Toward an Optimized Therapy for Tuberculosis? Drugs in Clinical Trials and in Preclinical Development

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KEYWORDS

• Tuberculosis • Chemotherapy • Novel mechanism of action
• Drug combination • Drug resistance
• Drug persistence • MDR-TB • XDR-TB

After decades of neglect, tuberculosis (TB) drug research and development is attracting renewed interest, with the discovery of several promising new drug candidates over the past 10 years that spark hope for the possibility to improve the treatment and control of this terrible scourge. The situation is indeed critical: According to the World Health Organization (WHO), there were an estimated 9.27 million new cases of TB in the world in 2007, of which about 4 million were sputum smear–positive, the most infectious form of the disease.[1] About 1.7 million people died of TB in 2007, including 456,000 patients who were coinfected with HIV. About 9% of the new TB cases in the world today are attributable to human immunodeficiency virus (HIV), and this amounts to 31% in sub-Saharan Africa, where nearly 40% of TB deaths are attributable to HIV/AIDS. Multidrug-resistant TB (MDR-TB) is becoming prevalent in many parts of the world, with 0.5 million estimated new cases in 2007, and extensively drug-resistant TB (XDR-TB) is emerging rapidly. An improved therapy that can shorten and simplify the treatment of both drug-susceptible and drug-resistant TB, be effective against MDR-TB and XDR-TB, and be compatible with antiretroviral therapy (ART) for the treatment of TB and HIV coinfections will clearly have significant impact on the prevention, treatment, and control of this devastating disease.

HISTORY OF TUBERCULOSIS DRUG DISCOVERY AND DEVELOPMENT

The discovery of streptomycin the first effective antituberculosis agent, in 1943, brought much excitement and hope to the world: a cure against this ancient disease was finally in sight.[2] However, this hope was short lived. It was soon observed that *Mycobacterium tuberculosis*, the causative pathogen, developed resistance to this drug rapidly and a stable cure was clearly unattainable with streptomycin monotherapy. To prevent the development of resistance and produce a stable cure, a combination therapy was needed.[3] Since that time the search for better TB therapy has been driven by two intertwining activities: the search for new drugs and the development of efficacious regimens (**Fig. 1**).

Since the discovery of streptomycin, huge progress has been made in the development of an efficacious treatment of TB, with the aim of obtaining rapid sterilization of lesions and avoiding patients' failure to comply with long-lasting treatments.[3] In the first-ever conducted randomized controlled TB trial, streptomycin (S) was found to be very

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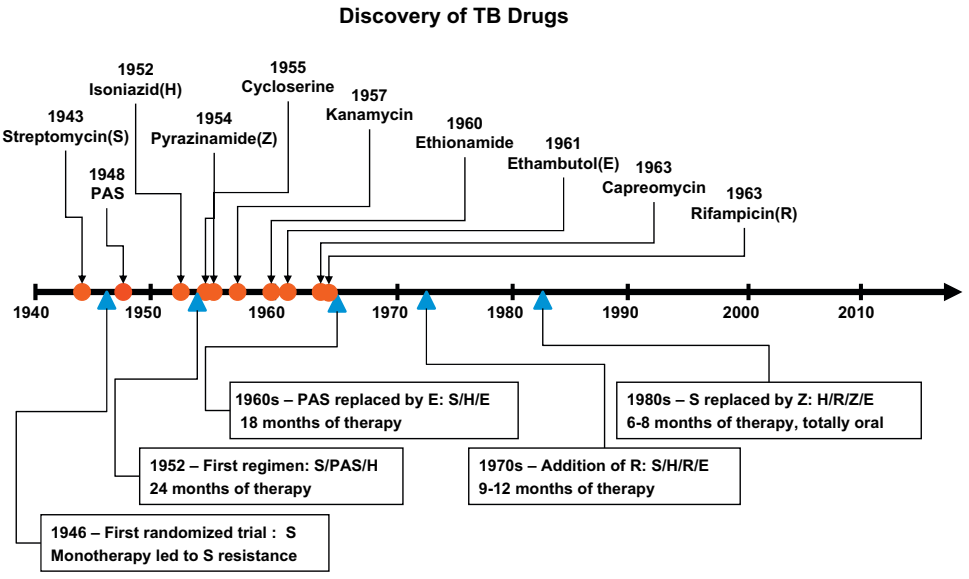

Fig. 1. History of TB drug discovery and regimen development.

efficacious compared with bed rest alone. The occurrence of high rates of resistance to this drug in the 5 years following treatment, however, led to the joint introduction of *para*-aminosalicylic acid (PAS) and isoniazid (H) in addition to streptomycin. This first combination therapy, given for 24 months, became the basis for treatment of TB in the developed world for about a decade. In the mid 1960s, PAS was replaced by ethambutol (E), a better-tolerated drug, and the treatment duration was reduced from 24 to 18 months. The discovery of rifampicin in the late 1960s was a major advance that allowed the development of a more powerful therapeutic combination when added to the isoniazid, ethambutol, and streptomycin regimen. This rifampicin-containing regimen offered a predictable cure in more than 95% of patients with 9- to 12-month duration of therapy. Another significant improvement was realized in the early 1980s with the discovery of the effect of adding pyrazinamide (Z) in the intensive phase of treatment, thus accelerating time to culture conversion and decreasing the duration of a fully orally administered treatment to 6 to 8 months. Studies conducted in East Africa showed that the relapse rate after a 6-month regimen was reduced from 22% to 8% by the addition of pyrazinamide, and to 3% by the addition of rifampicin.[4]

Since the 1980s the 6- to 8-month regimen, using a 4-drug combination (HRZE) in the initial phase followed by a 2-drug combination (HR or HE) in the continuation phase, has been widely accepted for the treatment of drug-susceptible TB.[5] This treatment norm was challenged, however, in 2004 with the results of a multicenter randomized clinical trial (Study A), showing higher efficacy of the 6-month regimen (2 months of HRZE plus 4 months of HR: 2HRZE/4HR) compared with the 8-month therapy (2HRZE/6HE).[6] Subsequent to this and recent meta-analyses, the current WHO treatment guidelines are being revised.

CURRENT THERAPIES

Drug-Susceptible Tuberculosis

The accepted standard regimen for the treatment of drug-susceptible TB at present is the 6-month, 4-drug combination therapy (2HRZE/4HR). A classic model established by Mitchison[7] suggests that there are at least 4 different populations of TB bacilli present in lung lesions: (1) bacteria that are actively growing, killed primarily by isoniazid; (2) bacteria that have spurts of metabolism, mainly killed by rifampicin; (3) bacteria that are characterized by low metabolism and reside in an acidic environment, killed by pyrazinamide; and (4) bacteria that are ''dormant'' or ''persistent'' that are not killed by current drugs. The 4 drugs used in the 2-month initial phase of therapy have been selected to kill actively metabolizing bacilli in the lung cavities, to destroy less actively replicating bacilli in acidic and anoxic closed lesions, and to kill near-dormant bacilli that may cause relapse.