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Review Article

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RECENT ADVANCES IN ANTI TUBERCULAR DRUGS

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ABSTRACT

Tuberculosis is a scourge for human race for millennia with huge morbidity and mortality. Among the main obstacles to the global control of the disease are the HIV epidemic that has dramatically increased the risk for developing active TB, the increasing emergence of multi-drug resistant TB (MDR-TB), Extensive drug resistant tuberculosis (XDR-TB) and the recalcitrance of persistent infections to treatment with conventional anti-TB drugs. Anti-tuberculosis drug resistance is a major public health problem that threatens the success of Directly Observed Treatment Short Course (DOTS), the WHO-recommended treatment strategy for detection and cure of TB, as well as global tuberculosis control. This has made the currently available anti tubercular drugs into less effective and futile tools to control tuberculosis. Not only to radically transform the fight against tuberculosis but also to shortening the current six to eight-month treatment to two months or less. This in turn will improve patient adherence, increase cure rates, and lessen the likelihood of patients developing drug resistance. New drugs are also needed to benefit the growing number of people around the globe who are co-infected with TB and HIV, as well as those who have been exposed to TB but are not yet ill with disease i.e. latent TB.

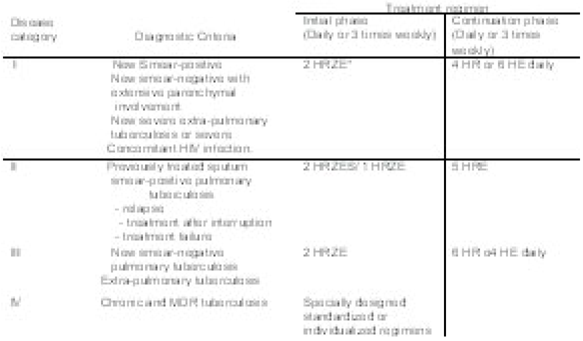
Keywords: *Tuberculosis; Anti-tuberculosis drug; Fluoroquinolones.*

INTRODUCTION

World health organization has recommended several regimens for successful treatment of tuberculosis. Although the current tuberculosis treatment regimens are highly effective, they require multiple drug, long term treatment with unpleasant side effects. This leads to patient non adherence that in turn leads to increased mortality and drug-resistant cases. Treatment of MDR-TB (Multiple drug resistance–Tuberculosis) and XDR - TB (extensive drug resistance–Tuberculosis) may become the primary health scourge of the 21st century. Multi drug resistant (MDR-TB) tuberculosis is defined as the resistance to atleast isoniazide and rifampicin, the two most powerful first line antitubercular drugs. Extensively drug resistant (XDR) TB is MDR-TB, that is resistant to any fluoroquinolone and at least one of the three injectibles, second line anti tubercular drugs (capreomycin, kanamycin, amikacin). To assess the frequency and distribution of XDR-TB, the WHO/CDC surveyed an international network of TB laboratories. The survey during 2000 to 2004, determined that among 17,690 isolates from 49 countries, 20% were MDR-TB and 2% were XDR-TB. WHO once again announced that there is a upsurge in resistance by 2006.[1] The increasing emergence of MDR-TB along with HIV pandemic threatens disease control. Approximately one-third of the world's population are infected with the mycobacterium that causes TB, and each year 9 million people become ill with the disease, with 2 million deaths. More than 40% of the cases are in Southeast Asia and India has 53.3% of that.[2] Currently available antitubercular drugs are not substantial to combat MDR-TB and prevent an emerging multidimensional problems.

The treatment regimen for tuberculosis as recommended by the WHO is described in Table 1. The current standard "short-course" treatment regimen requires at least 6 months which cannot be reduced using optimal combination of available antitubercular drugs. Because the existing anti TB drugs acts by the inhibition of cell processes such as cell wall biogenesis and DNA replication and thus can only kill actively growing bacteria. Actively growing mycobacteria are killed in initial period of therapy but it takes longer for

