Antimycobacterial Drug Development

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Outline

- Background Information
- Clinical Trials
- Endpoints
- Data Standards
- Resources
- Division Contacts
- GAIN

TB Global Disease Burden

- Incidence
  - 8.8 million new TB Cases in 2010
- Mortality
  - 1.4 million deaths from TB in 2010, including 0.35 million people with HIV
- Treatment
  - 5.7 million new and recurrent TB cases treated in 2010

Source: WHO Global Health Observatory
http://www.who.int/topics/tuberculosis/en/

TB - Challenges

- Many of the drugs that we rely upon to treat TB were approved many years ago
- Resistance has developed to these drugs for treating patients with TB
- Economic Factors – Global disease burden for TB is considerable and found in many regions of the world where resources to provide care are limited

- Recent increase in activity in development of new drugs for TB

Approved Drugs for TB - 1

- Isoniazid – tablets 100 & 300 mg; solution for injection
  - Treatment and prevention of TB ("all forms of tuberculosis")*
- Rifadin & Rifadin IV (rifampin) – capsules 150 & 300 mg; solution for injection (IV)
  - Treatment of "all forms of tuberculosis"*
- Myambutol (ethambutol hydrochloride) – tablets 100 & 400 mg
  - Treatment of pulmonary tuberculosis*
- Pyrazinamide (pyrazinamide) tablets 500 mg
  - Initial treatment of active tuberculosis*
- Priftin (rifapentine) – tablets 150 mg
  - Treatment of pulmonary tuberculosis*

* When combined with other antituberculous drugs

Approved Drugs for TB - 2

- Streptomycin (streptomycin sulfate) - injection - lyophilized powder for solution; 1 gram vial
  - Treatment of tuberculosis – 4th drug in a regimen*
- Paser (aminosalicylic acid) – granules 4 gram; for po use
  - Treatment of tuberculosis* - most commonly when INH and Rif resistant or can't be used
- Capastat sulfate (capreomycin) – injection; powder for solution (1g vial)
  - Treatment of pulmonary tuberculosis* when primary agents not effective or can't be used.
- Seromycin (cycloserine) – capsules 250 mg
  - Treatment of active pulmonary and extrapulmonary tuberculosis when treatment with primary meds is inadequate
- Trecator (ethionamide) – tablets 250 mg
  - treatment of active tuberculosis when resistant to isoniazid or rifampin, or intolerance

* When combined with other antituberculous drugs

Approved TB FDCs

- Rifamate & Isonarif (rifampin and isoniazid) 300/150 mg
  - Capsules
  - Treatment of pulmonary tuberculosis
- Rifater (rifampin, isoniazid, pyrazinamide) 120/50/300 mg
  - tablets

Preclinical

- Preclinical work - Toxicology
  - Standard nonclinical safety studies
  - Reproductive toxicology studies
  - Carcinogenicity studies - initiate if >6 months exposure
- Preclinical Work – Activity
  - Animal models to evaluate activity
  - Animal models to evaluate activity in regimens
  - Rational approaches to making choices for future development

Early Phase Clinical Development

- Tissue distribution of Drug to relevant body sites
- Early Bactericidal Activity Studies
  - Daily quantitative cultures
  - Minimize risk of development of resistance
    - short duration, immune-competent, treatment naïve, at low risk of infection with a resistant strain
- Phase 2 trials that evaluate microbiological outcomes at early timepoints
  - Absence of AFB in sputum
  - Proportion of no growth of M. tb at an early time point
- Rational approaches to inform drug and regimen selection for ph3 trials

Patient Population(s) for Phase 3 Considerations

- Previous trials have generally enrolled patients with pulmonary TB
- Patients with HIV/AIDS – immune compromised patients
- Patients with extra-pulmonary TB
  - Tissue levels achieved?
  - Appropriate endpoint?
- Patients likely to have drug-resistant TB
  - Regimen of other drugs appropriate?
  - Longer duration therapy?

Guidance for Industry - Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products - 1

In 1962, Congress amended the Federal Food, Drug, and Cosmetic Act to add a requirement that, to obtain marketing approval, manufacturers demonstrate the effectiveness of their products through the conduct of adequate and well-controlled studies.

