Linezolid Experience Among MDR-TB Patients in Mumbai

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BACKGROUND

- Tuberculosis (TB) is the #1 infectious disease killer worldwide, and 26% of cases occur in India. The city of Mumbai is particularly affected, with 12% of India’s Multi-drug-resistant TB (MDR-TB, TB resistant to isoniazid and rifampin).
- MDR-TB, Pre-XDR (resistant to isoniazid, rifampin, and one to two additional first-line injectable drug), and Extensively Drug Resistant TB (XDR, resistant to isoniazid, rifampin, a quinolone, and a second-line injectable drug) require longer treatment than drug susceptible TB, and rely on less effective and more toxic drugs, causing significant morbidity.
- Linezolid is a repurposed bacteriostatic antibiotic that is associated with increased rates of culture-conversion (Lee M, et al. NEJM 2013) and is being used in novel treatment regimens trials including the Nix-TB trial (Corradine, F et al. CROI Abstract 2017). Unfortunately, linezolid is also associated with significant side effects including painful peripheral neuropathy and bone marrow suppression.
- We reviewed the data from a prospective observational cohort of MDR-TB patients in Mumbai to document our experience of the safety and efficacy of linezolid in India.

METHODS

- MDR-TB patients seeking care at the Outpatient Chest Clinic at PD Hinduja National Hospital and Medical Research Centre were recruited by research clinicians, and consented to enrollment into a prospective observational cohort. Participants had TB history, prescriptions, labs, and imaging reviewed and entered into a Microsoft Access database. Data were cleaned and analyzed in R.
- The impact of linezolid was evaluated by the following variables:
  - Patient-Reported Side Effects
    - Hearing Loss
    - Tingling, Burning, or Numbness
    - Self-Reported Neuropathy
    - Neutropenia
    - Joint Pain
    - Self-Reported Depression
    - Skin Discoloration
    - Subjective Fever
    - Objective Side Effect
    - Kidney Injury
    - Amylase
    - Pancreatic
    - Leukopenia
  - Culture Conversion
  - Time to Neuropathy and Hematologic Side Effects
  - Time to Neuropathy and Marrow Suppression During Linezolid
  - Time to Neuropathy and Marrow Suppression During Linezolid

RESULTS—Experience with Linezolid

- Many participants started with 600mg but transitioned to 300mg daily.
- Higher initial dose was significantly associated with earlier time to dose adjustment (p=0.018), but not total with shorter total duration of linezolid therapy (p=0.289).

TREATMENT ASSOCIATED SIDE EFFECTS AMONG PARTICIPANTS RECEIVING LINEZOLID, N (%)

- Moderate or Severe Anorexia (n=37 (16.6%))
- Thrombocytopenia (n=3 (1.4%))
- Neutropenia (n=49 (22.9%) )
- Any Hematologic Side Effects (n=49 (22.9%))
- Neuropathy and hematologic side effects were most associated with linezolid

RESULTS—Linezolid and Outcomes

- Use of linezolid was associated with significant improvement in cavitory lung disease measured by Ralph score (p=0.001). Odds of culture conversion increased with duration of therapy, as did odds of anemia. Odds of neutropathy was associated with ever having taken linezolid but not duration of therapy.
- No significant associations were identified between treatment, dose in mg or mg/kg, duration and improved chest X-ray % involvement or odds of leukopenia, thrombocytopenia, or severe anemia.

CONCLUSIONS

- In a cohort of MDR-TB patients with complex drug resistance, use of linezolid was common and rates of linezolid resistance were low.
- Linezolid dosing was highly variable, with higher initial doses frequently adjusted early in treatment. Median duration before dose adjustment was 4.5 months (600mg) and 6.8 months (300mg, p=0.04).
- Neuropathy and hematologic side effects were common and occurred well before dose adjustments.
- Linezolid was associated with improvement in cavitory lung disease culture conversion.
- Use of linezolid was associated with increased odds of neuropathy, but not with hematologic events after controlling for drug resistance and co-administered drugs.
- Linezolid doses (>100mg/kg or >15 mg/kg) were not associated with improved radiographic or microbiologic improvement.

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