***Table 1 :** WHO recommended treatment regimens for Tuberculosis*



Disease category	Diagnostic Criteria	Treatment regimen	
		Initial phase (Daily or 3 times weekly)	Continuation phase (Daily or 3 times weekly)
I	New Smear-positive New smear-negative with extensive parenchymal involvement New severe extra-pulmonary tuberculosis or severe Concomitant HIV infection.	2 HRZE*	4 HR or 6 HE daily
II	Previously treated sputum smear-positive pulmonary tuberculosis - relapse - treatment after interruption - treatment failure	2 HRZES/ 1 HRZE	5 HRE
III	New smear-negative pulmonary tuberculosis Extra-pulmonary tuberculosis	2 HRZE	6 HR o4 HE daily
IV	Chronic and MDR tuberculosis	Specially designed standardized or individualized regimens	

***Note** : H, isoniazid; R, rifampicin; Z, pyrazinamide; E, ethambutal; S, streptomycin*

** Streptomycin may be used instead of ethambutal. In meningeal TB ethambutal should be replaced by streptomycin. Number preceding regimens indicates months of treatment.*

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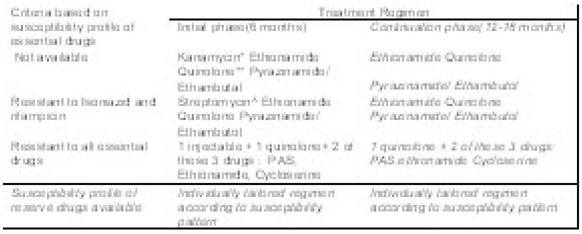
the drugs to kill slowly growing or slowly metabolizing bacteria. This implies that current TB chemotherapy is characterized by an efficient bactericidal activity but an extremely weak sterilizing activity, defined as the ability to kill the slowly growing or slowly metabolizing bacteria that persist after the growing bacteria have been killed by bactericidal drugs. Many *in vitro* studies showed that exponentially growing cultures of *M.tubercle* can be sterilized in a few days using combination of first line drugs like INH, RIF etc. But same combination of drugs take much longer time to achieve sterilizing action *in vivo*. The cause for variation in sterilizing activity (*in vivo* vs *in vitro*) was attributed to the heterogeneity of mycobacteria in human tissues. Based upon this the mycobacteria are classified into four different population viz., Bacteria that are actively growing, killed primarily by isoniazid (INH), bacteria that have spurts of metabolism, killed by rifampicin (RIF), bacteria that are characterized by low metabolic activity and reside in acid pH environment killed by pyrazinamide (PZA) and bacteria that are “dormant” or “persisters”, not killed by any current TB drug. Hence newer antitubercular drugs are needed to simplify or reduce the necessary duration of treatment to 2 months or less; to effectively treat MDR-TB, XDR-TB and mycobacteria in state of latency.[3] Table 2 describes the WHO recommended regimen for XDR-TB.

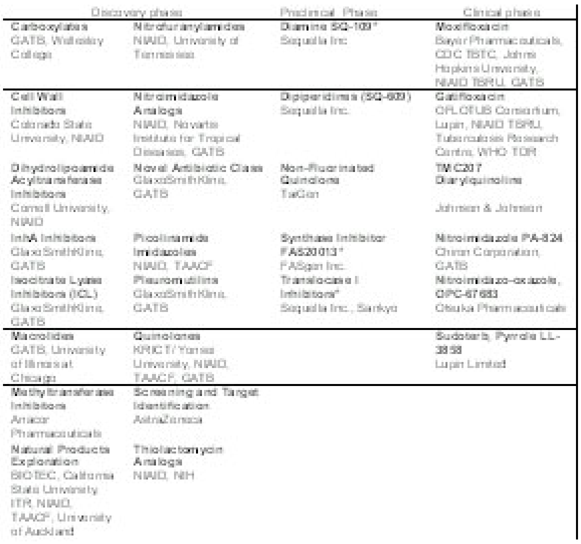
Table 2: *WHO recommendations for the treatment of multidrug resistant tuberculosis (MDRTB)*



Criteria based on susceptibility profile of essential drugs	Treatment Regimen	
	Initial phase(6 months)	*Continuation phase(12-18 months)*
Not available	Kanamycin* Ethionamide Quinolone** Pyrazinamide/ Ethambutol	*Ethionamide Quinolone* *Pyrazinamide/ Ethambutol*
Resistant to Isoniazid and rifampicin	Streptomycin^ Ethionamide Quinolone Pyrazinamide/ Ethambutol	*Ethionamide Quinolone Pyrazinamide/ Ethambutol*
Resistant to all essential drugs	1 injectable + 1 quinolone + 2 of these 3 drugs : PAS, Ethionamide, Cycloserine	*1 quinolone + 2 of these 3 drugs: PAS ethionamide Cycloserine*
Susceptibility profile of reserve drugs available	*Individually tailored regimen according to susceptibility pattern*	*Individually tailored regimen according to susceptibility pattern*

