

Linezolid-containing regimens for the treatment of drug-resistant tuberculosis in South African children*

P. C. Rose, U. M. Hallbauer,
J. A. Seddon, A. C. Hesselning, H. S. Schaaf

*Rose PC, et al. Inter J Tuberc Lung Dis. 2012 Oct 2 [Epub Ahead of Print]



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Background (1)

- Increasing recognition of the importance of MDR-TB in children
 - 2007-2009 – 8.9% of children with culture-confirmed TB - MDR¹
- Good treatment outcomes
 - 81.7% favorable
- Limited options for treatment of XDR-TB
 - Less experience in children

¹ Seddon JA, et al. The evolving epidemic of drug-resistant tuberculosis among children in Cape Town, South Africa. *Int J Tuberc Lung Dis* 2012 Jul;16(7):928-33.

Background (2)

- Linezolid – oxazolidinone antibiotic
 - Adult data increasingly showing efficacy in MDR- and XDR-TB treatment regimens
 - Substantial rates of adverse events
- Linezolid in paediatric MDR- or XDR-TB
 - 4 case reports of 7 children (1 HIV pos) ^{2,3,4,5}
 - 7/7 favorable outcome - cure or clinical response
 - 3/7 adverse events
 - 1 child – lactic acidosis - linezolid stopped
 - 1 child - anaemia and neuropathy – linezolid dose reduced
 - 1 child - urticarial rash – linezolid dose reduced

² Condos R, et al. *Chest* 2008; 1334: 187-192. ³ Schaaf HS, et al. *Pediatr Infect Dis J* 2009; 28: 748-750.

⁴ Pinon M, et al. *Pediatrics* 2010; 126: e1253-e1256. ⁵ Kjollerstrom P, et al. *Scand J Infect Dis* 2011; 43: 556-559.

Methods

- Objective - To describe additional experience with linezolid in children with MDR- or XDR-TB
- Study Design – Retrospective chart audit
- Patient Population
 - <15 years of age
 - treated with linezolid for drug-resistant TB
 - Feb 2007 and Mar 2012
 - Brooklyn Hospital for Chest Disease, Cape Town, and Pelonomi Hospital, Bloemfontein
- Patient management
 - Optimized background treatment regimen based on DST
 - Routine clinical monitoring for side-effects
 - Lab monitoring every 2 months and if clinically indicated (full blood picture, thyroid function tests, liver enzymes)

Results (1) – Patient Characteristics

	Age at XDR- or MDR-TB diagnosis	Gender	Previous TB episode	Comorbid conditions at diagnosis	Chest radiographic findings at diagnosis	Resistance Profile of TB Strain	TB Source Case
1	1 year	Female	No	None, non-HIV-infected	Expansile RUL pneumonia with bronchial compression and perihilar lymphadenopathy	HREAmkOfx	MDR-TB, no second-line drugs tested (mother; died)
2	13 years 8 months	Male	No	None, non-HIV-infected	Left upper lobe cavity with bronchopneumonic picture in left lung	HRAmk	XDR-TB (mother; died)
3	10 years 4 months	Male	Yes – 5 years earlier	HIV-infected , deaf mute, epilepsy	Bilateral extensive upper lobe cavitation	HREAmkOfx	MDR-TB, no second-line DST performed (caregiver; died)
4	13 years 6 months	Female	No	None, non-HIV infected	Bilateral upper lob opacification with left upper lobe cavitation	HREAmkEthOfx	XDR-TB (mother, 3 adult siblings; all died)
5	7 months	Male	No	Ex-premature, very low birth weight; ventilated for severe pneumonia at age 3 months; chronic lung diseases; non-HIV-infected	Expansile RML pneumonia with hilar and paratracheal lymphadenopathy and bilateral broncho-pneumonic infiltrates	HREAmkOfx	Unknown, multiple chronic defaulters (1 died, no DST)
6	10 years	Female	No	HIV-infected , unilateral chronic suppurative otitis media	Bilateral cavitations	HREEthKmS	None identified
7	5 years 11 months	Female	Yes – 2 years earlier	HIV infected , bronchiectasis, chronic suppurative otitis media with hearing loss	Miliary pattern with extensive bronchiectasis	HREKmSOfx	None identified

