Safety and efficacy of linezolid for the treatment of cholangitis in liver transplant recipients

Danielle McKimmy, P4; Margaret Jorgenson, PharmD; Jillian Fose, PharmD; Jeannina Smith, MD

UW Health, Madison, WI

UW Health Pharmacy Services

School of Pharmacy
UNIVERSITY OF WISCONSIN–MADISON

Background

- Bacterial infections remain a leading cause of morbidity and mortality following liver transplantation.
- Linezolid is an oxazolidinone antibiotic with efficacy against a number of resistant gram positive organisms, including vancomycin-resistant *Enterococcus faecium*, which is an important pathogen after liver transplantation.
- The ability of linezolid to effectively penetrate into biliary fluid makes it a promising option for treating severe biliary infections.
- Linezolid is available orally as well as parenterally, making it an attractive candidate for outpatient drug therapy.
- Thrombocytopenia was a known toxicity of linezolid in clinical trials, reported at approximately 3% incidence. However, this effect, as well as overall myelotoxicity manifested as leukopenia, neutropenia, and anemia has been shown to be more prevalent in clinical practice, with thrombocytopenia specifically occurring in up to 30-48% of courses.
- The incidence of myelotoxicity appears to increase with duration of linezolid use, with risk being greatest in courses exceeding 14 days.
- The solid organ transplant population is at higher risk of myelotoxic drug effects in general due to required concomitant myelotoxic therapies such as mycophenolate and other myelosuppressive antimicrobials.
- Liver transplant patients in particular have increased risk of thrombocytopenia due to hypersplenism.

Purpose and Objectives

Purpose: To determine the safety and efficacy of short-course (≤14 days) linezolid for the treatment of cholangitis in liver transplant recipients.

Objectives:

1) Determine the efficacy of linezolid for the treatment of cholangitis in the liver transplant population as determined by:
   a) Resolution of symptomatology
   b) Normalization of liver function tests

2) Determine the incidence of adverse effects attributable to linezolid during short-course therapy for cholangitis
   a) Myelosuppression defined as anemia, thrombocytopenia, leukopenia
   b) Severe infrequent side effects: Serotonin syndrome, lactic acidosis

Methods

Study Design:
- Single center retrospective electronic chart review

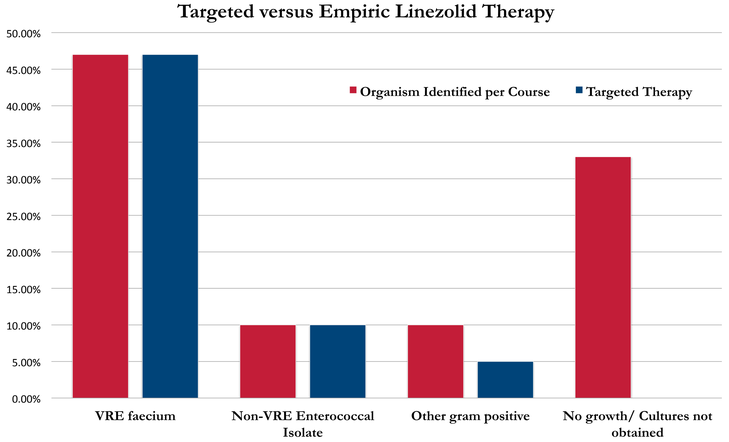
Inclusion Criteria	Exclusion Criteria
• ≥ 18 years old • Liver transplant recipient • Confirmed or suspected cholangitis • Receipt of oral or parenteral linezolid for ≤ 14 days • Prescribed linezolid from UWHC provider between 1/1/2012 and 12/31/2014	• < 18 years old

Results

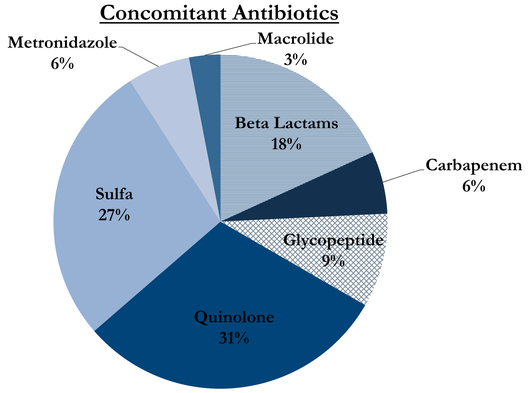
Table 1. Demographics per linezolid course (n=21)

Age, mean ± SD (years)	60 ± 12
Gender	
Male	13 (62%)
Female	8 (38%)
Transplanted Organ	
Liver	19 (91%)
Liver + Kidney	2 (9 %)
Transplant Type	
Donation after Brain Death	18 (86%)
Donation after Cardiac Death	3 (14%)
Reason for Native Organ Failure	
Alcoholic Liver Disease	4 (19%)
Alpha-1-antitrypsin Deficiency	2 (10%)
Hepatocellular Carcinoma	1 (5 %)
Hepatitis C	3 (14%)
Primary Biliary Cirrhosis	5 (24%)
Primary Sclerosing Cholangitis	5 (24%)
Nonalcoholic Steatohepatitis	1 (5 %)
Linezolid Therapy	
Inpatient	6 (29%)
Outpatient	15 (71%)

Targeted versus Empiric Linezolid Therapy



Concomitant Antibiotics



Efficacy Results

Table 2. Efficacy endpoint data (n=19)

Clinical Cure		
Abatement of symptoms at course completion	**17**	**(81%)**
Liver function tests within normal limits*		
AST	12	(63%)
ALT	10	(53%)
Total Bilirubin	11	(58%)

*19 out of 21 total courses reported liver function tests upon course completion. Reported percentages for liver function tests use total n=19.

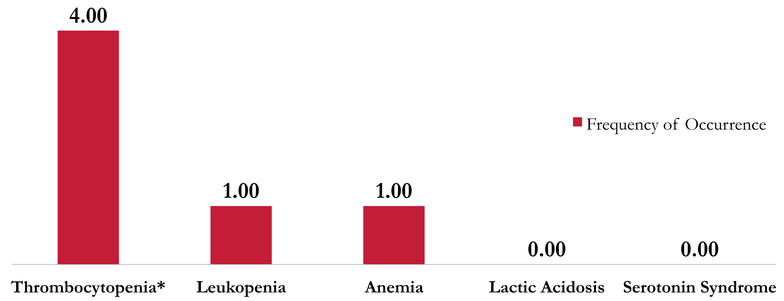
Table 3. Microbiology results obtained at course completion (n=4)

Microbiological Cure	
Cultures obtained at course completion	4 (19%)
No growth at course completion*	3 (75%)

*4 out of 21 total courses obtained cultures upon course completion. Reported percentage for growth at course completion uses total n=4.

Safety Results

Adverse Effects



*Thrombocytopenia was the reason for discontinuation of two linezolid courses (10%)

Conclusions

- Linezolid appears to be effective for the treatment of cholangitis in orthotopic liver transplantation as evidenced by 81% treatment success and > 50% of patients achieving normalization of liver function tests.
- Linezolid appears to be safe for the treatment of cholangitis in orthotopic liver transplantation in short courses of ≤14 days as evidenced by 5% incidence of leukopenia, 5% incidence of anemia, 10% incidence of thrombocytopenia leading to discontinuation, and no incidence of serotonin syndrome* or lactic acidosis.

*All SSRIs, SNRIs, and other psychiatric serotonergic agents were held upon linezolid initiation in 100% of courses

Disclosures

The authors have nothing to disclose.