Most pharmaceutical companies were not interested to pursue tuberculosis research because of the high investment required to bring a innovative drug to the market and the lack of likely commercial return. After decades of standstill in TB drug development, the drug pipeline has begun to fill up during the last 5 years. Established in 2000 and largely funded by the Bill & Melinda Gates Foundation, the Global Alliance for TB Drug Development (TB Alliance) has played a critical role in changing the TB research and development (R&D) landscape and is associated with approximately half of all compounds (or projects aimed to identify candidate compounds) in development. The drug candidates in the portfolio originate from either analogue of existing molecules where innovative chemistry is used to help optimize compounds or novel chemical entities. In novel chemical entities, molecules like the fluoroquinolone (moxifloxacin and gatifloxacin), nitroimidazole analogs (PA-824), the diarylquinoline (TMC207), carboxylates, nitrofuranylamides, diamine (SQ-109), dipiperidines (SQ-609); dihydrolipoamide acyl transferase inhibitors, Non fluorinated quinolone, diaryl quinoline, InhA inhibitors, picolinamide imidazoles, synthase inhibitors (FAS20012), nitroimidazo-oxazole (OPC67683), macrolides, sudoterb, pyrrole LL-3858, methyltransferase inhibitors and thiolactomycin analogs are in pipeline. All of them show potent activity *in-vitro* against *M.tuberculosis.* Table 3 describes few of the antitubercular drugs that are in the development process. The objective of the present article is to describe the application of newer chemical entities with evidence of efficacy in the treatment of TB, their potential benefits and disadvantages.

Table 3 : *List of tubercular drugs in recent development*



Discovery phase		Preclinical Phase	Clinical phase
Carboxylates GATB, Wellesley College	**Nitrofuranylamides** NIAID, University of Tennessee	**Diamine SQ-109*** Sequella Inc	**Moxifloxacin** Bayer Pharmaceuticals, CDC TBTC, Johns Hopkins University, NIAID TBRU, GATB
Cell Wall Inhibitors Colorado State University, NIAID	**Nitroimidazole Analogs** NIAID, Novartis Institute for Tropical Diseases, GATB	**Dipiperidines (SQ-609)** Sequella Inc.	**Gatifloxacin** OFLOTUB Consortium, Lupin, NIAID TBRU, Tuberculosis Research Centre, WHO TDR
Dihydrolipoamide Acyltransferase Inhibitors Cornell University, NIAID	**Novel Antibiotic Class** GlaxoSmithKline, GATB	**Non-Fluorinated Quinolone** TaiGen	**TMC207 Diarylquinoline** Johnson & Johnson
InhA Inhibitors GlaxoSmithKline, GATB	**Picolinamide Imidazoles** NIAID, TAACF	**Synthase Inhibitor FAS20013*** FASgen Inc.	**Nitroimidazole PA-824** Chiron Corporation, GATB
Isocitrate Lyase Inhibitors (ICL) GlaxoSmithKline, GATB	**Pleuromutilins** GlaxoSmithKline, GATB	**Translocase I Inhibitors*** Sequella Inc., Sankyo	**Nitroimidazo-oxazole, OPC-67683** Otsuka Pharmaceuticals
Macrolides GATB, University of Illinois at Chicago	**Quinolones** KRICT/ Yonsei University, NIAID, TAACF, GATB		**Sudoterb, Pyrrole LL-3858** Lupin Limited
Methyltransferase Inhibitors Anacor Pharmaceuticals	**Screening and Target Identification** AstraZeneca		
Natural Products Exploration BIOTEC, California State University ITR, NIAID, TAACF, University of Auckland	**Thiolactomycin Analogs** NIAID, NIH		

