250 - 2423

Effectiveness and Safety of Ceftolozane/Tazobactam (TOL/TAZ) Treatment for Multidrug-Resistant *Pseudomonas* Infections in Children

Leah Molloy[1,4], Ibrahim Abdulhamid[2,4,5], Ruma Srivastava[2,4,5], Jocelyn Y. Ang[3-5]

Department of Pharmacy[1]; Division of Pulmonary Medicine[2]; Division of Infectious Diseases[3]; Children's Hospital of Michigan[4]; Department of Pediatrics, Wayne State University School of Medicine, Detroit, MI[5]

Address correspondence to: Leah Molloy, Pharm.D.; LMolloy@DMC.org

Background and Methods

- Evidence for TOL/TAZ use in children is limited
- We describe safety and clinical outcomes of children who received TOL/TAZ from 2014 – 2017 at our institution for infections caused by multidrug-resistant *Pseudomonas aeruginosa*
- Clinical cure defined as resolution of infection at the end of TOL/TAZ therapy with no additional treatment needed

Patient Characteristics and Treatment

Pt #	Site	Comorbidities	Age, y	Wt, kg	TOL Dose, mg/kg	TOL Dose, g	LOT, d	LOS, d
1	IAI	Burn	14	72.5	13.8	1	19	142
2	OM	Hurler-Scheie syndrome	16	61.7	16.2	1	61	221
3	CF	CF	19	57.5	34.8	2	9	14
4	VAP	Chronic trach	17	61.9	32.3	2	17	65
5	CF	CF	14	33	30.3	1	15	36
6	CF	CF	11	46.9	21.3	1	5	11
7	VAP	CV surgery	0.25	3.92	20.4	0.08	12	98
8	VAP	Neurosurgery	3	13.3	18.8	0.25	10	81
9	PNA	Burn	5	25.8	27.2	0.701	31	202
10	IAI	Lymphoma	13	48.7	20.5	1	34	48
11	PNA	Chronic trach	9	39.3	20.4	0.8	11	522
12	PNA	CV surgery	0.83	8.4	19	0.16	5	348

IAI, intra-abdominal infection; OM, osteomyelitis; CF, cystic fibrosis; VAP, ventilator-associated pneumonia; PNA, pneumonia; trach, tracheostomy; CV, cardiovascular; Wt, weight; TOL, ceftolozane component; LOT, length of TOL/TAZ therapy; LOS, length of stay

Minimum Inhibitory Concentrations (mg/L)

Pt #	FEP	MEM	IMI	TZP	TOL*
***Pseudomonas aeruginosa* (PA)**					
1	>16	>8	>8	>64/4	2
2	32*	>8	>8	>64/4	1
3	64*	>32*	>32*	n/a	2
4	>16	>8	>8	>64/4	2
5	32*	>32	>32	32/4*	0.5
6	>16	>8	>8	>64/4	0.06
7	2¥	4	8	4/4¥	0.5
8	>16	>8	>8	>64/4	1
9	>16	>8	>8	>64/4	4
10	8#	>8	>8	64/4	1
11	16	2†	2†	32/4	1
12	16	>8	8	32/4	1
Concomitant ESBL *Escherichia coli*					
4	>16	≤0.125	≤0.25	n/a	1
12	4‡	≤0.125	≤0.25	n/a	0.06

FEP, cefepime; MEM, meropenem; IMI, imipenem; TZP, piperacillin/tazobactam; TOL, ceftolozane; *E-test

- ¥respiratory culture 5 days earlier grew PA with FEP MIC=16 mg/L, MEM MIC>8 mg/L, TZP MIC=32/4 mg/L
- #wound culture from same site collected 3 days earlier grew PA with FEP MIC>16 mg/L
- †carbapenems contraindicated per drug interaction
- ‡reported as resistant per extended spectrum beta-lactamase (ESBL) detection

Clinical Cure, Tolerability, Development of Resistance

Clinical Cure

- Achieved by all but 3 patients:
  - Pt #2: Acute infection (sacral osteomyelitis) resolved, changed to levofloxacin for newly diagnosed VAP with TOL/TAZ-resistant *P. aeruginosa* isolated from respiratory culture
  - Pt #7: Died during treatment from causes unrelated to infection (CV decompensation)
  - Pt #12: Changed to PO ciprofloxacin per lost IV access; otherwise achieved clinical cure
- Both patients with concomitant ESBL-producing *E. coli* infections improved, though Pt #12 received 8 days of carbapenem treatment before TOL/TAZ monotherapy

Adverse Effects

- No serious adverse events were incurred by children receiving TOL/TAZ
- Laboratory abnormalities requiring dose reduction occurred in 2 patients:
  - Pt #5: LFTs increased on treatment, dose reduced 50%, LFTs returned to normal limits
  - Pt #10: ANC decreased on treatment, dose reduced 20%, ANC recovered with filgrastim

Development of TOL/TAZ Resistance

TOL/TAZ-resistant *P. aeruginosa* (MIC>256 mg/L) was isolated from 2 patients:

- Respiratory culture from Pt #2 after 2 months of therapy for OM
- Respiratory culture from Pt #6 after 7 courses of therapy for CF over ~16 months

Institutional TOL/TAZ Dosing

< 45 kg	20 mg/kg/dose, ceftolozane component, every 8 hours (may increase to 30 mg/kg for severe respiratory infection)
≥ 45 kg, general infection	1000 mg ceftolozane component every 8 hours
≥ 45 kg, CF or pneumonia	2000 mg ceftolozane component every 8 hours

Conclusions and Future Directions

- TOL/TAZ was generally effective and well tolerated in the treatment of children with various multidrug-resistant *Pseudomonas aeruginosa* infections
- Reduced TOL/TAZ susceptibility after prolonged or repeated courses was observed and presents potential opportunities for dose optimization and antimicrobial stewardship

Authors of this presentation have the following to disclose concerning possible financial or personal relationships with commercial entities that may have a direct or indirect interest in the subject matter of this presentation:
Leah Molloy, Ibrahim Abdulhamid, Ruma Srivastava: Nothing to disclose; Jocelyn Ang: Received institutional research funding from Merck & Co., Inc.