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NEWER ANTIMYCOBACTERIAL DRUGS AND THEIR ROLE IN THE TREATMENT OF TUBERCULOSIS PATIENTS

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Chemotherapy of pulmonary tuberculosis : current concepts and need for newer drugs

The main lesion in pulmonary tuberculosis, the pulmonary cavity, contains a large number of mycobacteria (about 10^8 colony forming units). Of these, a large bacillary population is located in the thin liquid caseous layer that covers the inner part of the cavitary wall. Here, the bacilli are extracellular which multiply actively because of the availability of oxygen and nutritive substances. There are at least 2 other bacillary populations, one inside macrophages and another inside solid caseous foci; both these populations are limited in size because environmental conditions are unfavourable for their growth.[1] Among the organisms in these 3 populations, which are normally drug sensitive, drug resistant mutants develop at a mean frequency of about 10^{-6}.

In the early sixties, chemotherapy for tuberculosis relied on the administration of 18 to 24 months of 3 drugs : Isoniazid (H), Para-amino salicylic acid (PAS) and Streptomycin (S), the last being given during the initial few months of. treatment. The drugs were given together to Prevent the emergence of resistance and prolonged treatment was given until the microbial population was eliminated in order to prevent relapse. Despite such prolonged treatment the relapse rate after discontinuation of treatment was about 10%.[1]

The introduction of Rifampicin (R), in the seventies, brought a marked change in the chemotherapy of tuberculosis.[2] Rifampicin was effective not only against actively multiplying organisms but also against the dormant or persisting organisms, responsible for relapse after treatment was stopped. Around this time, the bactericidal activity of Pyrazinamide (Z), a drug highly active against organisms located in an acid environmental, especially inside macrophages, was also rediscovered These developments formed the basis of controlled clinical trials which established the efficacy of 6-month regimens. The high success rate of antituberculosis regimens of only 6 months duration in the treatment of extensive sputum positive, pulmonary tuberculosis was clearly demonstrated in a large scale study in East Africa.[3] This led to the recommendation by numerous health authorities of the 6-month short course chemotherapy (SCC) for tuberculosis that is presently used in many countries, including India

The major drugs, whose potency and acceptability have resulted in their widespread use in the current chemotherapy of pulmonary tuberculosis are H, R Z, S, Ethambutol (Emb) and Thioacetazone (TB1).[4] The usefulness of a drug in the treatment of tuberculosis depends mainly on its sterilising activity; ability in combination with H to prevent-emergence of resistance and early bactericidal activity. The time taken for organs to be sterilised, in experimental animal tuberculosis and the relapse rate after SCC in man are measures of a drug's action against semidormant tubercle bacilli and its sterilising activity. The ability of a drug to prevent the emergence of resistance is assessed during treatment with the drug concerned in combination with H, and is graded according to the proportion of patients who fail, with the emergence of H resistance; this proportion is about 0.5% for Rifampicin (high activity) and 13-15% for Thioacetazone (low activity).[5] The fall in the count of viable tubercle bacilli during the first few days of treatment, when the actively growing bacilli are killed, is termed the early bactericidal activity (EBA) and can be measured *in vitro*, or in man.

Tubercle bacilli in a special population which show spurts of metabolism are particularly susceptible to Rifampicin and the ones in a special population surrounded by an acid environment are suceptible to Pyrazinamide. H and R are highly

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effective in preventing the emergence of resistance, H has high EBA, R and Z have high sterilising action, and H, R, Z Emb and S are highly suitable for intermittent use.[4]

Despite the introduction of effective, nontoxic antituberculosis drugs and therapeutic regimens, pulmonary tuberculosis still affects millions of people in the developing world.[6] The results of a recent evaluation done by the Tuberculosis Research Centre (TRC), Madras[7] show that the reality of the tuberculosis problem remains grim even after the implementation of SCC. Of the 3357 smear-positive pulmonary tuberculosis patients initiated on antituberculosis treatment in North Arcot district between April 1986 and March 1988, 2306 had been prescribed a SCC regimen and 1051 had accepted a standard regimen. Only 43% receiving the SCC and 35% receiving the standard regimen had completed 80% or more of their treatment. The overall mortality was 28%. Of the remaining, 31% had active disease and were excreting bacilli, including 65% whose cultures were resistant to H and 12% to R, combined resistance to R & H was seen in 6% and to S & H in 19%. H resistance was significantly higher in those who had been prescribed standard regimens and R resistance was seen even in those who had not received the drug.