Fluoroquinolones

Fluoroquinolones are fluorine-containing nalidixic acid derivatives and few of them are recommended for use in MDR-TB, due to potent anti-mycobacterium activity, good pharmacokinetics, in terms of tissue and cellular distribution, fewer adverse effects.[4] Although included in antituberculous regimens (particularly for MDR-TB) since late 1980s, their role in tuberculosis treatment still remains controversial. Ciprofloxacin (CPFX), ofloxacin (OFLX), sparfloxacin (SPFX), and levofloxacin (LVFX) have good anti-mycobacterium activity against experimental tuberculosis in animal models and are clinically effective in control of tuberculosis (including MDR-TB) when given in combination with other anti TB drugs.[5]

But in contrast it was reported that substituting or adding fluoroquinolones to established first-line antituberculous drug regimens gave no additional benefit or risks. Fluoroquinolones have antitubercular activity, but are not considered as lone standard. Ciprofloxacin should not be used as a substitute drug in the standard antituberculous regimen, because of higher relapse rate in drug sensitive tubercular patients, longer duration of treatment and no added advantage in terms of therapeutic efficacy and safety over existing antitubercular agents. Sparfloxacin was no better than ofloxacin when added to antituberculous regimens in drug-resistant tuberculosis.[6]

Novel fluoroquinolones like Moxifloxacin and gatifloxacin are of special interest in treatment of tuberculosis since they are considered to have greater activity than ciprofloxacin, ofloxacin, levofloxacin, and sparfloxacin. Hu et al.reported that ciprofloxacin had the least bactericidal activity, ofloxacin and levofloxacin had greater activities while moxifloxacin and gatifloxacin had the greatest activities.[7] Superiority of moxifloxacin and gatifloxacin over older fluoroquinolones against mycobacterium has raised the hopes that these agents can be used in combination with other first line regimen to reduce the treatment duration. However Burman et al. showed that, substitution of moxifloxacin for ethambutal did not have an effect on 2-month sputum culture status, but resulted in a higher frequency of negative cultures at earlier time points in patients with smear-positive pulmonary tuberculosis. Higher frequency of negative cultures at earlier time points among patients with smear-positive pulmonary tuberculosis with moxifloxacin indicates that it may have the potential for treatment shortening.[8] The reason for decline in activity of moxifloxacin, when used in combination with first line antitubercular drugs demands further research. An *in vitro* study by Lu T and Drlica K concluded that the combination of moxifloxacin and isoniazid was slightly more lethal to mycobacteria than either compound when used alone.[9] The same is true for combination of moxifloxacin and rifampicin at low rifampicin concentrations. However, when rifampicin concentration increased, lethality is reduced. Interference with quinolone lethality by rifampicin is a well known phenomenon with *Escherichia coli*. Presumably, treatment with rifampicin, an inhibitor of RNA synthesis, or chloramphenicol, an inhibitor of protein synthesis, blocks the expression of a suicide protein involved in the lethal action of quinolones. The ability of chloramphenicol to interfere with the lethal action of ciprofloxacin during treatment of Mycobacterium bovis support the idea that a similar phenomenon occurs in mycobacteria. Nuremberger et al reported that combination of moxifloxacin with rifampicin and pyrizinamide in place of isoniazid improved the anti mycobacterial activity. Moxifloxacin with isoniazid in standard regimen could relieve a possible antagonism among the currently used drugs.[10] Conflicting results have been reported about gatifloxacin's activity when added to isoniazid or rifampicin in cell cultures, with one study suggesting synergy but another reporting little additive.[11] However, it is not clear how clinically applicable these test tube studies are and what would happen *in vivo.*

Moxifloxacin

In vitro, moxifloxacin appeared to kill a sub population of tubercle bacilli not killed by rifampicin, i.e. rifampicin-tolerant persisters. Ciprofloxacin and ofloxacin did not have any such effect. In murine models the anti tubercular activity of moxifloxacin was comparable to isoniazid.[12] Moxifloxacin appears to be a poor substrate for efflux pumps in other pathogens such as *S. pneumonia*. This might be due to the bulky C-7 substitute that characterizes this compound. The hydrophilic fluoroquinolones such as ciprofloxacin are good substrate and easily effluxes out of bacteria). Inhibition of effluxes results in building of higher concentrations resulting in improved activity.

