Trial Design Considerations in Pediatric Trials of Antituberculosis Drugs

Jeffrey R. Starke, M.D.
Professor of Pediatrics
Baylor College of Medicine
Disclosures and Acknowledgments

- Dr. Starke is a member of the Data Safety Monitoring Board for the pediatric pK trials of delamanid conducted by Otsuka Pharmaceuticals

- I would like to thank Dr. Tony Garcia-Prats and the TB Alliance for their help in preparing this talk
How Childhood TB Differs From Adult TB

- Develops more rapidly after infection [< 2 years]
- Smaller burden of organisms
- Only 30% of cases can be confirmed microbiologically
- Diagnostic tetrad: symptoms, radiology/physical examination, test of infection, epidemiology [recent contact] – *Standardized research definitions exist*
- Increased propensity for extrathoracic disease, especially meningeal and disseminated [miliary]
- Relapse and failure difficult to define, rarely marked by positive cultures
- Children tolerate most TB drugs better
- Fewer children have other significant medical problems – hepatic, renal, cardiac
AVERAGE AGE RISK FOR TB DISEASE AFTER INFECTION (PRE-BCG)

Childhood TB Burden

- Global burden of childhood TB (2015)
  - Estimated incident cases: 1 Million (5-10% HIV+)
  - Only 384,035 notified to WHO
  - Estimated mortality – 210,000 (40,000 HIV+)

- Global burden of MDR-TB in children
  - Estimated incident cases– 25,000-32,000/y
  - Small minority identified and properly treated
  - HIV-associated with poor outcome

Childhood TB Burden

- Est. burden of LTBI in children
  - DS-TB – Total currently infected 67,000,000
  - MDR-TB – Total currently infected 2,000,000
- Estimated child household contacts <5y eligible for LTBI treatment globally is 1.22 million (range 1.18-1.26)

Current TB Treatment in Children

<table>
<thead>
<tr>
<th>Drug-susceptible TB disease</th>
<th>2RHZ(E)/4RH (Rif 8-12mg/kg increased to 10-20mg/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug-susceptible TB infection</td>
<td>6-9H, 4R, 3HP (&gt;2 years)</td>
</tr>
<tr>
<td>Multidrug-resistant TB disease</td>
<td>9-12 months – 4-5 Km-Mfx-PTO-CFZ-hdINH-EMB-PZA/5-7 Mfx-PTO-CFZ-EMB-PZA; Other “local” regimens up to 18 months (6 months injectable)</td>
</tr>
<tr>
<td>Multidrug-resistant TB infection</td>
<td>Levofloxacin - ?duration, ? second drug</td>
</tr>
</tbody>
</table>
Some Current Knowledge Gaps in Treatment of Childhood Tuberculosis

- PK and adverse effect profiles of existing Group 2-5 TB drugs in children
- Optimal duration and follow up of TB regimens for DS- and DR-TB
- Adequate drug combinations and relevant doses for some forms of EPTB that are more common in children [osteoarthritis, meningitis]
- Optimal duration and combination of drugs for TB treatment in children living with HIV
- Optimal drug combinations and durations for MDR-TB in children, especially those with minimal disease
Some Barriers to Inclusion of Children in TB Studies

- Difficulty of microbiologic confirmation of disease, failure and relapse
- Difficulty in performing pK sampling in children, especially infants and toddlers
- Complacency about the effectiveness of existing regimens
- Trial design issues: endpoints, sample sizes
- Capacity: lack of adequate trial sites
- Complicating research oversight and regulatory concerns
- Taking research funds away from adult studies

However, children have >10% of the disease burden but pediatric studies have < 2% of the research funding
Regulatory Issues

**European Union**
- Regulation EC 1901/2006: requires an early Pediatric Investigation Plan no later than the completion of pK studies in adults

**United States**
- TB drugs qualify for orphan designation; inclusion of children in prelicensure trials is not required

**South Africa**
- No specific pediatric considerations – “Special attention to minors”
# Some TB Drug Trials in Children