Results (2) – Outcomes and Adverse Events

	Previous TB Treatment during this TB episode	Linezolid-containing TB Regimen	Time to Culture Conversion (from start of Linezolid)	Treatment Outcome	Linezolid Dosage	Adverse Events
1	Failed 4 months HR prophylaxis, and 7 months MDR-TB regimen	HEZEthCpmTrd ClmAmx/ClvLzd	23 days	Cured	10 mg/kg twice daily	None
2	Failed 6 months first-line treatment and 12 months MDR-TB treatment	HESMfxEthTrdPA S ClmAmx/ClvLzdCf z	3 months, 5 days	Cured	300 mg daily	None
3	Failed 6 months first-line treatment and received 1 month MDR-TB treatment	HZCpmEthTrdPAS ClrAmx/ClvLzd	4 months	Cured	300 mg daily	Pancreatitis (8 months)
4	Started XDR-TB treatment as known contact	HZCpmEthOfxTrd PAS ClmAmx/ClvLzd	2 months, 20 days	Cured	300 mg daily	None
5	Started MDR-TB treatment, switched to XDR-TB treatment after 1 month	HZCpmEthOfxTrd PASLzd	3 months	Treatment ongoing, but culture converted	10 mg/kg twice daily	None
6	Failed 6 months first-line treatment, 6 months MDR-TB treatment	HZCpmOfxTrdAm x/ ClvClrPASLzd	18 months (9 months after adherence treatment)	Treatment ongoing, but culture converted	300 mg/kg twice daily (reduced to 200 mg/kg twice daily)	Peripheral neuropathy (24 months); anaemia (25 months)
7	Failed 6 months first-line treatment and 9 months MDR-TB treatment	CpmMfxPASTrd ClmAmx/ClvLzdCf z	Already negative prior to commencing	Treatment ongoing, but culture converted	300 mg daily (discontinued)	Pancreatitis and lactic acidosis (7 months)

Results (3) – Adverse Events

	Antiretrovirals	Adverse Event	Time after starting linezolid	Cause	Action and Outcome
3	d4T, 3TC EFV	Pancreatitis	8 months	Attributed to combination of d4T, 3TC, anticonvulsants, linezolid, and high fat diet	No drugs were stopped; pancreatitis resolved
6	d4T, 3TC, EFV	Peripheral neuropathy Mild anaemia and leucopaenia	24 months	Peripheral neuropathy - attributed to multiple causes Bone marrow showed dyserythropoeisis, possibly HIV-related	Linezolid dose reduced, d4T changed to ABC, terizidone dose reduced, pyridoxine increased – symptoms resolved
7	ABC, 3TC, EFV	Neutropaenia, asymptomatic Elevated transaminases, asymptomatic (ALT 2x ULN; AST 6x ULN) Life-threatening pancreatitis and lactic acidosis – severely ill, requiring ICU admission	6 months	Pancreatitis, lactic acidosis – attributed to linezolid	All meds discontinued, recovered, restarted all medications other than linezolid

Discussion

- Linezolid efficacy
 - Culture conversion – 7/7
 - Favorable outcome – 7/7
 - Efficacious in very difficult cases
- Dosing of linezolid
 - PK differs in children – age-related
 - 10 mg/kg twice daily if <30 kg, if >30 kg 10 mg/kg once daily OR 300 mg once daily
- Adverse events
 - 3/7 with adverse events, including serious events
 - Similar to published adult data
 - Association of HIV and ART with AEs may need further evaluation
 - Few HIV-positive patients described in the literature
 - Close monitoring in HIV-infected patients

Conclusion

- Linezolid-containing regimens can be effective for children with XDR-TB and refractory MDR-TB
- Serious adverse events are frequent, requiring close monitoring
- Forthcoming adult data will help inform paediatric practice
- Children need to be considered in plans for evaluation of existing and novel drugs for DS- and DR-TB