Gatifloxacin

Gatifloxacin has demonstrated dramatically greater activity in preclinical studies but likely to be cross-resistant to moxifloxine. Early clinical indications of gatifloxacin's anti-TB activity have been found to be promising with identical activity to moxifloxacin and similar to isoniazid. The drug's toxicity and drug-drug interaction profile is similar to moxifloxacin. Likewise, the drug has not been adequately evaluated in children and pregnant or lactating women.[13]

Gemifloxacin

Gemifloxacin is a quinolone which has shown promising activity in various phase 3 trials and now been submitted for approval in the USA for the treatment of respiratory infections. In healthy volunteers, oral bioavailability is approximately 70%, well tolerated and has a mean elimination half life of 7.4 hours and hence suitable for once-daily dosing regimen. Extrapolating *in vitro* sensitivity data to serum concentrations of healthy volunteers suggests that, even at the highest non-toxic dose tested (800mg), gemifloxacin would not be effective for TB treatment.[14]

Sitafloxacin

Sitafloxacin is in Phase III trials in both Japan and the USA. Against broad range of bacteria, sitafloxacin has outstanding activity. In comparison to other quinolones like ciprofloxacin, trovafloxacin, clinafloxacin, levofloxacin, gatifloxacin and moxifloxacin, sitafloxacin has highest activity. Sitafloxacin has ability to equally inhibit both DNA gyrase and topoisomerase IV, and its IC_{50} against these enzymes were lowest amongst the quinolones. Potency of sitafoxacin is equal to that of gatifloxacin and sparfloxacin but exeeds to that of levofloxacin and ofloxacin when tested against strains of *M. tuberculi* MIC90 (MIC at which 90% of strains of *M. tuberculi* inhibited) was ~ 0.2mcg/ml.[15] However no published data are available against *M. tuberculi in vivo*.

Floroquinolones and mycobactreial resistance

There are reasons for concerns about the rapid development of resistance. In a study conducted in USA and Canada, resistance to ciprofloxacin was found to occur in 1.8% (33/1852) of isolates and 75.8% (25/33) of those were multidrug resistant. Despite widespread use of fluoroquinolones for common bacterial infection, the resistance to fluoroquinolones remains rare and occurs mainly in multi-drug resistant strains. Ginsburg et al. reported the incidence of fluoroquinolone resistance, was found high with prior fluoroquinolone exposure (2/19) in newly diagnosed tuberculosis patients.[16] Cross-resistance was observed among the different fluoroquinolones tested (ofloxacin, levofloxacin, gatifloxacin moxifloxacin, and ciprofloxacin). For this reason, it is suggested that fluoroquinolones might be better reserved for specific serious infections like MDR-TB.

Safety of floroquinolones

Newer floroquinolones seems to be much safer than isoniazid or rifampicin, however, there may be complications in patients with heart problems, and the drug has some rare CNS side-effects. The drug is used widely in treatment of bacterial infections in people with HIV and has no drug interactions with antiretrovirals. However, of crucial importance, the safety and effectiveness of moxifloxacin is yet to be established in pediatric patients, adolescents (less than 18 years of age), pregnant women, and lactating women. Thus rational behind the combination of newer fluoroquinolones with antitubercular drugs is not clear and demands further research.[17]

Newer rifamycin derivatives

Rifabutine

As determined by MIC, rifabutine (RBT) is about 4 to 8 times more active than rifampin (RIF) against *M.tuberculosis* and it possesses favorable pharmacokinetic features such as a long half-life and good tissue penetration. Owing to the better pharmacokinetic profile and potency of RBT in comparison to RIF, Centers for Disease Control and Prevention (CDC) in the U.S. has recommended use of RBT in place of RIF in multidrug regimens for the treatment of active TB in HIV patients. Prime reason for this is RBT can be co-administered with antiretroviral treatment that includes HIV protease inhibitors or nonnucleoside reverse transcriptase inhibitors. Compared to RIF; RBT is very weak inducer of cytochrome P-450 isoenzymes which are responsible for metabolism of antiretroviral drugs. Thus in contrary to RIF co-administation of RBT with antiretroviral drugs does not substantially decrease blood levels of these antiretroviral drugs.

Rifapentine

Rifapentine (RPT) is 2 to 4 times more active than RIF against *M.tuberculi* and is having better pharmacokinetic profile than RIF. