Ceftolozane-tazobactam for the Treatment of Multi-Drug Resistant *Pseudomonas aeruginosa* (MDRPA) Infections

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ABSTRACT

Background: Ceftolozane-tazobactam (TOL-TAZ) is a novel cephalosporin/beta-lactamase inhibitor combination with potent activity against *Pseudomonas aeruginosa,* including MDRPA. TOL-TAZ use for MDRPA infections has not been well-studied.

Objective: To describe outcomes of patients treated with TOL-TAZ for MDR *Pseudomonas aeruginosa* infections at 3 academic medical centers.

Methods: We conducted a retrospective study of patients of age ≥ 18 years who had MDRPA isolated in culture and received TOL-TAZ for at least 24 hours. The primary outcomes were 30-day and in-hospital mortality. Secondary outcomes were microbiological cure and clinical success. Microbiological cure was defined as negative culture at end of therapy; cure was presumed when clinical success occurred without follow-up cultures. Clinical success was defined as resolution of all signs and symptoms of infection. TOL-TAZ susceptibility results were collected when available.

Results:
The 30 day mortality was 20.6% and in-hospital mortality was 23.5%. Microbiological cure occurred in 61.8% and clinical resolution occurred in 70.6%.

Conclusions:
In this severely ill population, 61.8% of patients had microbiological cure, 70.6% had clinical success, and 76.5% were alive at the end of their hospital stay. TOL-TAZ is a potential option for patients with MDRPA infections.

BACKGROUND

Ceftolozane-tazobactam is a novel cephalosporin combined with a B-lactamase inhibitor that is FDA approved for complicated urinary tract infections (cUTI) and complicated intra-abdominal infections (cIAI).

Ceftolozane-tazobactam has shown activity against *Pseudomonas aeruginosa*, including drug resistant phenotypes[1]. Ceftolozane is largely stable against AmpC beta-lactamases, and is not affected by the up-regulation of efflux pumps and loss of prion channels in *Pseudomonas aeruginosa.* [1-3] The addition of tazobactam, a beta-lactamase inhibitor, extends its coverage to beta-lactamase producing gram negative organisms including ESBLs.[1,4] Ceftolozane-tazobactam has shown similar efficacy to carbapenems for ESBL-producing organisms in cIAI and cUTI.[5-7]

Ceftolozane-tazobactam may be especially beneficial for the treatment of MDR *Pseudomonas aeruginosa* (MDRPA) infections due to severely limited options for this organism. Multiple agents are often used in combination, increasing the probability of adverse effects. This is particularly relevant since the primary alternative drugs for MDRPA infections are aminoglycosides and polymyxins, two categories of agents with significant adverse effects and suboptimal pharmacokinetics that limit efficacy.

This observational study will add to the limited literature regarding the utility of ceftolozane-tazobactam for MDR *Pseudomonas aeruginosa* infections.

METHODS

This was a retrospective study of patients who had received ceftolozane-tazobactam (TOL-TAZ) for MDRPA infections. Case information was collected from Temple University Hospital as well as University of Maryland and Indiana University Health. All involved parties used the Research Electronic Data Capture (RedCap) database based at Temple University for data collection. Enrolled patients had received treatment as determined by the treating physicians. Investigators identified and consecutively enrolled eligible patients treated with TOL-TAZ between December 19, 2014 and May 1, 2016.

Data collected on enrolled patients includes: patient characteristics, microbiological results, co-morbidities (assessed by Charlson Comorbidity Index), severity of illness by APACHE II score at time of TOL-TAZ initiation, use of mechanical ventilation, renal replacement therapy, dose and duration of TOL-TAZ therapy, antibiotics given before and concomitantly with TOL-TAZ, and primary infection type. Infections met the categories for diagnosis set by the US CDC.

Outcomes evaluated were 30-day and in-hospital mortality, clinical cure, microbiological cure and patient outcome at end of hospital stay (discharge, mortality or still hospitalized at end of study period). Clinical cure was defined as resolution of signs and symptoms present on diagnosis. Microbiological cure was defined as repeated negative cultures and was presumed in patients without repeated cultures who had clinical resolution. Inclusion criteria were age ≥ 18 years, MDRPA isolated in culture from any source, defined infection per CDC criteria, and use of TOL-TAZ for at least 24 hours. Protected populations were excluded. MDRPA was defined as resistant to 3 or more classes of antibiotics.

