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Research Paper

Evalution and Impact of Anti-Tuberculosis Drug : A Review

Biotechnology

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ABSTRACT

Since the time of discovery of Mycobacterium tuberculosis as an agent causing tuberculosis , permanent eradication of this disease has been a cause of concern. Although a large number of drugs exit for the treatment of tuberculosis, 1.7 million people still die every year from this infection. Isoniazid and rifampin are effective anti-tuberculosis drugs only for the standard treatment of TB. Multidrug-resistant tuberculosis bacillus developed resistance against isoniazid and rifampin, therefore complicated problems came forward in treatment of MDR-TB due to which second line anti-tuberculosis drug like fluoroquinolone has invented. Recently an extensively drug-resistant (XDR) strain of M.tuberculosis had observed which has developed resistance against isoniazid, rifampin fluoroquinolone and an aminoglycoside. XDR-TB is the most severe form of tuberculosis, against which no effective drug has been registered till now. Although a new generation TBK-613 of fluoroquinolone is on medical trial for the treatment of this severe form of tuberculosis.

Introduction :

Tuberculosis, one of the deadliest diseases, described else where as *King's evil, Phthisis, Rajyakshma, Tapedic,* appears to be a disease as old as human history (Ayvazian, 1993). Laurent Bayle introduced the term tuberculosis whereas Benjamin Martin (1720) suggested tuberculosis to be an infectious disease (Menon, 1987).

The registered number of cases of TB worldwide roughly co-relates with economic condition, the highest prevalence is seen in the countries of Africa, Asia, and Latin America with lowest gross national products. An estimated 2-3 million people will die in the next decade from TB. WHO estimated that 8 million people get infected with TB every year, Of this 95% live in developing countries and the majority of infected individuals live in South East regions.

Tuberculosis is caused by a prokaryote *M. tuberculosis*. "Robert Koch" was able to isolated *M. tuberculosis* pure culture by inoculating healthy mice and guinea pigs. In the past two decades there has been a dramatic increase in the number of infections caused by *M. tuberculosis* complex which includes *M. tuberculosis, M. bovis, M. canetti* and it's BCG variant *M. africanum* and *M. microti* (Imaeda, 1985).

First line treatment of tuberculosis :

On March 24, 1882 Robert Koch announced his discovery of the causative agent of tuberculosis. It took more than 50 years when the first effective drug – streptomycin - was discovered for the disease. Over the next 25 years, a number of additional drugs were discovered. Effective pharmacological treatment of tuberculosis been available since the 1940s. The efficacy of regimens containing rifampicin and isoniazid is well established for treatment and prevention, even in HIV-positive people (Woldehanna, 2004 & WHO, 2003).

The first-line (or essential) antituberculous drugs are the most active agents with proven clinical efficacy that form the core of initial standardized treatment regimens. These are isoniazid, rifampicin, pyrazinamide, and ethambutol (Blumberg 2003). Streptomycin, a less commonly used drug, is still a first-line drug in the World Health Organization' list of essential antituberculous drugs (WHO, 2006 & WHO, 2007c).

Rifampin is considered to be the cornerstone in the current treatment of TB (**Burman,** 2001). Its standard dose for TB treatment, is 10 mg/kg of body weight, corresponding to 600 mg in most populations. Studies with mice and early bactericidal activity (EBA), which depicts fall in CFU during the first 2 days of treatment studied suggests that the standard dose of rifampin in TB treatment is at the lower end of the concentration-response curve (**Drlica & Zhao,** 2008). The minimum inhibitory concentration of rifampin was found to be 0.15 mg/liter in broth culture (**Burman,2001).** Efficacy study in mice predicted one-third reduction in TB treatment duration when the rifampin dose was increased by 50% (**Jayaram & Gaonkar,** 2003) Only a few data are available on the efficacy of regimens based on a higher dose of rifampin in humans. A short regimen of high dose of rifampin (1,200 mg daily or every other day) with a high dose of isoniazid (900 mg) and streptomycin (1,000 mg) daily yielded almost 100% sputum culture conversion after 3 months (**Kreis & Pretet, 1976)**. All patients remained culture negative for up to one year and then sixteen percent of patients relapsed next one year. If pyrazinamide had been included in the regimen, treatment response might have improved, as pyrazinamide accelerates sputum conversion rates significantly (British Thoracic Association, 1981). Another study in TB patients did not show any difference in efficacy between 600 mg or 750 mg rifampin daily combined with 300 mg isoniazid for 20 weeks (Lounis & Bentoucha, 2001).

Second line treatment :

Multiple-drug-resistant tuberculosis (MDR-TB), defined as in vitro resistance, to least at isoniazid and rifampicin, impairing the effectiveness of standard treatments that contribute to increased mortality (Pablos & Mendez 2002). It is common in countries, like the former Soviet Union, where, the rates of MDR-TB among 'newly enrolled' and 'non-responding' cases in prisons were 24.6% and 92.1%, respectively. In Mariinsk, in the Russian Federation, the high rates of MDR-TB have been associated with failure rates of 23%to 50% among sputum smear-positive cases receiving fully supervised short-course treatment with first-line drugs (Portaels, 1999). In USA, 3.5% of strains were resistant to isoniazid and rifampicin at the time of the outbreak of tuberculosis in early 1990s (Reichman, 1996).

WHO 2003 and WHO 2006 recommends second-line antituberculous drugs for those with MDR-TB or people in tolerant of first-line drugs. The treatment of MDR-TB is difficult due to certain adverse effects and it is an expensive treatment regimen that usually lasts upto two years. Therefore, strategies for effective treatment and prevention of MDR-TB are urgently sougth as there is no single prescription for treating MDR-TB; appropriate use of second line drug treatment must be considered over seriously. (Pablos & Mendez 2002 and WHO2006)

There are six classes of second-line drugs used for the treatment of TB -aminoglycosides fluoroquinolones, polypeptides, thioamides, cycloserine and *p*-aminosalicylic acid. Fluoroquinolones are registered as second-line anti-TB drugs (Blumberg & Burman 2003)**.** Moxifloxacin and gatifloxacin are candidates for shortening TB treatment, since they have the lowest MICs

and the greatest bactericidal activity (Gillespie, 2001). The approved dose for moxifloxacin and gatifloxacin is 400 mg/day . While the potential of moxifloxacin and gatifloxacin to shorten TB treatment is being investigated in clinical trials, a new generation of quinolones, including the promising TBK 613, is being developed in preclinical research (Spigelman, 2008).

Rifabutin is derived from rifamycin and is mainly used for the prevention and treatment of disseminated *Mycobacterium avium* complex disease in patients with advanced HIV infection **(Brogden, 1994)**. The MIC of rifabutin against rifampin-susceptible MTB strains is ≤0.08 mg/liter, 8 times less than the MIC of rifampin against the same strains (**Dickinson, 1987)**. In TB patients, the activity of rifabutin was not greater than that of rifampin .

Medicinal plants as for the treatment of tuberculosis :
Emergence of multi-drug resistant (MDR) and extensively-drug resistant (XDR) strains of *Mycobacterium tuberculosis* has further aggravated as concernto control tuberculosis. Medicinal plants offer a great hope for developing alternate medicines in the treatment of TB. Gupta, et al. (2008) reported the extracts of A. indica, A. vasica, A. cepa, A. sativum and A. vera to exhibit anti-tuberculosis activity in L-J medium; the magnitude of inhibition of these plants extract was 95, 32, 37, 72, 32 per cent, respectively for MDR isolate DKU-156; 68, 86, 79, 72, 85 percent, respectively for another MDR isolate JAL-1236 and 68, 70, 35, 63 and 41 per cent for sensitive M. tuberculosis H37Rv at 4 per cent v/v concentration in L-J medium. There was no inhibition against fast proliferating M. fortuitum (TMC-1529). In BacT/ALERT also, extracts of these plants showed significant inhibition against M. tuberculosis. Antony & James (2011), reported the Alstonia scholaris extract to have 73.09% inhibition against a clinical strain which was resistant to Streptomycin, Isoniazid, Rifampicin and Pyrazinamide.

Discussion and Conclusions:
Tuberculosis has been a major health issue for developing countries including India. Due to increase in MDR and XDR strains of *M. tuberculosis,* there is an immediate exigency find new antimycobacterial agents to combat this strain. TB is the leading killer of youths, women, and AIDS patients world wide (Mann et al., 2008). Although people with HIV/AIDS are dangerously vulnerable to a number of opportunistic infections, TB is still a major cause of death. People infected with HIV have the greatest risk for developing MDR-TB. When the first and second line drugs have failed to offer any tanpible result, hopes are pinned with traditional medicines only.

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