Available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072008.pdf

Guidance for Industry - Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products -2

In section 115(a) of the [FDA] *Modernization Act, Congress amended section 505(d) of the Act*

to make it clear that the Agency may consider "data from one adequate and well-controlled clinical investigation and confirmatory evidence" to constitute substantial evidence if FDA determines that such data and evidence are sufficient to establish effectiveness"

Available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072008.pdf

Trial Designs - 1

- Superiority in an add on design
  - Test + regimen > regimen
- Superiority of Test regimen when substituting the Test Drug for component
  - Test + ABC > ABCD
- Non-inferiority when substituting Test for one component of the regimen when contribution of the substituted component known
  - Substitution for rifampin in a regimen
  - Treatment shortening (Andrew Nunn)
- Superiority in dose response design
  - higher dose of Test + regimen > lower dose of Test + regimen

*July 30-31, 2009 workshop transcript available
http://www.fda.gov/Drugs/NewsEvents/ucm168975.htm

Trial Designs - 2

- Study Population may impact upon trial designs
  - For example, if XDR-TB
    - Studying two or more investigational drugs for use in combination
    - Guidance document - *Codevelopment of Two or More Unmarketed Investigational Drugs for Use in Combination*
- Availability and future availability of new diagnostics (e.g., rapid diagnostics) may impact trial designs and ethics of trial designs
- Consideration of trial feasibility, science, risk/benefit, degree of unmet need, ethics

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM236669.pdf

Endpoint Definitions

- 21 CFR 314.126(b)(6): *The methods of assessment of subjects' responses are well-defined and reliable. The protocol for the study and the report of results should explain the variables measured, the methods of observation, and criteria used to assess response.*

- Federal Register/Vol. 57, No.73/April 15, 1992: *A surrogate endpoint, or "marker", is a laboratory measurement or physical sign that is used in therapeutic trials as a substitute for a clinically meaningful endpoint that is a direct measure of how a patient feels, functions, or survives and that is expected to predict the effect of therapy.*

Endpoints

- Types of Endpoints
  - Clinical Response
  - Microbiological Response
- Early endpoints – Later endpoints
- Surrogate endpoints

Clinical Endpoints

- Clinical endpoint
  - an endpoint that assesses how a patient feels, functions, or survives
  - For TB studies
    - Traditional endpoint of relapse, recurrence, or death during and after treatment
    - Importance of minimizing loss to follow-up at later time point
  - For the future ?
    - Evaluation of an early clinical response endpoint could provide important information on early patient response to asses drug effect

Microbiological Endpoint

- Culture conversion to negative
- Solid culture media
  - Traditionally used in past trials of TB drugs
- Liquid culture media
  - Some are CDRH-cleared devices
  - Product label information (e.g., MGIT device)
    - Negative result = no growth of MTB
    - Positive result = additional work up to include identification (MTB or other mycobacteria) and susceptibility by traditional means on solid media

Microbiological Endpoint

- Liquid culture may be a more sensitive indicator for growth of MTB
  - Gler MT, et al, NEJM 2012;366:2151-60
- CPTR's Biomarkers & Clinical Endpoints Working Group plans to submit a DDT qualification package for liquid culture
- An ideal package of information for DAIP review
  - Goal is to incorporate the review findings of a liquid culture DDT qualification package into TB guidance document
- Future advances in rapid diagnostics

21 CFR 312.500
Subpart H – Accelerated Approval

- ***Scope.*** *This subpart applies to certain new drug products that have been studied for their safety and effectiveness in treating serious or life-threatening illnesses and that provide meaningful therapeutic benefit to patients over existing treatments (e.g., ability to treat patients unresponsive to, or intolerant of, available therapy, or improved patient response over available therapy).*

21 CFR 312.510
Subpart H – Accelerated Approval

- ***Approval based on a surrogate endpoint or on an effect on a clinical endpoint other than survival or irreversible morbidity.***
- *FDA may grant marketing approval for a new drug product on the basis of adequate and well-controlled clinical trials establishing that the drug product has an effect on a surrogate endpoint that is reasonably likely, based on epidemiologic, therapeutic, pathophysiologic, or other evidence, to predict clinical benefit or on the basis of an effect on a clinical endpoint other than survival or irreversible morbidity. Approval under this section will be subject to the requirement that the applicant study the drug further, to verify and describe its clinical benefit, where there is uncertainty as to the relation of the surrogate endpoint to clinical benefit, or of the observed clinical benefit to ultimate outcome. Postmarketing studies would usually be studies already underway. When required to be conducted, such studies must also be adequate and well-controlled. The applicant shall carry out any such studies with due diligence.*

Surrogate Endpoint

- Sputum culture conversion to no growth
  - Surrogate endpoint for accelerated approval for treatment of pulmonary TB
  - See AIDAC discussion and background materials 3 June 2009
    - http://www.fda.gov/AdvisoryCommittees/Calendar/ucm126290.htm
  - Confirmation of surrogate endpoint
    - Endpoints of relapse, recurrence, or death during and after treatment

