Patients and TB: Improving treatment outcomes through a patient centred approach and access to new treatments

5th TB Symposium – Eastern Europe and Central Asia
Ministry of Labour, Health and Social Affairs of Georgia
and Médecins Sans Frontières

22- 23 March , 2016 , TBILISI , GEORGIA

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

MEDECINS SANS FRONTIERES

MINISTRY OF LABOUR, HEALTH AND SOCIAL AFFAIRS OF GEORGIA

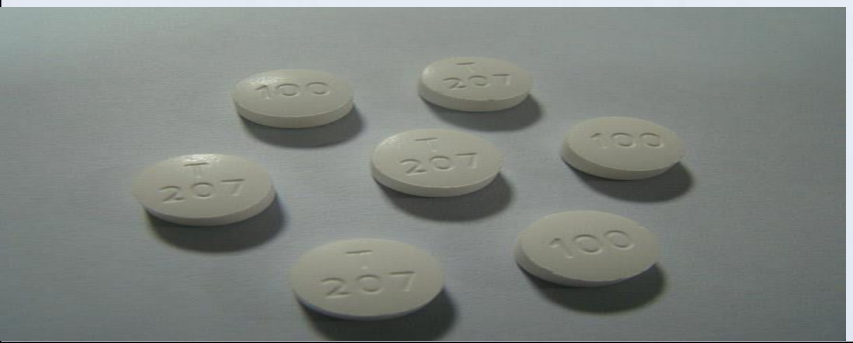
Pediatric MDR-TB: Current State of the Field

- 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



ICAAC 2015 Poster A-960

Pharmacokinetics and Safety of Delamanid in Pediatric MDR-TB Patients, Ages 6-17 Years

J.Hafkin[1], M. Frias[2], A. Hesseling[3], A. J. Garcia-Prats[3], H. S. Schaaf[3], M. Gler[4], N. Hittel[5], C. Wells[1], L. Geiter[1], S.Mallikaarjun[1]

[1]Otsuka Pharmaceutical Development & Commercialization, Rockville, MD, USA; [2]De La Salle Health Sciences Institute, Dasmariñas, Philippines; [3]Desmond Tutu TB Centre, Dept of Paediatrics and Child Health, Stellenbosch University, Cape Town, South Africa; [4]Otsuka Manila Research Center, Makati, Philippines; [5]Otsuka 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), 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-dihydro-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, to date there have 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 100mg and 50mg bid, respectively, in combination with an optimized background regimen (OBR) of anti-TB agents for 10 days followed by 8 days of OBR 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, 15, and 18. 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 C_{max}, t_{max}, AUC_{0-24}, and $t_{1/2,z}$ were determined for delamanid and DM-6705, and steady state oral clearance (CLss/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

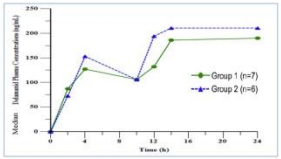
Baseline Demographics

Category	Group 1	Group 2
Age (Yrs) [Median (Range)]	15.0 (13-17)	9.5 (7-11)
Sex	Male = 4 (57%)	Male = 2 (33%)
	Female = 3 (43%)	Female = 4 (67%)
Weight (Kg) [Median (Range)]	38.5 (26-45)	25.0 (16-34)
BMI, Kg/m^2 [Median (Range)]	15.9 (15-20)	16 (14-21)

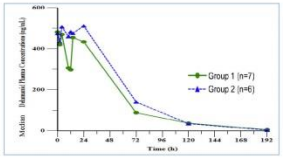
Baseline Clinical Features

Category		Group 1	Group 2
Diagnostic Class	Confirmed	6 (86%)	3 (50%)
	Presumptive	1 (14%)	3 (50%)
Site of Disease	Pulmonary	7 (100%)	2 (33%)
	Extrapulmonary	0	1 (17%)
	Both	0	3 (50%)

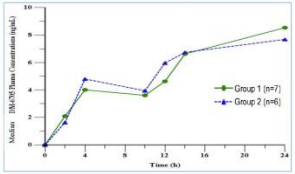
Median Delamanid Plasma Concentrations on Day 1



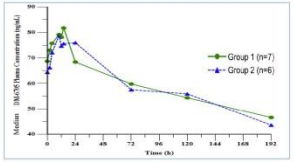
Median Delamanid Plasma Concentrations following Day 10 Dosing