Characteristics	Results, N=34
Male gender, n(%)	21 (61.8)
Age (median, IQR)	57 (42-66)
Charlson Comorbidity Index (median, IQR)	4 (2.25-5)
APACHE II score (median, IQR)	20 (13-27)
ICU, n(%)	23 (67.7)
Solid organ transplant recipient, n(%)	15 (44.1)
Primary infection, n(%)	
Pneumonia	21 (61.8)
Wound	4 (11.8)
Urinary tract	3 (8.8)
Intra-abdominal	2 (5.9)
Bone/joint	2 (5.9)
Bacteremia (primary)	1 (2.9)
Other (LVAD driveline)	1 (2.9)
Bacteremia associated with primary infection	5 (14.7)
Hospital day index infection diagnosed (median, IQR)	8 (1-35)
Hospital day TOL-TAZ started (median, IQR)	18.5 (3-52)
Patients receiving concomitant antibiotics for MDRPA, n(%)	20 (58.8)
Number of days of TOL-TAZ, median (range)	14 (3-42)

RESULTS

Primary Outcomes	30 Day Mortality n (n/N%)	In Hospital Mortality n (n/N%)
Pneumonia (N=21)	4 (19.1)	6 (28.6)
Wound (N=4)	1 (25)	1 (25)
Bacteremia (N=1)	1 (100)	-
Driveline Infection (N=1)	1 (100)	1 (100)
Total	**7/34 (20.6)**	**8/34 (23.5)**

Secondary Outcomes	Microbiological Cure n (n/N%)	Clinical Success n (n/N%)
Pneumonia (N=21)	10 (47.6)	14 (66.7)
Wound (N=4)	3 (75)	3 (75)
UTI (N=3)	3 (100)	3 (100)
Intra-abdominal (N=3)	2 (66.7)	2 (66.7)
Bone/joint (N=2)	2 (100)	2 (100)
Bacteremia (primary) (N=1)	1 (100)	-
Total	**21/34 (61.8)**	**24/34 (70.6)**

Concomitant Anti-pseudomonal Antibiotics	
Gentamicin, n(%)	5 (14.7%)
Polymyxin or colistin, n(%)	5 (14.7%)
Fluoroquinolone, n(%)	2 (5.9%)
Intravenous amikacin, n(%)	3 (8.8%)
Inhaled amikacin, n(%)	3 (8.8%)
Inhaled tobramycin, n(%)	3 (8.8%)
Intravenous tobramycin, n(%)	2 (5.9%)
No concurrent antibiotics, n(%)	**14 (41.2%)**

One patient had an isolate resistant to TOL-TAZ

- MIC >256
- Patient previously treated with TOL-TAZ for MDRPA
- Patient was discharged on course of TOL-TAZ and tobramycin with clinical improvement, no re-admissions up to date of abstract submission

RESULTS

Dosage of TOL-TAZ by Infection Type				
	375 mg q8hr	750 mg q8hr	1.5 g q8hr	3 g q8hr
PNA	1¥	4⊙	7■	9
Wound			4+	
UTI	1§		2	
Intra-abdominal		1§		1
Bone/joint			1¥	1
Bacteremia				1
Driveline			1	
Total n/N(%)	**2/34 (5.9)**	**5/34 (14.7)**	**15/34 (44.1)**	**12/34 (35.3)**

¥ dose adjusted for renal function to obtain effective dose of 3 g q8hr
§ dose adjusted for renal function to obtain effective dose of 1.5 g q8hr
⊙dose adjusted in two cases to obtain effective dose of 1.5 g q8hr and in another two cases to obtain effective dose of 3 g q8hr
■ dose adjusted in three cases to obtain effective dose of 3 g q8hr
+ one case was adjusted for renal function, received 1.5 g q12hr instead of q8hr

DISCUSSION

We present data on the use of ceftolozane-tazobactam in 34 patients with MDRPA. In this study, the patients had a median APACHE II score of 20, (IQR 13-26.8) and 67.7% of patients were in the ICU at the time of ceftolozane-tazobactam initiation. In this severely ill population, 61.8% of patients had microbiological cure, 70.6% had clinical success with resolution of infection, and 76.5% were alive at the end of their hospital stay. Not all patients with clinical success demonstrated microbiological cure as some patients had persistent positive cultures despite clinical resolution, possibly representing colonization.

CONCLUSIONS

Ceftolozane-tazobactam was useful for the treatment of MDR *Pseudomonas aeruginosa* infections in this severely ill population.

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