Antimycobacterial Drug Development Theory and Practice - 1

- Most would want
  - A robust pipeline of new antimycobacterial drugs – especially drugs with new mechanisms of action
  - Precise characterization of safety and efficacy
  - Agents already available that are active against new resistance mechanisms that will emerge in the future
  - Little uncertainty
- All of these goals may not be achievable
  - economic, scientific, regulatory, practical issues/challenges

Antimycobacterial Drug Development Theory and Practice - 2

- Appropriate balance of risk and benefit and how this may impact antimycobacterial drug development
- Important to also consider practical and feasibility aspects of clinical trial design and ways we can improve the efficiency of clinical trials improve follow-up
- Ultimately these decisions can have an impact on patients and public health
- We look forward to the development of new safe & effective antimycobacterial drugs
- Antimicrobial stewardship
  - It will be essential that the drugs be used prudently and appropriately in order to slow the rate at which resistance develops (e.g., DOTS)

21 CFR 312 Subpart E

The purpose of this section is to establish procedures designed to expedite the development, evaluation, and marketing of new therapies intended to treat persons with life-threatening and severely-debilitating illnesses, especially where no satisfactory alternative therapy exists…

The Food and Drug Administration (FDA) has determined that it is appropriate to exercise the broadest flexibility in applying the statutory standards, while preserving appropriate guarantees for safety and effectiveness. These procedures reflect the recognition that physicians and patients are generally willing to accept greater risks or side effects from products that treat life-threatening and severely-debilitating illnesses, than they would accept from products that treat less serious illnesses. These procedures also reflect the recognition that the benefits of the drug need to be evaluated in light of the severity of the disease being treated.

Looking Forward

- Even after a drug is approved there may be additional questions that a sponsor may choose to evaluate that could provide additional valuable information
  - Durations of therapy
  - Combinations with particular drugs
  - Treating other sites of infections
  - Other questions

Safety

- Important to characterize the safety of a new TB drug
- Inform healthcare providers and patients of adverse evnt profile to facilitate decision making steps to reduce risk
- Some of the current drugs have notable adverse event profiles and/or drug interactions
- Balancing Risks – Benefits – Uncertainty
- Size of safety population balanced against benefits that drug provides and degree of unmet need it can address
  - A drug for treating patients with many existing options
    vs.
  - A drug for the treatment of patients with MDR or XDR TB
- Ideally, well-tolerated drugs with minimal drug interactions

Data Standards Development

- Development
  - Roadmap Project standard data elements and terminology led to balloted HL7 standard
- Validated
  - simulated NDA review of data converted in standard terminology and content format -- CDC study 22
  - additional simulated review of legacy datasets successful
- Modeling and Refinement
  - CPTR collaborative – curated and released a Supplement to the SDTM Use Guide (CDISC standard)
  - Implementation – use of the data standard in review of new drug applications submitted in the standard
- The Critical Path to TB Drug Regimens (CPTR) and the CDISC SDS team released v1.0 of the Tuberculosis Therapeutic Area Supplement to the Study Data Tabulation Model User Guide 6/2012

GAIN

- Provides for a 5-year exclusivity extension upon approval for certain antibacterial or antifungal drugs
- Defines a Qualifying Infectious Disease Product (QIDP) as *an antibacterial or antifungal drug for human use intended to treat serious of life-threatening infections, including those caused by…*
- QIDPs eligible for Fast Track and Priority Review

Division of Anti-Infective Products (DAIP)

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Some Resources

- Guidance for Industry
  - Neglected Tropical Diseases of the Developing World: Developing Drugs for Treatment or Prevention, August 2011 (Draft)
  - Tropical Disease Priority Review Vouchers, October 2008 (Draft)
  - Codevelopment of Two or More Unmarketed Investigational Drugs for Use in Combination, December 2010 (Draft)
- Draft Guidance on Developing Drugs for TB – well along in preparation

Upcoming AIDAC Meeting Announced in Federal Register

- **November 28, 2012: Anti-Infective Drugs Advisory Committee Meeting Announcement**
- November 28, 2012, 8:00 a.m. to 5:00 p.m.

  DoubleTree by Hilton Hotel, Washington DC/Silver Spring 8727 Colesville Road, Silver Spring, MD
- **Agenda:** On November 28, 2012, the committee will discuss the safety and effectiveness of new drug application (NDA) 204384, bedaquiline tablets, submitted by Janssen Therapeutics, Division of Janssen Products, LP. The proposed indication (use) for this product is for the treatment of patients with multi-drug resistant pulmonary tuberculosis.

http://www.fda.gov/AdvisoryCommittees/Calendar/ucm321011.htm

- Thank you