Review Article

New drugs in resistant tuberculosis

Nisar Ahmed Rao

Department of Pulmonology, Ojha Institute of Chest Diseases, Dow University of Health Sciences, Karachi.

Abstract

The World Health Organization estimates that up to 50 million persons worldwide may be infected with drug resistant strains of TB. The fatality rate of MDR-TB is 20-80%.

Drug resistant tuberculosis cases are on the rise in Pakistan. The reasons for this menace are multiple including improper prescription, compliance and over the counter sale of anti-TB drugs. The treatment cost of drug-resistant TB is high, both to the individual patient and society.

This article is written to create awareness about the available second line drugs and those in the pipeline. Considering the fact that resistant tuberculosis is difficult to manage, it is suggested that these drugs should only be used after consultation with a physician experienced in the treatment of drug resistant TB. The most frequent mistake made by treating physicians is addition of one drug in the failing regimen.

At present, 27 potential anti-TB drugs are at various stages of development. The aim is that by 2010 at least one of these molecules completes the journey and should come in the market.

Introduction

Tuberculosis infects one third of world population and every 15 second one patient dies of TB. Tuberculosis takes global economic burden of $12 billion a year. During the last thirty years no new anti-tuberculosis drug has been introduced for clinical use. Now research is on going for developing new drugs in this field. There is a great need to win the war against tuberculosis. Some of the drugs have been very effective against Mycobacterium Tuberculosis like Rifamycin derivatives, combination of betalactum inhibitor and betalactum agents and fluoroquinolones. The purpose of this article is to discuss new emerging drugs and their efficacy in the treatment of tuberculosis.

New Anti-Tuberculosis Drugs

Rifamycin derivatives: The rifamycins are a group of antibiotics, which are synthesized either naturally by the bacterium Amycolatopsis mediterranei, or artificially. Rifamycin acts by binding specifically to the ß-subunit of bacterial DNA-dependent RNA-Polymerase, RpoB.[1] Rifamycins are particularly effective against mycobacteria, and are therefore used to treat tuberculosis, leprosy and mycobacterium avium complex (MAC) infections.

The rifamycin group includes the following drugs:
* Rifamycin A, B, C, D, etc. (the "classic" rifamycin drug)
* Rifampicin
* Rifabutin: an orally active, semi synthetic antibiotic which is derived from Rifamycin S. It is used for the prevention of disseminated Mycobacterium avium complex.
* Rifamide: a derivative of Rifamycin B is used against gram-positive cocci causing respiratory tract infections and against gram-negative and gram-positive organisms in biliary tract infections.
* Rifapentine: has a longer half-life than Rifampin and is similar to it.

Rifabutin

Rifabutin is a semisynthetic spiropiperidyl derivative. Rifabutin inhibit mycobacterial RNA polymerase like Rifampicin. Its activity is better against Mycobacterium Avium Complex (MAC). This lipophilic drug after absorption from the GI tract is eliminated in the urine and bile. In patients with renal impairment dose adjustment is not needed. It has been shown that Rifampicin sensitive M. tuberculosis strains were also sensitive against Rifabutin and about one third Rifampicin resistant strains still sensitive to Rifabutin.[2]

Therapeutic uses: It is effective for the prevention of MAC infection in HIV-infected individuals. At 300 mg/day, it decreases the frequency of MAC bacteremia by 50%. Rifabutin is commonly substituted for Rifampicin in the treatment of tuberculosis in HIV-infected patients due to its less profound interaction with indinavir and nelfinavir.[3] In combination with clarithromycin and ethambutol, it is also used in the treatment of MAC disease.

Side effects: Rifabutin is generally well tolerated. Reported side effects when used in HIV patients are rash (4%), GI upset (3%), and neutropenia (2%).

There is a need to evaluate Rifabutin in randomized controlled trials for the treatment of new smear positive pulmonary tuberculosis and MAC pulmonary disease. Its long half-life suggests that it would be useful in intermittent therapy. It is suggested that before such trials are initiated, it is important to determine the optimal dose, lest failure to show effect be attributed to a sub therapeutic dose. It is imperative that controlled studies of various drug regimens that contain higher doses of Rifabutin be undertaken for the treatment of patients with disseminated MAC disease and AIDS.

