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Linezolid for Children with Tuberculous Meningitis: More Evidence Required

Robindra Basu Roy, MRCPCH and James A. Seddon, PhD

Department of Academic Paediatrics, Imperial College London

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To the Editor,

Tuberculous meningitis (TBM) is a devastating disease. With the currently available treatment regimens one in five children die and only a third of surviving children escape neurologic sequelae.¹ We were interested to read the study by Li *et al* regarding the use of linezolid in children with TBM in Beijing.²

Linezolid is an attractive therapeutic option given its good bioavailability, excellent CSF penetration and proven efficacy against *M. tuberculosis*. However, three major obstacles currently limit the use of linezolid in the treatment of pediatric TBM: efficacy, safety and current high cost. Until this report the only described use of linezolid in pediatric TBM had been in the successful treatment of a South African case of extensively drug-resistant TBM.³

Caution is warranted in interpreting the efficacy of linezolid in the treatment of pediatric TBM from this report. The retrospective design, unrandomized nature of group allocations, and unblinded ascertainment of outcomes limit how much can be inferred. In terms of patient selection, children were given linezolid if they remained febrile after two weeks of receiving conventional treatment and had no neurologic improvement in that time. It is therefore unclear why greater than 50% of children in the control group had a fever clearance time of greater than 4 weeks. It would be useful for the authors to further clarify on the criteria for using linezolid, and from what common reference point during therapy fever clearance time comparisons were made. Persistent fever following initiation of anti-tuberculous therapy with confirmed drug susceptible strains of *M. tuberculosis* is a recognized, although unusual, clinical phenomenon.⁴

It would also be important to know if the improved outcomes were due to linezolid improving the treatment of TBM generally, or if the advantage was the result of improved treatment in cases with drug resistance. It would be interesting to know if there are any

Corresponding Author: Dr. R. Basu Roy, Department of Academic Paediatrics, 2nd Floor, Medical School Building, St. Mary's Campus, Imperial College London, Norfolk Place, London, W2 1PG, United Kingdom, r.basu-roy@imperial.ac.uk, Tel: +4420 7594 8839, Fax: +4420 7594 3984.

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molecular or phenotypic drug resistance results available from either the 14 microbiologically confirmed TB cases, or from the TB source cases identified in 50 of the children.

Regarding safety, the authors report no significant difference in adverse events between the 36 children treated with linezolid and those who received standard treatment. However, it is unclear from the report how the children were evaluated for adverse events and whether they may have experienced any other side effects (such as lactic acidosis, optic neuropathy, impaired renal function, raised amylase or hypoglycemia⁵).

We commend the authors on reporting these cases and providing some much-needed data. We look forward to learning from their experiences in even more depth. In our opinion however, there is currently still insufficient evidence to warrant use of linezolid in pediatric TBM without information strongly suggestive of drug resistance.

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References

1. Chiang SS, Khan FA, Milstein MB, Tolman AW, Benedetti A, Starke JR, et al. Treatment outcomes of childhood tuberculous meningitis: a systematic review and meta-analysis. *Lancet Infect Dis*. 2014 Oct; 14(10):947–57. [PubMed: 25108337]
2. Li H, Lu J, Liu J, Zhao Y, Ni X, Zhao S. Linezolid is Associated with Improved Early Outcomes of Childhood Tuberculous Meningitis. *Pediatr Infect Dis J*. 2016 Jun; 35(6):607–10. [PubMed: 26901441]
3. Alsleben N, Garcia-Prats AJ, Hesselink AC, Willemse M, Donald PR, Schaaf HS. Successful Treatment of a Child With Extensively Drug-Resistant Tuberculous Meningitis. *J Pediatric Infect Dis Soc*. 2015 Sep; 4(3):e41–4. [PubMed: 26407442]
4. Coulter JBS, Baretto RL, Mallucci CL, Romano MI, Abernethy LJ, Isherwood DM, et al. Tuberculous meningitis: protracted course and clinical response to interferon-gamma. *Lancet Infectious Diseases*. 2007;225–32. [PubMed: 17317604]
5. Viswanathan P, Iarikov D, Wassel R, Davidson A, Nambiar S. Hypoglycemia in patients treated with linezolid. *Clin Infect Dis*. 2014 Oct 15; 59(8):e93–5. [PubMed: 24965346]