trends in laboratory values in patients during and after therapy with linezolid or comparators.**
- **Median platelet counts for patients in both groups rose from baseline but remained within normal limits throughout treatment and follow-up period.**
- **The median platelet count for linezolid patients who developed at least 1 substantially low platelet count was near the LLN, dropping below the LLN at end of treatment, and rising back into the normal range at follow-up. The median count for the comparator group remained below the LLN for most of the study period.**
- **The median platelet counts over time in patients who discontinued during the study period did not decline and remained within the normal range throughout the study period, regardless of increasing duration of therapy.**
- **Patients treated with linezolid for more than 2 weeks have mild, reversible decreases in platelet counts.**