Median DM-6705 Plasma Concentrations on Day 1



Median DM-6705 Plasma Concentrations following Day 10 Dosing



Median Delamanid Plasma Pharmacokinetic Parameters

Parameters	Group 1		Group 2	
Day	1	10	1	10
N	7	7	6	6
C_{max} (ng/mL)	268	557	315	573
t_{max} (h) [Range]	14.00 (2.0 - 24.0)	4.00 (0.0 - 24.0)	12.00 (2.0 - 14.0)	12.00 (2.0 - 24.0)
AUC_{0-24} (ng×hr/mL)	3880	9730	4110	12000
CLss/F (L/h/kg)	ND	0.591	ND	0.368
$t_{1/2,z}$ (h)	ND	28.4	ND	23.5

Median DM-6705 Plasma Pharmacokinetic Parameters

Parameters	Group 1		Group 2	
Day	1	10	1	10
N	7	7	6	6
C_{max} (ng/mL)	8.60	81.7	7.68	90.0
t_{max} (h) [Range]	24.00 (14.0 - 24.0)	12.00 (10.0 – 14.0)	19.00 (12.0 - 24.0)	12.00 (2.00 – 24.00)
AUC_{0-24} (ng×hr/mL)	113	1780	122	1870
$t_{1/2,z}$ (h)	ND	216	ND	257

Results

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

No patients discontinued delamanid or study participation prior to trial completion. No patient experienced any serious adverse events; none had an absolute QTcF >500ms or an increase in QTcF 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 C_{max} and AUC_{0-24} values 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 OBR in children in these age ranges and in younger children (0-5 years) is ongoing.

References

1. WHO Global Tuberculosis Report 2014.
2. Jenkins H. Lancet 2014.
3. Seddon J. Thorax 2014.
4. Thee S. Antim Agent Chemo 2014.
5. Thee S. Clin Infect Dis 2014.
6. Matsumoto M. PLoS Med 2006.
7. Diacon A. Int J Tuberc Lung Dis 2011.
8. Gler M. N Eng J Med 2012.
9. Skripconoka V. Eur Respir J. 2013.
10. Wells C. Eur Respir J. 2013.
11. Gupta R. N Engl J Med 2015.
12. Assessment report Deltyba, Proc No.: EMEA/H/C/002552. EMA, CHMP; 2013.

Contacts

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

Suresh Mallikaarjun PhD
Suresh.Mallikaarjun@otsuka-us.com

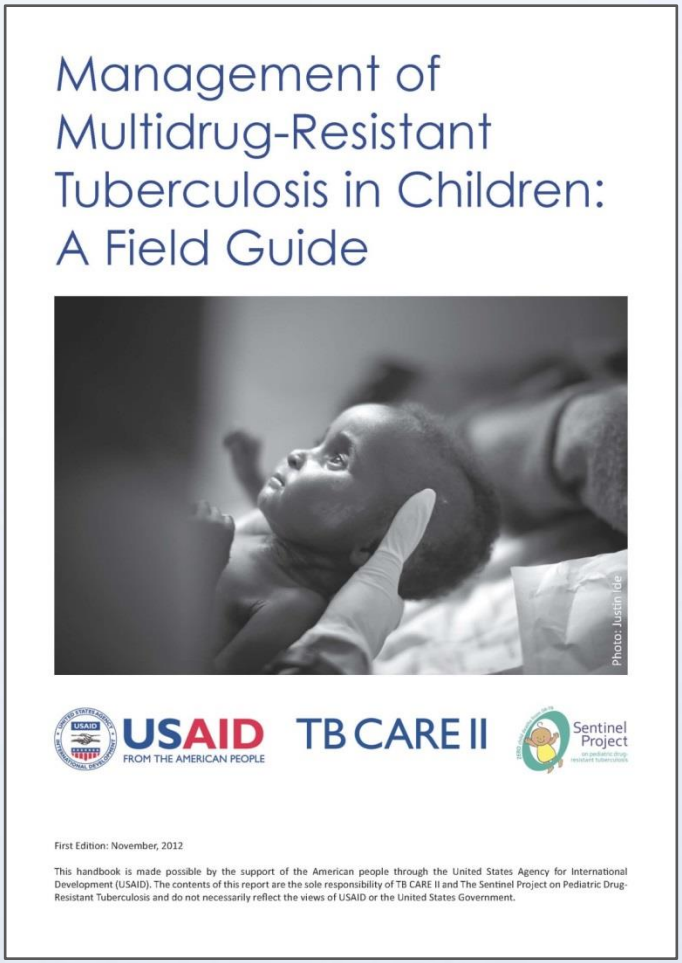
Otsuka Pharmaceutical Development and Commercialization
2440 Research Blvd, Rockville, MD 20850, USA

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