Rifapentine

Rifapentine is a semi synthetic Ansamycin antibiotic similar in structure to Rifampin. The in vitro activity of Rifapentine is 2-4 times that of Rifampicin against a variety of clinical mycobacterial isolates. Rifapentine is bactericidal against actively growing bacilli, with a rate of killing similar to that documented for Rifampicin. Rifapentine half-life is ~4-fold greater in humans than Rifampicin. The prolonged elimination half-life of Rifapentine is likely due to its higher lipophilicity, which facilitates tissue penetration of the drug and lack of biotransformation to antimicrobially inactive metabolites.[4] Absorption is enhanced when the drug is taken after a meal.

Mode of action: Rifapentine inhibits DNA-dependent RNA polymerase activity in susceptible microorganisms. Specifically, these antibiotics interact with bacterial RNA polymerase interfering with initiation of biosynthesis but not elongation. The mammalian enzyme is unaffected by the Rifamycins.

Uses: Rifapentine is approved for the treatment of pulmonary tuberculosis in combination with other effective antituberculosis drugs. Initial results of a study[5] of Rifapentine in tubercular patients, indicated comparable efficacy with Rifampin in producing negative sputum cultures for M. tuberculosis. Higher relapse rates were reported in the Rifapentine-treated group (10%) than the Rifampin-treated group (5%) during follow-up.

In a TRC study[6], of 103 strains of M. tuberculosis tested, 52 strains were sensitive to both. The remaining 51 strains resistant to Rifampicin were also resistant to Rifapentine, indicating complete cross- resistance. It was interesting to note that among sensitive strains Rifapentine has a 2 to 16 fold higher activity than Rifampicin.

The results of Rifapentine in pulmonary TB with HIV are disappointing. A randomized trial[4] compared Isoniazid / Rifapentine (600mg once a week) with Isoniazid / Rifampicin (600mg twice weekly) in 71 HIV-positive people with TB. Four people on Rifapentine developed drug resistance compared with none of the Rifampicin group. The author was of the opinion that the once weekly Rifapentine / Isoniazid should not be used among people with HIV.

Adverse Reactions: The adverse reaction profile of Rifapentine is similar to that of other Rifamycin antibiotics. Rifapentine is an inducer of cytochromes P450 3A4 and P450 2C8/9 isoforms and may increase the metabolism of other drugs that are metabolized by these enzymes.

Dosage/administration: During intensive phase 600 mg with an interval of not less than three days between doses is continued for two months. Rifapentine may be given with food if stomach upset, nausea or vomiting occurs. During continuation phase, treatment is continued once weekly for four months in combination with Isoniazid or an appropriate agent for susceptible organisms.

Fluoroquinolones

Fluoroquinolones(FRQs) have bactericidal activity against M. tuberculosis.

FRQs inhibit the gyrase, an enzyme involved in DNA replication.[7] There is no cross resistance between these agents and other antituberculosis drugs. Ofloxacin, Ciprofloxacin, Lomifloxacin, levofloxacin, sparfloxacin and Moxifloxacin have shown activity against M. tuberculosis.

Ofloxacin

Ofloxacin is a bactericidal drug. It is active in vitro against M.tuberculosis as well as against M. kansasii, M. xenopi, M. fortuitutum, and M. marinum. Mycobacterium avium and most strains of M. chelonei are resistant to ofloxacin.

Natural resistance to Ofloxacin appeared to occur in about 1 in 105 organisms, a proportion similar to that for other drugs.[8]

The MIC for Ofloxacin is less than 4 mg/l and after normal oral dose of Ofloxacin peak serum level attained is 10.7 mg/l, which is quite high./

Uses: Ofloxacin has an excellent activity against M. tuberculosis in clinical investigations. In a recently reported study from Hong Kong[9], use of Ofloxacin in MDR TB patients was associated with favorable outcome. The author concluded that the presence of cavitation, resistance to Ofloxacin in vitro and poor adherence emerged as variables significantly associated with adverse outcomes.

Levofloxacin

It is less neurotoxic than Ofloxacin.[10] Its efficacy against M. tuberculosis is proven in clinical trials. One of the studies concluded that levofloxacin-containing regimen resulted in a similar rate of adverse events compared with conventional first-line regimens when used for treatment of active tuberculosis.[11]

Ciprofloxacin

Ciprofloxacin[12] is active against all strains of M. tuberculosis sensitive to Streptomycin, INH, Rifampicin, and Ethambutol and inhibited almost all strains showing intermediate sensitivity or resistance to one or more of the above agents. Nearly all isolates, including atypical one were inhibited at a concentration of 3.2 mg/1. Efficacy of Ciprofloxacin is proven in clinical trials.[13] Other fluoroquinolones like Lomifloxacin and Sparfloxacin have also shown efficacy in appropriate clinical settings.