Even with the standard regimens, it was possible to achieve 98% cure rate and reduce mortality rate to as low as 1% in clinical trials.[8] However, when these regimens were applied under field conditions, less favourable results were obtained, the reason being the difficulty in delivering the presently available complex regimens to patients in tuberculosis control programmes, particularly in developing countries like India.[9] Partly as a consequence of poor adherence, a sizeable proportion of patients harbour tubercle bacilli resistant to one or more established drugs, which further complicates treatment.[10-12]

Thus, new chemotherapeutic drugs are needed to improve adherence and to treat disease due to drug resistant tubercle bacilli and nontuberculous mycobacteria (NTM). At present, and in the near future, the control of tuberculosis will depend on better case-finding, case-holding and treatment. For this, the availability of well tolerated and rapidly curative drugs that can be delivered by peripheral centres is essential.[4] The new drugs must be developed with the aim of increasing the sterilising activity of regimens because they might allow further shortening of the period of treatment to less than the current 6 months and, thus, improve adherence and acceptability.

The duration of treatment, the number of drugs used and the frequency of administration of each drug determine the complexity of therapy. Complexity and toxicity often lead to poor adherence. Several strategies have been developed to simplify treatment, to reduce medication errors and to discourage intentional avoidance of the ingestion of one or more drugs. New formulations containing 2 or more drugs, such as combination tablets containing both R and H, and more recently R, H and Z, with bioavailability of the components equivalent to that when single drugs are administered have been developed. Implants of biodegradable polymeric systems such as polyactic polyglycolic and poly (lactic/glycolic) acid copolymers containing antituberculosis drug, for sustained release of the drug, could help in solving the non-adherence problem. However, with the potency of the present antituberculosis drugs, the implants will have to be very large and the cost of surgical implant and removal after drug cessation increases the cost of chemotherapy.[13]

The financial resources and time needed for developing a new antituberculosis drug and assessing its efficacy *in vitro* and in clinical trials, the decline of tuberculosis in developed countries, the inability of developing countries to purchase expensive drugs and the ready availability of effective antituberculosis drugs are some of the reasons why new agents for the treatment of tuberculosis have not appeared.[14] However. the current increase in the incidence of tuberculosis associated with HIV infection, and the occurrence of multiple-resistant tubercle bacilli have led to a pressing need for the rapid development of new antituberculosis drugs. The second urgent need for new drugs arises because of anticipated future increase in the incidence of R resistant strains. In the treatment of tuberculosis, SCC regimens are effective in patients with strains resistant to H or S, but the results in patients with initial R resistance are poor.[4]

Methods of assessing new drugs

Apart from pharmaceutical firms which

develop them, new drugs have to be assessed independently through *in vitro* studies, animal experiments and clinical investigations to allow unbiased comparisons between drugs and to make such assessments as free as possible from commercial interests. *In vitro* studies include determination of the minimal inhibitory concentration (MIC) and the bactericidal activity against appropriate mycobacterial species. Animal experiments include estimation of blood levels, chemotherapeutic studies, preferably in mouse and occasionally also in guinea pig, and measurement of sterilising activity. In clinical investigations of antituberculosis drugs, a series of single increasing doses of the new drug is given to patients or healthy volunteers, while information on pharmacokinetics and side effects is obtained. The effective dose size is estimated by measuring EBA of the new drug at different dose sizes in comparison with a standard drug such as Rifampicin. These studies have to be followed by pilot and full scale clinical trials.[4]

Promising newer antimycobacterial drugs

Based on all or some of the above mentioned methods of assessment, a few classes of drugs show promise in the treatment of tuberculosis. These include the Rifamycin derviatives, fluoroquinolones, combination of beta lactam agents and beta lactamase inhibitors, and others.

Rifamycin derivatives

The dose required when Rifampicin is given Once weekly may lead to a high incidence of serious adverse reactions. This can be avoided by using a Rifamycin with a long half-life which gives sustained blood levels between doses. Many novel Rifamycin molecules with a long elimination half-life have been designed with this aim.[2] Such long lasting Rifamycins (LLRs) include Rifabutin (LM 427, Ansamycin-Farmitalia), Rifapentine (DL 473-Merrel Dow), CGP 29861, CGP 7040 and CGP 27557 (Ciba-Geigy), FCE 22250 (Farmitalia). and R-76-l (Rifadine) developed in China.

