Reduced-Duration Tuberculosis Treatment: TB Alliance and Bayer HealthCare

Tuberculosis (TB) is caused by *Mycobacterium tuberculosis*, slow-growing bacteria that thrive in areas of the body that are rich in blood and oxygen. TB in the lungs is easily spread to other people through coughing or laughing. *M. tuberculosis* infects one-third of the world's population, resulting each year in nine million new cases of active TB and two million deaths, 90 percent of them in developing countries. China and India alone account for 35 percent of all estimated new TB cases each year. An estimated one billion people will be newly infected between 2000 and 2020; 200 million will fall ill and 35 million will die. TB is a leading cause of death among people living with HIV/AIDS, and multi-drug resistant strains are spreading at a rate of 300,000 newly diagnosed cases a year.

THE R&D CHALLENGE

The TB drug market will require sufficient incentives to support the research needed to develop a pipeline of continually improving drugs. Even with the market potentially reaching US$700 million by 2010, it is concentrated in poor countries, and no single industry player has been able to pursue the full development of an anti-TB drug. The Global Alliance for TB Drug Development (TB Alliance)[1] was designed by the international community as the primary instrument to fill this vacuum and to ensure that new anti-TB drugs are affordable and accessible in endemic countries.

Current TB therapy is based on four drugs for preventing multi-drug-resistant TB. These drugs were discovered 40 or more years ago and must be administered for six to eight months, often under the direct observation of a health-care provider. The four-drug regimen consists of isoniazid, rifampin, pyrazinamide, and ethambutol. There is a real need for new treatments that are less expensive, of shorter duration, and easier to manage.

Moxifloxacin is an antibiotic that was first approved in 1999 and is currently used in 104 countries to treat certain bacterial respiratory, skin and intra-abdominal infections. The antibiotic has been used by more than 47 million patients worldwide. It is generally well tolerated but treatment may result in certain usually mild side effects, including nausea, diarrhea, and dizziness. In vitro and in vivo studies have demonstrated moxifloxacin activity against *M. tuberculosis*. Investigators at Johns Hopkins discovered that substitution of moxifloxacin for isoniazid in the TB treatment regimen reduced treatment time by two months in mice. The treatment regimen included rifampin, pyrazinimide, and either moxifloxin or isoniazid.[2]

In October 2005, the TB Alliance and Bayer Healthcare AG[3] announced a partnership to coordinate a global clinical development program to study the potential of moxifloxacin to shorten the standard six-month treatment of TB by two to three months. The trials will evaluate whether the substitution of moxifloxacin for one of the standard TB drugs (ethambutol or isoniazid) eliminates TB infection faster than the current standard therapy. If successful and approved by the respective regulatory agencies, a new, shorter regimen could be available within the five years.

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The Phase II and III clinical trial program involves countries in four continents and will enroll close to 2,500 patients with TB. The trials will be carried out in Brazil, Canada, South Africa, Spain, Tanzania, Uganda, the United States, and Zambia. If the trials are successful, the partnership aims to register moxifloxacin for a TB indication. Upon regulatory approval, the partnership is committed to making it affordable and accessible in developing countries, where the disease is most prevalent and deadly.

For this project, Bayer will donate moxifloxacin for each trial site and will cover the costs of regulatory filings, and the TB Alliance will coordinate and help cover the costs of the trials, seeking to leverage support from the U.S. Centers for Disease Control and Prevention (CDC), the Orphan Products Development Center of the U.S. Food and Drug Administration (FDA) and the European and Developing Countries Clinical Trials Partnership (EDCTP). In May 2006, the TB Alliance received a US$104 million grant from the Bill and Melinda Gates Foundation. The grant will be used in part to fund Phase II and III trials of moxifloxacin with the goal of showing the efficacy of moxifloxacin in reducing TB treatment times by two months by 2010.

THE BENEFITS

Public health experts note that a shorter TB regimen would help ease the economic burden of the disease, estimated at US$16 billion a year, and enable healthcare workers to treat more patients. A shorter treatment protocol may improve patient adherence to therapy and, thereby, help save lives. When patients complete treatment successfully, there is less chance of relapse or of the emergence of drug resistance.

PARTNERS

Major partners in the TB treatment project are:

- pharmaceutical company Bayer HealthCare AG
- nonprofit organization the Global Alliance for TB Drug Development
- government entities the U.S. Centers for Disease Control and Prevention, the FDA, and the EDCTP

Clinical studies would be carried out by the following entities:

- Tuberculosis Trials Consortium (TBTC) of the Centers for Disease Control (CDC)
- Columbia University
- Johns Hopkins University
- University College London
- British Medical Research Council

No commercialization plan for the improved treatment has been announced.

Funding has been provided to the TB Alliance by:

- the Bill and Melinda Gates Foundation
- the U.S. Agency for International Development

PROGRESS, CURRENT STATUS, AND GOALS

Goals of the TB Alliance are:

- to devise, coordinate, and support a global clinical-development program to register a moxifloxacin-based regimen for shortening the time required for treatment of TB, at an affordable price (to be carried out in parnership with Bayer)
- to carry out clinical trials compliant with ICH and FDA cGCP/cGLP/cGMP
- to create a unified global safety database
- to establish clinical data sharing
- to provide affordable treatment for patients most in need

Clinical trials are underway:

- CDC TBTC Study #27: Moxifloxacin replaces ethambutol. United States, Canada, Uganda, and South Africa. 336 patients. Status: completed June 2005.
- CDC TBTC Study #28: Moxifloxacin replaces isoniazid in United States, Canada, Uganda, South Africa, Brazil, and Spain. 410 patients. Status: Enrollment initiated February 2006.
- JHU: Moxifloxacin replaces ethambutol. Brazil. 170 patients. Status: Trial initiated in February 2005.
- UCL-BMRC: Moxiflaxacin replaces ethambutol; moxifloxacin replaces isoniazid. Tanzania, South Africa, and Zambia. 1500 patients.

DEALS

Licensing deals include the following terms:

- field of use: tuberculosis drugs
- payments/royalties: to be made available in developing countries at cost, for use against tuberculosis
- patent strategy: patents previously issued ■

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1 Global Alliance for TB Drug Development (TB Alliance): www.thealliance.com.

2 Nuermberger EL, T Yoshimatsu, S Tyagi, K Williams, I Rosenthal, RJ O'Brien, AA Vernon, RE Chaisson, WR Bishai and JH Grosset. 2004. Moxifloxacin-Containing Regimens of Reduced Duration Produce a Stable Cure in Murine Tuberculosis. Am J Respir Crit Care Med. 170(10): 1131-1134.

3 Bayer HealthCare AG: www.bayer.com. See also Chapter 11.6 William T. Tucker and Gavin S. Ross, titled Use of Trademarks in a Plant-Licensing Program, p. 1059.