Moxifloxacin

ATS guidelines[14] stress that among the new fluoroquinolones, Moxifloxacin appears to be the most promising in the treatment of resistant tuberculosis. In an experimental study, Lounis[15] proved that addition of Moxifloxacin as a companion drug provide better protection against development of drug resistance.

The most potent of the currently available FQNs in descending order of in vitro activity against M. tuberculosis are moxifloxacin, gatifloxacin, levofloxacin, ofloxacin, and

Co-amoxyclav

Amoxicillin is a semi synthetic beta-lactam antibiotic, with a broad spectrum of bactericidal activity against many gram-positive and gram-negative microorganisms. The addition of a beta-lactamase inhibitor to amoxicillin greatly improves its in vitro activity against M. tuberculosis.[17] The beta-lactam inhibitors (i.e., clavulanic acid) possess no intrinsic antimycobacterial activity, but they are able to inhibit the enzyme in part responsible for the resistance of M. tuberculosis to beta-lactam antibiotics. There are no in-vivo studies using this drug combination against M. tuberculosis. Beta-lactam antibiotics penetrate poorly into mammalian cells, and this characteristic may limit the effectiveness of these agents in therapy for tuberculosis.

Tuberactinomycin

Tuberactinomycin[18] (Enviomycin) resembles Viomycin structurally as well as in its mode of action. It acts by inhibiting protein synthesis.

Tuberactinomycin containing regimens have shown good clinical response.[19] Negative sputum culture at six months ranged from 73% to 80% in the Tuberactinomycin containing regimens compared to 63% in a similar Viomycin containing regimen. In advanced cases, this ranged from 67% to 76% in the Tuberactinomycin containing regimens compared to 59% in the Viomycin containing regimen. Thus Tuberactinomycin was better than Viomycin.

Clarithromycin

The second generation macrolide, Clarithromycin, is effective against Mycobacterium avium-complex, and other NTM (Non-tubercular mycobacteria) including M. paratuberculosis.[12] It is also recommended in the treatment of infections caused by Mycobacterium marinum and Mycobacterium fortuitum complex. It has been shown to cause a reduction in the bacillary load and clinical improvement of M. avium disease in AIDS patients.[20]

Amikacin

Amikacin[21], an aminoglycoside, is highly bactericidal against M. tuberculosis. It is given five days a week in a dose of 15 mg/kg/day as a single dose, usually by intramuscular injection. The major side effect of Amikacin is nephrotoxicity and vestibular damage. Hearing loss, hypocalcaemia, hypokalaemia and hypomagnesaemia are other side effects. In comparison to kanamycin, it is less ototoxic and less painful.

Capreomycin

Capreomycin[21] is an aminoglycoside which is bactericidal against M. tuberculosis. It is given in a dose of 15 mg/kg/day intramuscularly with maximum of 1 Gram. It is toxic to the eighth cranial nerve, causing high frequency

hearing loss in 3.2 to 9.4% of patients before vestibular dysfunction occurs. Renal toxicity is somewhat more common with Capreomycin than with streptomycin, and it may be associated with electrolyte disturbances secondary to tubular damage. It is suggested that in elderly patients when there is similar susceptibility to Capreomycin and Amikacin, Capreomycin should be used since older patients seem to experience more renal and ototoxic effects with Amikacin than with Capreomycin.

Clofazimine

Clofazimine[21] is a substituted iminophenazine bright-red dye that inhibits mycobacterial growth and binds preferentially to mycobacterial DNA causing inhibition of transcription. The MlCs of clofazimine against M. tuberculosis have not been published.

Adverse reactions include discolouration of the skin, gastrointestinal upset, severe and life-threatening abdominal pain and organ damage caused by clofazimine crystal deposition, and asymptomatic discolouration of the eye.

Potential compounds of the future
Nitroimidazopyran

A series of new compounds containing a nitroimidazopyran nucleus that possess antitubercular activity has been reported.[22] This compound is related to metronidazole. It seems that it will be available in future for clinical evaluation. After activation by a mechanism dependent on M. tuberculosis F420 cofactor, nitroimidazopyran inhibited the synthesis of protein and cell wall lipid. In contrast to current antitubercular drugs, nitroimidazopyrans exhibited bactericidal activity against both replicating and static M. tuberculosis. Lead compound PA-824 showed potent bactericidal activity against multi-drug resistant M. tuberculosis and promising oral activity in animal infection models.

The nitroimidazopyran compound PA-824 has bactericidal activity comparable to that of INH. However, additional preclinical evaluation of PA-824 is needed before clinical studies could begin.

Oxazolidinones

Oxazolidinones (eperezolid and linezolid) are an appealing class of antimicrobials due to their unique bacteriostatic mechanism of action, lack of cross-resistance with other agents, good oral bioavailability, potential for structural manipulation, and broad spectrum of activity. The mechanism of action appears to be the ability to inhibit protein synthesis by binding to the 50S subunit and preventing the 30S complex from forming the 70S complex, resulting in inhibition of translation.[23] Eperezolid and linezolid were shown to have activity against a wide variety of organisms, including gram-positive cocci, gram-negative anaerobes, and mycobacteria. Due to their predominantly gram-positive activity, these agents were compared to vancomycin, penicillins, macrolides, minocycline, and similar antibiotics.[23] Linezolid have shown activity against M. tuberculosis in a murine model.[24]

Linezolid appear to be well tolerated when given both orally and parenterally. Drug related adverse events[25] occurred in 32.7% of patients, which were mild to moderate in severity and which resolve on discontinuation of therapy. They were nausea (5.4%), diarrhoea (5.2%), tongue discolouration (2.5%), oral thrush (2.3%), taste perversion (2.3%) and headache (2.3%). Thrombocytopenia (2.4%) is related to duration of therapy.

Role of surgery: Recently few studies on the role of surgery emerged as a light of hope in the management of difficult to treat pulmonary tuberculosis. Pomerantz BJ[26] reported in his patients with severe drug resistance (about 5 drugs) benefited from the resection of cavitary or badly damaged lung tissue when compared with historical control. A recent study[27] concluded that the use of resection lung surgery was associated with overall improved outcome in patients with highly resistant MDR-TB, with a trend toward improvement for those taking fluoroquinolone antibiotics.

It is hoped that in future we will have more data on the role of surgery but it is a disease, which can be managed medically, and surgery is the last hope as an adjuvant not as sole mode of treatment.

Immunotherapy for tuberculosis
Mycobacterium vaccae

M. Vaccae is found in the soil, first described in a study from Uganda. It was found that prior sensitization of animals with M. vaccae could optimize the protective effect of subsequently administered BCG vaccine.[28] A single intradermal injection of 0.1 ml suspension of dead M. vaccae containing 109 bacilli is administered a week or more after starting effective chemotherapy. Following effects have been noted: weight gain, rapid clearance of tubercular bacilli from sputum and decrease ESR.[29]

Further work is needed to evaluate the role of M. vaccae in the management of tuberculosis.

Interleukin-2

It is believed that immunity against M. tuberculosis is mediated by T-lymphocytes that produce the type 1 (Th1) helper T cell cytokines IFN and interleukin (IL)-2.[30] In TB patients, Th1 cytokines predominate at the site of disease, but the systemic immune response in peripheral blood is characterized by enhanced production of the type 2 (Th2) helper T cell cytokine IL-4, and by reduced secretion of IFN and IL-2 by peripheral blood T cells.[31] The systemic Th1 response in TB patient is low which inclined researchers to use IL-2 as an immunotherapeutic adjunct to treat tuberculosis. IL-2 strongly induces IFN and is a potent growth factor for CD4+ and CD8+ T cells, both of which contribute to immunity against tuberculosis.[30]. Furthermore, IL-2 stimulates expansion and enhanced functional capacity of natural killer cells, which can eliminate intracellular M. tuberculosis.[32]

Rapid sputum conversion was noted in a pilot study from Bangladesh and South Africa, in which intradermal IL-2 (225, 000 IU) twice daily was used during the first month of TB therapy as an adjuvant.[33] A later randomized trial in South Africa comparing daily and pulsed IL-2 with placebo in MDR TB found improved sputum clearance with daily treatment.[34] A recent study[35] concluded that IL-2 did not enhance bacillary clearance or improvement in symptoms in human immunodeficiency virus-seronegative adults with drug-susceptible tuberculosis.

It seems that we have again gone into an era similar to that of early forties when no cure for tuberculosis was available and only hope was fresh air, rest, good diet and sunlight. The present era when anti-TB drugs are available, is more dangerous because of the development of MDR tuberculosis due to irregular use of ATT, problems in implementation of effective TB control programme in many countries, over the counter sale of ATT and others. It is hoped that effective implementation of TB control programme under DOTS strategy, awareness of the mass as well as the health care providers about tuberculosis, judicious use of presently available medication, and control over the counter sale of ATT would have an impact on the control of MDR menace of tuberculosis.

Recently WHO published current drugs in pipeline for the resistant tuberculosis.[36] Diarylquinoline TMC207 is bactericidal, and is currently in phase-IIa clinical trial. Pyrrole LL-3858 is active against drug sensitive mycobacteria and currently in phase-I clinical trial. Other promising drugs are Pleuromutilins, Didiperidine SQ-609, ATP Synthetase Inhibitor FAS20013 (FASgene), Translocase I Inhibitor, InhA Inhibitors and Isocitrate Lyase Inhibitors.

References

1. Campbell EA, Korzheva N, Mustaev A, Murakami K, Nair S, Goldfarb A, et al. Structural mechanism for rifampicin inhibition of bacterial RNA Polymeras Cell 2001;104:901-12.

2. Chaisson RE, Schecter GF, Theur CP, Rutherford GW, Echenberg DF, Hopewell PC. Tuberculosis in patients with the acquired immunodeficiency syndrome. Am Rev Respire Dis 1987;136:570-4.

3. Haas DW. Mycobacterium tuberculosis In, Mandel, Douglas and Bennet's principles and practice of Infectious Diseases, 5th ed. (Mandell, G.L; Dolin, R; and Bennet, J.E; eds.) Churchill living-stone Inc Philadelphia 2000, pp. 2576-2607.

4. Jarvis B, Lamb HM: Rifapentine. Drugs 1998; 56:607-16.

5. Tam CM, Chan SL, Law SW, Leung LL, Kam KM, Morris JS, et al. Rifapentine and isoniazide in continuation phase of treating pulmonary tuberculosis. Am J Respir Crit Care Med 1998;157:1726-33.

6. Venkataraman P, Paramasivan CN. Prabhakar R: In vitro activity of Rifampicin, Rifampentine and Rifabutin against south Indian isolates of Mycobacterium tuberculosis. Ind J Tub 1993;40:17-20.

7. Drlica K, Zhao X. DNA gyrase, topoisomerase IV, and the 4-quinolones. Microbiol. Mol Rev 1997;61:377-92.

8. Tsukamura M, Nakamura E, Yoshii S, Amano H. Therapeutic effect of a new antibacterial substance Ofloxacin DL 8280 on pulmonary tuberculosis. Am. Rev Repir. Dis; 1985,131:352.

9. Yew WW, Chan CK, Chan CH, Tam CM, Leung LL, Wong PC, et al. Outcomes of patients with multidrug-resistant pulmonary tuberculosis treated with ofloxacin/levofloxacin-containing regimens. Chest. 2000;117:744-51.

10. Davis R, Bryson HM. Levofloxacin: a review of its antibacterial activity, pharmacokinetics and therapeutic efficacy. Drugs 1994;47:677-700.

11. Marra F, Marra CA, Moadebi S, Shi PElwood RK, Stark G, et al. Levofloxacin treatment of active tuberculosis and the risk of adverse events. Chest.2005; 128:1406-13.

12. Parent F. New experimental drugs for the treatment of tuberculosis. Rev Infec Dis 1989;11:S479-83.

13. Venkatraraman P, Paramasivan CN, Prabhakar R. In vitro activity of Capreomycin and Ciprofloxacin against south Indian isolates of M. tuberculosis. Ind. J. Tub.1993;40:21-4.

14. Blumberg HM, Burman WJ, Chairron RE, Daley CL, Etkind SL, Freidman LN, et al. American thoracic society/centers for disease control and prevention/infectious diseases society of America: treatment of tuberculosis. Am J Respir Crit Care Med 2003;167:603-62.

15. Lounis N, Bentoucha A, Truffot-Pernot C, Ji B, O'Brien RJ, Vernon A, Roscigno G, Grosset J. Effectiveness of once-weekly rifapentine and moxifloxacin regimens against Mycobacterium tuberculosis in mice. Antimicrob Agents Chemother 2001;45:3482-3486.

16. Saito H. Comparative antimicrobial activities of the newly synthesized quinolone BAY 12-8039 and gatifloxacin. Drugs 1999;58:400-1.

17. Wong CS, Palmer GS, Cynamon MH. In vitro susceptibility of Mycobacterium tuberculqis, Mycobacterium bovis, and Mycobacterium kansasii to amoxycillin and ticarcillin in combination with clavulanic acid. J Antimicrob Chemother 1 968;22:663-6.

18. Toyohara M, Nagata A, Hayano K, Abe J: Study on the antitubercular activity of tuberactinomycin, a new antimicrobial drug. Am Rev Repir Dis 1986;100: 228-30.

19. Tsukamura M, Ichiyama S, Miyachi T.: Superiority of Enviomycin or Streptomycin over Ethambutol in initial treatment of lung diseases caused by Mycobacterium avium complex. Chest 1989,95,1056-8.

20. Stover CK, Warrener P, VanDevanter DR, Sherman DR, Arain TM, Langhorne MH, et al. A small-molecule nitroimidazopyran drug candidate for the treatment of tuberculosis. Nature 2000,405:962-6.

21. Dresser LD, Rybak MJ. The pharmacologic and bacteriologic properties of oxazolidinones, a new class of synthetic antimicrobials. Pharmcotherapy 1998;18:456-62.

22. Moellering RC. A novel antimicrobial agent joins the battle against resistant bacteria. Ann Intern Med 1999;130:155-157.

23. Narang M, Gomber S. Linezolid, Drug therapy. Indian pediatrics. 2004;41:1129-32.

24. Bass JB Jr, Farer LS, Hopewell PC, O'brien R, Jacobs RF, Ruben F, et al: Treatment of tuberculosis and tuberculosis infection in adults and children. Am J Respir Crit Care Med. 1994;149:1359-74.

25. IseLan Md, Madsen LA. Drug-resistant tuberculosis. Clin Chest Med 1969; 10:341-53.

26. Pomerantz BJ, Cleveland JC Jr, Olson HK, Pomerantz M. Pulmonary resection for multi-drug resistant tuberculosis. J Thorac Cardiovasc Surg 2001;121:448-53.

27. Chan ED, Laurel V, Strand MJ, Chan JF, Huynh ML, Goble M, Iseman MD. Treatment and outcome analysis of 205 patients with multidrug-resistant tuberculosis. Am J Respir Crit Care Med. 2004;169:1103-9.

28. Stanford JL, Sheila MJ, Rook GA. How envirenmental mycobacteria may predetermine the protective efficacy of BCG. Tubercle 1981;62:55-62.

29. Stanford JL, Bahr GM, Rook GAW, et al. Immunotherapy with Mycobacterium vaccae as an adjunct to chemotherapy in the treatment of pulmonary tuberculosis. Tubercle 1990;71:87-93.

30. Kaufman SH. How can immunology contribute to the control of tuberculosis? Nature Rev Immunol 2001;1:20-30.

31. Hirsch CS, Toossi Z, Othieno C, Johnson JL, Schwander SK, Robertson S, et al. Depressed T-cell interferon responses in pulmonary tuberculosis: analysis of underlying mechanisms and modulation with therapy. J Infect Dis 1999; 180:2069-73.

32. Brill KJ, Li Q, Larkin R, Canaday DH, Kaplan DR, Boom WH, Silver RF. Human natural killer cells mediate killing of intracellular Mycobacterium tuberculosis H37Rv via granule-independent mechanisms. Infect Immun 2001;69:1755-65.

33. Johnson BJ, Ress SR, Willcox P, Pati BP, Lorgat F, Stead P, et al. Clinical and immune responses of tuberculosis patients treated with low-dose IL-2 and multidrug therapy. Cytokines Mol Ther 1995;1:185-96.

34. Johnson BJ, Bekker LG, Rickman R, Brown S, Lesser M, Ress S, et al. IL-2 adjunctive therapy in multidrug resistant tuberculosis: a comparison of two treatment regimens and placebo. Tuber Lung Dis 1997;78:195-203.

35. Johnson JL, Ssekasanvu E, Okwera A, Mayanja H, Hirsch CS, Nakibali JG,.et al. Randomized Trial of Adjunctive Interleukin-2 in Adults with Pulmonary Tuberculosis. Am J Respir Crit Care Med 2003; 168: 185-91.

36. WHO document: WHO drug information Vol 20, No.4, 2006.

-ã