Rifabutin (LM 427, Ansamycin)

Rifabutin is a semisynthetic spiropiperidyl derivative. The discovery of its activity against *M. avium-intracellulare* and the emerging problem of disseminated *M. avium intracellulare* infection in patients with AIDS led to the use of the drug in USA on 'compassionate' grounds, before clinical trials, but with disappointing results.[15-16]

Rifabutin was also active against approximately one third of the Rifampicin resistant strains of *M. tuberculosis* tested.[16] All *M. tuberculosis* strains susceptible to Rifampicin were susceptible to Ansamycin, and the MICs were similar. The strains that were highly resistant to Rifampicin were resistant to Ansamycin. However, it showed activity against some Rifampicin resistant *M. tuberculosis* strains. Typical MIC for *M. tuberculosis strains was* observed to be 0.006 mg/l for Rifampicin sensitive strains and 6-16 mg/l for Rifampicin resistant strains. The MICs for resistant strains are much higher than clinically achievable concentration in blood (C max-0.5 mg/l blood after 300 mg given orally; C max 3 mg/l in lung tissues)."

Dickinson and Mitchison[18] observed that 31% of 35 Rifampicin resistant strains tested had MICs of 0.6 mg/l or less for Rifabutin and could be classified as relatively sensitive. The MICs of Rifabutin were much lower among sensitive *M. tuberculosis* strains. As an explanation for the low MICs of Rifabutin against Rifampicin resistant strains, it has been claimed that the mode of action of Rifabutin is different from that of Rifampicin. Alternatively, this would also suggest that the activity of Rifabutin and other Rifamycins against resistant strains might be proportional to their activity against sensitive strains. These findings raise the possibility that Rifabutin might be of use in the treatment of some patients with Rifampicin resistant strains.

In a study done at TRC, a total of 103 *M. tuberculosis* strains were tested against Rifampicin and Rifabutin.[19] In 42 out of the 52 Rifampicin susceptible strains Rifabutin showed as least 4-fold higher effectiveness than Rifampicin. The geometric mean MIC of the 52 strains was 1.3 mg/l with Rifabutin compared to 13.3 mg/l with Rifampicin, showing on an average 10-fold higher effectiveness. Of 51 strains resistant to Rifampicin, 11(22%) were susceptible to Rifabutin.

In animal models, Rifabutin is quite active

against *M. tuberculosis* and its relatively high tissue levels and long half-life suggest that the drug might be effective if given intermittently in tuberculosis. It is about 6 times more active than Rifampicin in experimental infection of mice with *M. tuberculosis* or *M. avium.* The considerable activity in murine disease may reflect high intracellular concentrations in mouse macrophages while caseating lesions in cavitary walls containing numerous acid fast bacilli, characteristic of human pulmonary tuberculosis might contain lower concentrations corresponding to those in plasma. Thus. it is uncertain whether Rifabutin concentrations in these human sites are sufficiently high for effective antimicrobial activity.[20]

The fall in viable counts of *M. tuberculosis* in sputum collections during the first 2 days of treatment (EBA) suggested that Rifabutin was inactive or less active than Rifampicin in pulmonary cavities.[20] This may be due to the low plasma concentrations which are not fully compensated for by the slightly greater antituberculosis activity of Rifabutin *in vitro.*

Recently, a controlled study of Rifabutin in the retreatment of patients with pulmonary tuberculosis resistant to SHR has been reported by the Hong Kong Chest Service/BMRC.[21] Bacteriological results in the 22 patients studied showed no evidence of sustained benefit in any patient with Rifampicin or Rifabutin. The results suggested that Rifabutin does not have a useful role in the retreatment of patients with multi-drug resistant pulmonary tuberculosis, which includes Rifampicin resistance except possibly in a small proportion of patients who have Rifabutin susceptible strains.