Selected ongoing or planned pediatric TB trials – DS-TB, TB-HIV

<table>
<thead>
<tr>
<th>Trial</th>
<th>Summary</th>
<th>HIV</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>DATiC (NIH)</td>
<td>PK and safety of <strong>first-line TB drugs</strong> in children using 2010 WHO dosing</td>
<td>HIV+/-</td>
<td>Completed enrolment HIV-</td>
</tr>
<tr>
<td>Infant TB (TBA)</td>
<td>Evaluate the PK and safety of <strong>first line TB drugs</strong> using 2010 WHO dosing in infants &lt; 12 months</td>
<td>HIV+/-</td>
<td>Completed 2015</td>
</tr>
<tr>
<td>Opti-Rif (TBA)</td>
<td>Evaluate optimal dosing and safety of rifampicin in HIV-uninfected children</td>
<td>HIV- only</td>
<td>Anticipated opening in 2017</td>
</tr>
<tr>
<td>Study 35 (CDC/TBTC)</td>
<td>PK and safety study of RFPT/INH co-formulation in children for prevention of TB</td>
<td>HIV+/-</td>
<td>Anticipated opening 2017</td>
</tr>
<tr>
<td>IMPAACT P1101 (NIH)</td>
<td>Phase I/II, dose-finding, safety, tolerance, and PK study of RAL- naïve children on RIF-based TB therapy</td>
<td>HIV+ only</td>
<td>Enroling</td>
</tr>
<tr>
<td>RTV super-booster for HIV-TB coinfection (DNDi)</td>
<td>Phase I/II, PK and safety, to develop a stand-alone ritonavir (RTV) booster formulation to be added to the optimized LPV/r-based paediatric ARV regimen</td>
<td>HIV+ only</td>
<td>Completed enrolment</td>
</tr>
<tr>
<td>IMPAACT P1106 and P1026s (NIH)</td>
<td>PK of ARVs and TB medications in low-birth wt and premature infants, and pregnant women</td>
<td>HIV+/-</td>
<td>Ongoing</td>
</tr>
</tbody>
</table>
# Some TB Drug Trials in Children

## Selected ongoing or planned pediatric TB trials – MDR-TB

<table>
<thead>
<tr>
<th>Trial</th>
<th>Summary</th>
<th>HIV</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>232/233 (Otsuka)</td>
<td>Phase I/II, PK and safety of delamanid PK and safety in children with MDR-TB</td>
<td>HIV- only</td>
<td>Paed formulation; completed enrolment Gr 1-3, enrolling Gr 4</td>
</tr>
<tr>
<td>C211 Paediatric</td>
<td>Phase I/II study of bedaquiline PK and safety in children with MDR-TB</td>
<td>HIV- only</td>
<td>Paed formulation; enrolling Gr 1 from 2016</td>
</tr>
<tr>
<td>Bedaquiline (Jannsen)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IMPAACT P1108</td>
<td>Phase I/II study of bedaquiline PK and safety in children with MDR-TB</td>
<td>HIV+-/-</td>
<td>? Paed formulation; anticipated opening Q1 2017</td>
</tr>
<tr>
<td>(NIH)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MDRPK1 (NICHD)</td>
<td>PK and safety of second-line TB medications in HIV-infected and –</td>
<td>HIV+-/-</td>
<td>Completed enrolment</td>
</tr>
<tr>
<td></td>
<td>uninfected children</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MDRPK2 (NICHD)</td>
<td>Optimized dosing of key second-line TB medications (Mfx, Lfx, Lzd) in</td>
<td>HIV+-/-</td>
<td>Enrolling</td>
</tr>
<tr>
<td></td>
<td>children with MDR-TB (crushing, palatability)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TB-CHAMP (BMRC/SAMRC)</td>
<td>Phase III, to evaluate the efficacy of Lfx vs. placebo for the</td>
<td>HIV+-/-</td>
<td>Anticipated opening 2016</td>
</tr>
<tr>
<td></td>
<td>prevention of MDR-TB in child household contacts</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Figure 2: Paediatric studies decision tree
Reproduced from the US Food and Drug Administration.66 ER=exposure-response. PD=pharmacodynamic. PK=pharmacokinetic.
TB Drug Trials in Children: Challenges and Lessons Learned

**Efficacy**

- Difficult to study regimens [as opposed to individual drugs] in children – sample size, cost, capacity, lack of microbiologic markers
- Efficacy studies of regimens for intrathoracic TB in children usually not necessary to allow pediatric treatment
- Aim is to match pK of individual drugs in children with pK in adults proven to be safe and effective
- Efficacy studies in children might be needed for some forms of EPTB and prevention
- Some children with milder forms of disease may require fewer drugs for a shorter period of time
Enrollment of children in drug research after:

- Full range of non-clinical studies in adult animals
- Safety, pharmacology and genotoxicity studies and appropriate juvenile animal studies do not suggest cause for concern
- Animal and human studies have substantiated anti-
  Mycobacterium tuberculosis activity
- pK and PD data from adults allow for selection of appropriate pK targets for children, or a safe dose has been established for adults [Phase IIb]
- Data on drug interactions with ARV drugs used in children
TB Drug Trials in Children: Challenges and Lessons Learned

When to Begin Pediatric Studies

- Previous practice to wait until licensure ensured lack of data on pK, safety and tolerability and lack of pediatric dosage forms
- Pediatric studies should begin when safety and basic pK are established in adults – Phase IIb
- Adolescents [> 10 years old] should be included in late phase [IIb] adult studies
- Begin development of pediatric dosage forms at Phase IIa so available after Phase IIb
<table>
<thead>
<tr>
<th>Development strategy</th>
<th>Historical</th>
<th>Current</th>
<th>Proposed/accelerated pediatric development</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No specific pediatric development; children are given adult doses, or doses are adjusted according to weight</td>
<td>Pediatric development is generally initiated once a drug or regimen is approved for adults, starting with adolescents and gradually moving to younger children</td>
<td>Single-dose PK studies begin as soon as successful phase II adult studies are complete. Study multiple dose/comprehensive PK and safety in all children (no age de-escalation) in parallel with phase III (in adults)</td>
</tr>
<tr>
<td>Challenges</td>
<td>Drugs in regimens are administered using ad hoc methods (administering adult-sized pills, crushing, dispersion in liquids etc.). Pediatric safe/efficient dosing often unknown</td>
<td>Significant delays for access to new drug or regimens for children</td>
<td>Overcoming traditional clinical and ethical considerations of how children can be studied</td>
</tr>
</tbody>
</table>

PK = pharmacokinetic.
TB Drug Trials in Children: Challenges and Lessons Learned

Pharmacokinetics and Study Design

- Conservative approach was step-wise age de-escalation, often took years
- Age de-escalation now widely accepted as unnecessary for the vast majority of drugs unless there are specific safety concerns
- Developmental pK and PD especially important for infants and toddlers
- Suggested age ranges for study: 0-3 months; 3-24 months; 2-4 years; 5-10 years; and > 10 years.
TB Drug Trials in Children: Challenges and Lessons Learned

Pharmacokinetics and Study Design Issues

- Appropriate sample size for pK within each age group
- Single-dose sampling in all age groups, then move to multiple dose sampling
- Rationalizing sample points – reducing the burden of number and size of blood draws
- Drug concentrations in CSF
- Use of dosing simulations
- Trial design for children with HIV infection
TB Drug Trials in Children: Challenges and Lessons Learned

Dosage formulations
- Age-specific, palatability, taste, acceptability

Trial capacity
- Need a more robust trial network in various geographic locales with sustained funding
- Need to develop pediatric investigators

Incentives for child studies and formulations
- Extended market exclusivity and priority review vouchers have been ineffective for pediatrics
- Advance Market Commitment?
- Include pediatric experts on DSMBs
- Require pediatric studies for public funding
Traditional Development vs. Accelerated Development

TRADITIONAL:

Adult Drug Development Process: 7+ years

Pediatric Drug Development Process: 7+ years

ACCELERATED:

- Preclinical
- Phase 1
- Phase 2
- Phase 3
- Approval for Adults
- Approval for Children

- Juvenile toxicology
- Formulation Work
- BE Studies

- Single- and multiple-dose pK studies simultaneously in ages 0 to 16

- Consider inclusion of children (≥10 Y) and adolescents in adult Phase 3 studies

An accelerated pediatric drug development pathway could allow life-saving treatments to reach children sooner than they do today

Integrated Adult & Pediatric Development Process
Figure  Optimized anti-tuberculosis drug development: integrated adult and pediatric clinical trials. PK = pharmacokinetic; DS-TB = drug-susceptible TB; DR-TB = drug-resistant TB; TB = tuberculosis.
Overview of Approach to Studying TB Drugs in Children

- Create regulatory and economic incentives for industry and academia to develop and study pediatric formulations of old and new drugs
- Create capacity building for pediatric trials
- Start development of “child-friendly” pediatric drug formulations earlier
- Start pediatric pK studies concomitantly with Phase IIb studies in adults
- Establish function within childhood TB community similar to the Pediatric Antiretroviral Drug Optimization efforts
  - Develop consensus priorities on key drugs, formulations, strengths
  - Identify key research gaps
  - Include specific representation of pediatric HIV expertise
An overzealous attempt to protect some children from the possible harms of research perversely causes harm, by either denying access to treatment or through exposing children to the risks of inappropriate dosages of new medications.

“Children have the same right to benefit from research as do adults.”