The Use of New and Repurposed Drugs in Children with Multidrug-Resistant TB: An Overview

Jennifer Furin, MD., PhD
Department of Global Health and Social Medicine
Harvard Medical School
Pediatric MDR-TB: Current State of the Field

- Estimated 33,000 children with MDR-TB each year
- Few diagnosed or offered treatment but those that are have excellent outcomes
- Dosing and safety of currently used agents only recently assessed
- Children with resistance or intolerance to SLDs receive a lower standard of care than adults
New Drugs for Children

- Bedaquiline: PK and safety study planned; no child-friendly formulation; recommended dose 6mg/kg loading followed by 3mg/kg maintenance

- Delamanid: Excellent PK and safety data in children as young as 6 years; pediatric formulation being developed; 100mg twice daily if >35kg; 50mg twice daily if 20-35kg; 3-4 mg/kg daily as a general guide
**Pharmacokinetics and Safety of Delamanid in Pediatric MDR-TB Patients, Ages 6-17 Years**

J. Hafkin1, M. Frias2, A. Hesseling3, A. J. Garcia-Prats3, H. S. Schaaf3, M. Gler4, N. Hittel5, C. Wells5, L. Geiter6, S. Mallikarjun1

1Otsuka Pharmaceutical Development & Commercialization, Rockville, MD, USA; 2De La Salle Health Sciences Institute, Dasmariñas, Philippines; 3Desmond Tutu TB Centre, Dept of Paediatrics and Child Health, Stellenbosch University, Cape Town, South Africa; 4Otsuka Manilla Research Center, Makati, Philippines; 5Otsuka Novel Products GmbH, Munich, Germany

**Background**

A sizable proportion of global multidrug-resistant tuberculosis (MDR-TB) cases occur each year in children <15 years (1,2). Treatment of MDR-TB in children, however, remains complicated by the difficulty in confirming a microbiologic diagnosis, the requirement for prolonged, potentially toxic regimens, and the lack of child-friendly formulations. Although recent cohort studies have reported high rates of treatment success in children with MDR-TB (3,4), only a handful of the commonly used second-line anti-TB drugs have been assessed in prospective pediatric pharmacokinetic (PK) studies (4-5).

Delamanid, a nitro-dihydroxy-imidazooxazole anti-TB agent with bactericidal activity, was shown to improve two month sputum culture conversion and long-term treatment outcomes in clinical trials of adults with pulmonary MDR-TB (6-11). Thus far, the main safety signal identified is QT prolongation. Nevertheless, there has been no clinical serious adverse events (SAEs) associated with this finding. Study 242-12-232 (Trial 232) is a Phase 1, open label, uncontrolled, multiple-dose trial of delamanid in children with MDR-TB (ages 6-17) in the Philippines and South Africa. The aim of this trial was to assess the short-term safety, tolerability and PK of delamanid in children, with the ultimate goal of defining a dosing regimen for pediatric patients with MDR-TB.

**Methods**

Children with confirmed or presumptive MDR-TB were enrolled in two sequential age treatment groups: Group 1 (12-17 years) and Group 2 (6-11 years). Those with HIV infection, cardiac, renal or hepatic abnormalities were excluded from enrollment. Groups 1 and 2 received delamanid 1000 mg and 500 mg bid, respectively, in combination with an optimized background regimen (OB) or anti-TB agents for 10 days followed by 8 days of OB alone. Clinical and safety assessments, including ECGs, were performed at screening, baseline, days 1, 10, and 18.

Serial PK sampling was performed on days 1 and 10; sparse PK sampling was done on days 2, 11, 13, and 15. A validated liquid chromatography-tandem mass spectrometry method was used to determine plasma concentrations of delamanid and DM-6705, a key metabolite thought to be most closely associated with QT prolongation (12). PK parameters Cmax, Cmin, AUC0-24h and f1(24h) were determined for delamanid and DM-6705, and steady state oral clearance (CL/F) was calculated for delamanid using noncompartmental methods. Patients completing this study were eligible to enroll in a long-term 6-month trial of delamanid (Study 242-12-233).

**Results**

13 patients were enrolled in this trial: 7 in Group 1 (4 male, 3 female); all from the Philippines; median weight = 38.5 kg) and 6 in Group 2 (2 male, 4 female; 4 from the Philippines; 2 from South Africa; median weight = 25 kg).

No patients discontinued delamanid or study participation prior to trial completion. No patient experienced any serious adverse events; none had an absolute QT/EF >500ms or an increase in QT/EF from baseline >60ms.

Key PK parameters for delamanid and DM-6705 on Day 1 and Days 10 are presented in the preceding Tables. Median delamanid and DM-6705 peak plasma concentrations and AUC on Day 10 were higher for Group 2 compared to Group 1, with similar elimination half-lives, likely due to lower body weights of patients in Group 2.

**Conclusions**

Delamanid was well tolerated by this cohort of pediatric patients. The median delamanid exposures were higher in the pediatric patients compared to similar doses administered to adult patients. This is likely due to lower body weights of the pediatric patients compared to the adults and is consistent with the differences observed between Group 1 and 2. Overall, the range of Cmax and AUC0-24h was in both age groups were within the ranges observed in adult clinical trials. A follow up study to confirm the longer term safety, tolerability and PK of delamanid in combination with OB in children in these age ranges and in younger children (0-5 years) is ongoing.

**References**

1. NAP Global Tuberculosis Report 2014.

**Contacts**

Jeffrey Hafkin, MD
jeffrey.hafkin@otsuka-us.com

Sureh Mallikarjun PhD
sureh.mallikarjun@otsuka-us.com

Otsuka Pharmaceutical Development and Commercialization
2404 Research Blvd, Rockville, MD 20850, USA
Repurposed Drugs and Children

• Linezolid: Good PK and safety data from bacterial infections; available as a suspension but global shortage; recommended dose is 10mg/kg twice daily (<10years) or 300mg once daily

• Clofazimine: Limited PK and safety data; no child friendly formulation; recommended dose is 2-3mg/kg daily; can dose every other day in smaller children if unable to get gelcaps <100mg
Pediatric MDR-TB

• Don’t be afraid of treating; be afraid of NOT treating
• Community of experts: http://sentinel-project.org/
• Contact me at any time: jenniferfurin@gmail.com
Conclusions

- Children should NOT be denied access to new and repurposed drugs while waiting for ideal dosing recommendations
- Use of new drugs can minimize toxicity
- DLM is the new drug of choice for children
- Advocacy needed to ensure children also benefit from advances in treatment regimens