O'Brien and associates[17] have reported their findings in patients with pulmonary *M.avium* complex (MAC) disease and drug resistant tuberculosis receiving Rifabutin. Conversion rates were 9% for pulmonary MAC and 35% for drug resistant tuberculosis. In another study, these authors have concluded that some patients with Rifampicin resistant tuberculosis may benefit from the addition of Rifabutin to the treatment regimen.[22] However, when resistance to all first line drugs is present, the outcome remains poor. To obtain an irrefutable answer regarding its efficacy, Rifabutin should be evaluated in controlled tests for the treatment of both newly diagnosed pulmonary tuberculosis and MAC pulmonary disease. The drug's long half-life suggests that it may be especially valuable for intermittent administration. Whether or not this drug is more effective than Rifampicin can be answered only by randomized clinical trials. However, 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 (DL 473)

Rifapentine, a cyclopentyl Rifamycin has been shown to have antimycobacterial properties. The *in vitro* activity of Rifapentine is 2-4 times that of Rifampicin against a variety of clinical mycobacterial isolates; the range of MICs is 0.025-0.1 mg/l as compared with 0.05-0.8 mg/l for Rifampicin. Rifapentine is bactericidal against actively growing bacilli, with a rate of killing similar to that documented for Rifampicin.

In a TRC study, of 103 strains of *M. tuberculosis* tested, 51 strains resistant to Rifampicin (MIC>128) were also resistant to Rifapentine, indicating complete cross-resistance.[19] The remaining 52 strains were sensitive to both; in these strains Rifapentine has a 2 to 16 fold higher activity than Rifampicin.

In experimental tuberculosis in mouse, Rifapentine has a 50% effective dose (ED 50), 10 times lower than that of Rifampicin. Rifapentine administered to experimentally infected mice once a week is as effective as Rifampicin administered daily, in the initial as well as the continuation phase, and retains considerable efficacy when given once every 3 weeks. In most rat tissues, Rifapentine concentrations are about 40 times greater than that observed for Rifampicin.[2] All animal toxicity studies including long term assessment have been completed.

Rifapentine has been used in 2 clinical studies, in man, one in Britain and the other in Finland, far the treatment of chlamydial urethritis, where it has been given at 600 mg per day in up to 6 consecutive doses without evidence of toxicity. It is taken up into the cytosol fraction of neutrophils

and macrophages and retains intracellular activity. It binds weakly to serum albumin. After administration of a single oral dose of 600 mg to healthy volunteers, peak serum concentrations of 20 mg/l were observed with Rifapentine. The half-life of Rifapentine after 1st and 3rd once weekly administration was found to be the same. It has not yet been used in the treatment of human tuberculosis. It is potentially of great value in the chemotherapy of tuberculosis for use in supervised widely intermittent regimens.[4]

Fluoroquinolones

Flouroquinolones such as Ofloxacin, Ciprofloxacin, Norfloxacin, Pefloxacin, Enoxacin, Lomefloxacin and Sparfloxacin are synthetic compounds active against a wide variety of microorganisms. Their activity is exerted through inhibition of gyrase, an enzyme involved in DNA replication. As expected, there is no cross resistance between these agents and other antituberculosis drugs.[2]

Ofloxacin (DL 8280)

In 1983, Tsukamura[23] showed that Ofloxacin was active *in vitro* against *M.tuberculosis* as well as against the potentially pathogenic NTM, *M. kansasii*. *M. xenopi*. *M. fortuitum* and *M. marinum.* While most *M. intracellulare* serotypes of the *M. avium* complex were inhibited by Ofloxacin, 'avium' serotypes were generally resistant as were most strains of *M. chelonei.* In 1985, Tsukamura[24] reported that the drug might be beneficial in the treatment of drug resistant tuberculosis because no cross resistance between Ofloxacin and other antituberculosis drugs was seen *in vitro.* Spontaneous resistance to Ofloxacin appeared to occur in about 1 in 10^6 organisms, a proportion similar to that for other drugs. It showed considerable bactericidal activity at concentrations a little higher than the MIC. The combined effect with other antituberculosis agents seemed to be additive. The development of resistance to DL 8280 was of an obligatory 2 step pattern. There are 2 phenotypes. The resistance levels of these phenotypes are 5 mg/l and 100 mg/l respectively. There was no resistance beyond 100 mg/l.

Davies et al[25] reported in 1987 on the comparative *in vitro* efficacy of Ofloxacin, Ciprofloxacin, Pefloxacin, Enoxacin and Norfloxacin, on 50 *M. tuberculosis* strains. The authors concluded that since Ofloxacin and Ciprofloxacin were shown to have the highest *in vitro* activity against mycobacteria, these 2 drugs could be used in the treatment *of M. tuberculosis* resistant to standard drugs. However, in these studies only *M. tuberculosis* strains sensitive to antituberculosis drugs were tested. A study concluded recently at TRC shows that there is no difference in the activity of Ciprofloxacin and Ofloxacin in drug resistant and susceptible strains.[26] The geometric means MICs were also similar for both of these drugs for both categories of strains tested. None of the strains showed an MIC>4 mg/l in LJ slopes incorporated with the drugs. Since the mean MIC of Ofloxacin is far below the peak serum level of 10.7 mg/l attainable in normal dosage, this drug may have a role in the treatment of drug resistant tuberculosis.

A few clinical studies have been carried out with Ofloxacin. Tsukamura[27] administered Ofloxacin in a daily dose of 300 mg in combination with other drugs for 6-8 months to 19 tuberculosis patients who had failed on conventional therapy and had organisms resistant to most of the commonly used antituberculosis drugs. The patients had been previously treated for tuberculosis for an average of 16 years; all had Isoniazid resistant bacilli, and with one exception had organisms resistant to Rifampicin as well. Ofloxacin had a demonstrable effect in decreasing the number of viable *M. tuberculosis* organisms in these patients. Moreover, the fact that 12 patients acquired *in vitro* resistance to Ofloxacin and 4 of these 12 patients had culture conversion indicated drug activity. Plasma concentrations in excess of the MICs were generally achieved. No serious toxic effects were shown among this small group of patients.

In the uncontrolled study of Ofloxacin in the retreatment of patients with pulmonary tuberculosis resistant to SHR reported by Hong Kong Chest Service/BMRC,[21] of a total of 17 patients who had shown no evidence of a sustained benefit with Rifampicin or Rifabutin and subsequently retreated with Ofloxacin, 10 showed a response, disease becoming and remaining quiescent in 3. Ofloxacin appeared to be a better drug to use, in combination with any companion drugs still available.

Ciprofloxacin

Marinis and Legakis[28] reported that Ciprofloxacin was active against all strains of *M. tuberculosis* sensitive to S, H, R, and Emb and inhibited almost all strains showing intermediate sensitivity or resistance to one or more of the above agents. Nearly all isolates were inhibited at a concentration of 3.2 mg/l. The same phenomenon was also observed with atypical isolates.

An investigation conducted at TRC on 53 isolates of *M. tuberculosis* sensitive to SHR and 54 isolates resistant to SHR/HR also revealed more or less similar findings.[29] The percentage distribution of the MICs with the different categories of strains was similar, there being no difference between sensitive and resistant strains, the geometric means being 3.7 and 3.8 mg/l, respectively.

The expected mean levels of Ciprofloxacin in plasma after oral doses of 250 and 500 mg are 1.45 and 2.0 mg/l respectively. However, the drug may achieve levels in pulmonary tissue in excess of those in serum. In that respect and in the light of the present results, the achievable Ciprofloxacin level is expected to inhibit almost all of the clinically important species of mycobacteria including those showing resistance to one or more of the primary antimycobacterial agents.[28]

Lomefloxacin

Lomefloxacin is a new difluoroquinolone that has the additional advantage of having a relatively long half-life (7-8 h).[30] In a study carried out by Piersimoni et al,[31] the MICs of Ciprofloxacin, Ofloxacin and Lomefloxacin were determined for 90 *M. tuberculosis* strains isolated from both AIDS and other patients, including 11 (2.2%) which showed *in vitro* resistance to one or more first line antituberculosis drugs. The MIC range for Ciprofloxacin was 0.125 to 4.0 mg/l; for Ofloxacin 0.25 to 4.0; and for Lomefloxacin 0.5 to 4.0 mg/l. On the basis of these data and also based on studies by Chen et al,[32] the authors proposed the MIC of 1.0 mg/l as susceptible break point for both Ciprofloxacin and Ofloxacin and 2 mg/l for Lomefloxacin. These MICs are below the peak concentrations of the drugs in human serum, that is, 10.7 mg/l for Ofloxacin, 2.9 mg/l for Ciprofloxacin and 4.9 mg/l for Lomefloxacin. These peak concentrations were attained after single oral doses of 600, 1000 and 400 mg respectively. The authors felt that although none of these quinolones had been approved for use against *M. tuberculosis,* combination therapy will probably be recommended for fluoroquinolones as for other antimycobacterial drugs. Lomefloxacin, because of its pharamacokinetic property (long serum elimination half-life) should merit further evaluation as a potential supplementary drug for the intermittent treatment of tuberculosis.

