RESIST-TB

Research Excellence to Stop TB Resistance

Testimony to the FDA Anti-Infective Drugs Advisory Committee, June 3, 2009

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RESIST-TB

An organization of concerned patients, physicians, research scientists and other stakeholders

Mission: To promote and conduct clinical research to cure and prevent drug-resistant Tuberculosis throughout the world

RESIST-TB: Promoting Clinical Trials for Drug-Resistant TB

- Workshop on Clinical Trials for DR-TB, held in Cambridge, MA, USA (June, 2008)
- Cambridge Declaration (Int J Tuberc Lung Dis 2009;13:1-2).
- Website: http://www.resisttb.org
- Support from WHO, CDC, IUATLD, Treatment Action Group, Partners in Health, Médecins Sans Frontières

Outline of Presentation

- The urgent need for new drugs for MDR-TB
- Predicting the outcome of MDR-TB treatment
- Expanding access to new drugs while avoiding creation of XDR-TB
- Developing regimens for HIV-infected and HIV-uninfected persons with MDR-TB
- Developing regimens for children with MDR-TB
- Developing regimens to prevent MDR-TB disease in contacts

The urgent need for new drugs for MDR-TB

- Half a million new cases of MDR-TB every year
- Less than 20,000 receive effective treatment
- 1 to 1.5 million cases persist, untreated, every year
- Of those receiving treatment, only 60% are cured
- No new drug classes in 30 years
- Current regimens have substantial toxicity
- Accelerated approval process for new MDR-TB drugs is justified

Predicting the outcome of MDR-TB treatment

- Sputum culture conversion is a direct reflection of drug efficacy
- Culture conversion correlates with symptomatic improvement (fever, chills, weight loss)
- Failure to convert sputum always predicts clinical failure
- When culture conversion occurs but the patient is not cured, this is often the result of toxicity or nonadherence
- Accelerated approval for new MDR-TB drugs should be granted on the basis of culture conversion as evidence of clinical benefit

Expanding access to new drugs while avoiding creation of XDR-TB

- Use of a single new drug without effective companion drugs could lead to widespread resistance to a new agent
- 18 (21%) of 87 patients being treated for MDR-TB developed XDR-TB (NEJM 2008;359:2398-2400)
- Accelerated approval for new MDR-TB drugs should require clinical trials to establish optimal companion drugs and duration of therapy

Developing regimens for HIV-infected and HIV-uninfected persons with MDR-TB

- As many as 30% of MDR-TB patients may have HIV co-infection
- HIV/MDR-TB co-infected patients have poorer treatment outcomes
- Different treatment regimens may be needed for HIV/MDR-TB co-infected patients
- Accelerated approval for new MDR-TB drugs should require clinical trials to establish optimal therapy for HIV co-infected patients

Developing regimens for children with MDR-TB

- The number of children with MDR-TB is underestimated and likely substantial
- Children will need prompt access to new drugs for MDR-TB
- Such access will require pediatric formulations and PK studies to establish pediatric dosing
- Accelerated approval for new MDR-TB drugs should require pediatric formulations and PK studies

Developing regimens for contacts of patients with MDR-TB

- Patients with MDR-TB infect at least 8-10 contacts
- 10% of HIV-uninfected and 50-80% of HIV-infected contacts with MDR-TB infection will progress to disease
- Even a single new MDR-TB drug may be able to prevent this progression
- Accelerated approval for new MDR-TB drugs should require contact prevention trials

Conclusions

- Accelerated approval is appropriate for MDR-TB indications and should be based on culture conversion
- Accelerated approval should require:
  - Trials to establish optimal regimen and duration
  - Trials to establish optimal therapy in HIV-infection
  - Pediatric formulations
  - Trials to establish pediatric PK
  - Trials of prevention in contacts