Sparfloxacin

Sparfloxacin is a new difluorinated quinolone with *in vitro* activityand *in vivo* efficacy equal to or better than Ofloxacin and Ciprofloxacin. In a study carried out by Rastogi and Goh, comparison of bactericidal action with reported serum peak concentration has shown that Sparfloxacin has a potential for use against the tubercle bacillus and on 10 strains of *M. tuberculosis,* the MICs by 7H12 broth testing ranged from 0.5 to 1.0, 0.25 to 0.5, and 0.1 to 0.2 mg/l for Ofloxacin, Ciprofloxacin and Sparfloxacin, respectively, whereas MICs in solid medium ranged from 0.5 to 1.0, 0.5 to 1.0, and 0.2 to 0.5 mg/l, respectively.[33]

Combination of beta lactam agents and beta lactamase inhibitors

Mycobacteria produce beta lactamase and are resistant to beta lactam antibiotics. Beta lactamase stable penicillin like Dicloxacillin do not have sufficient intrinsic activity against *M. tuberculosis.* Recently, a group of beta lactam drugs have been produced which, although devoid of antibacterial activity, are potent inhibitors of beta lactamase. The addition of one such inhibitor, Clavulanic Acid, increased the antimycobacterial activity of Amoxycillin/Ampicillin.[2] The best combination was found to be Ampicillin and Clavulanic Acid in 1 : 1 ratio which gave a MIC 90 value of 11 mg/l. *In vitro* studies have also shown that augmentin (Amoxycillin and Clavulanic Acid) inhibits and kills most strains of *M. tuberculosis* at a concentration of 4-8 mg/l of Amoxycillin and 2-4 mg/l of Clavulanic Acid. Another good combination was Ticarcillin and

Clavulanic acid, which inhibited all strains of *M. tuberculosis* at <32 mg/l, a clinically achievable serum concentrations[34]. Ampicillin/ sulbactuam combination has been found to have MIC values of 8/8 mg/l in 13 *M. tuberculosis* strains[35].

Tuberactinomycin (Tuberactin, Enviomycin)

Tuberactioomycin is elaborated by strain *Streptomyces griseoverticillatus* var *tuberacticus* This water soluble drug resembles structurally Viomycin. The mechanism of action is surmised to be similar to that of Viomycin, i.e. inhibition of protein synthesis[36].

In a study carried out at TRC, cross-resistance was not observed between Tuberactin and Streptomycin, H, Emb, R and Ethionamide.[37] However, 15 (54%) of 28 Kanamycin-resistant strains were not susceptible to Tuberactinomycin at 25 mg/l.

Clinical studies with Tuberactinomycin containing regimens have been conducted in Japan[38]. The rate of sputum conversion by culture after 6 months ranged from 73% to 80% in the Tuberactin regimens compared to 63% in a similar Viomycin containing regimen. In advanced cases, this ranged from 67% to 76% in the Tuberactin regimens compared to 59% in the Viomycin regimen. Thus Tuberactin was better than Viomycin and daily administered regimen was better than biweekly administered regimen.

Amikacin and Capreomycin

The aminoglycoside antibiotic Amikacin is a semisynthetic derivative of Kanamycin A. It has been reported to inhibit *M. tuberculosis* at a concentration lower than that for Kanamycin or Streptomycin and to be more active than either of them in experimental murine tuberculosis and also to be active in experimental tuberculosis in the guinea pig.

In a study carried out by Hoffner and Kallenius,[39] out of a total of 585 *M. tuberculosis* strains isolated during a 3-year period in Sweden, resistance to S was seen in 27 (4.6%) isolates. All but one of the S resistant isolates were susceptible to Amikacin and none of the 263 S susceptible isolates tested was resistant to Amikacin. From these results, Amikacin appeared to be an alternative to S in the treatment of patients with S resistant *M. tuberculosis.*

Earlier, Allen et al[40] had reported the results of treating 4 patients with Amikacin, each of whom had a long history of previous chemotherapy and had multiple-resistant organisms. The activity of Amikacin was very low, although emergence of resistance indicated that it had some activity. Amikacin was no more active than Kanamycin. Since Amikacin is considerably more expensive than Kanamycin and there appeared to be complete cross resistant between the 2 antibiotics, they bad concluded that there was probably no place for its use in the chemotherapy of tuberculosis.

Capreomycin is a polypeptide antibiotic produced by *Streptomyces* spp and has the same pharmacokinetics and toxicities as the other aminoglycosides. It is no more effective than Streptomycin and has an incomplete cross-resistance with Amikacin and Kanamycin.[41]

Clarithromycin

Clarithromycin, a newer erythromycin derivative, has been shown to be highly active against multiple drug resistant MAC organisms, besides having promising activity against various other potentially pathogenic NTM including *M. paratuberculosis.*[42] It has been shown to cause a reduction in the bacillary load and clinical improvement of *M. avium* disease in AIDS patients.[41]

Conclusions

From the available information it is clear that **among the newer drags which have antituberculosis activity and are promising, Rifapentine shows extensive cross reaction with Rifampicin, and Rifabutin shows lower MIC values in only about 10-30% *M. tuberculosis* strains resistant to Rifampicin. Only the fluoroquinolones do not cross resistance with Rifampicin.** The other drugs like Amikacin, Capreomycin and beta lactam antibiotics may not have any additional benefits or have not yet been evaluated fully.

In India, under the National Tuberculosis Programmme, SCC is being implemented at present in about 250 districts. As a result, Rifampicin is

being used freely in these districts in the primary chemotherapy of sputum positive pulmonary tuberculosis patients under programme conditions. A large number of patients who do not seek treatment in government institutions get treated by private practitioners and also by other agencies, often with Rifampicin in addition to other drugs. A similar situation prevails in most of the other developing countries also. In these places, the prognosis for patients harbouring sensitive *M. tuberculosis* strains and also those who harbour *M. tuberculosis* strains with initial drug resistance to S/H will be good if the patients are regular and complete the full course of treatment. However, under programme conditions only about 50% of patients under SCC and about half of them under standard chemotherapy complete the full course of treatment. In respect of patients harbouring strains with initial resistance to Rifampicin, the prognosis is even more bleak. The problem gets more complicated if these patients are also infected with HIV.

The treatment of tuberculosis in immunosuppressed patients is not well established. A regimen of Rifampicin, Isoniazid and Ethambutol for 6 months, supplemented with Pyrazinamide during the first 2 months has been reported to be quite effective and able to bring about sputum conversion in more than 80% after 3 months,[43] although relapse has been reported[44] and adverse reactions to antituberculosis drugs are frequent.[45] It has been reported that corticosteroids added to the antituberculosis chemotherapy give dramatic clinical improvement.[46] It is also known that patients can tolerate concurrent therapy with Azidothymidine and antimycobacterial drugs without unacceptable toxicity.[47] Currently, the American Thoracic Society and CDC[48] recommend that antituberculosis chemotherapy should be started whenever acid-fast bacilli are found in a specimen from a patient with AIDS or suspected HIV infection. The treatment should be with H, R and Z, and should be continued for a minimum of 9 months and for at least 6 months after culture conversion: For any person, regardless of age, who has a positive tuberculin test reaction and is HIV seropositive, preventive therapy with H is recommended. Studies have to be undertaken to see if HIV infected individuals treated for tuberculosis in whom subsequent immunosuppression may lead to relapse, would benefit from continued administration of one or more antituberculosis drugs.[49] The ideal duration of treatment remains to be determined because in a recent study with a longer duration of follow-up, 6% of the patients who completed the 1 year treatment had relapse.[50] In this study, relapse was frequent in cases of poor adherence with premature discontinuation of treatment In India, the guidelines for treating tuberculosis in HIV positive persons and chemoprophylaxis using Isoniazid alone or in combination with other drugs have to be worked out.

In essence, the time has come for rational thinking and judicious use of the available alternative drugs in the treatment of failure patients. It is even more important to acknowledge the fact that at present there is no better substitute. than regular treatment with the currently available antituberculosis drugs and regimens.

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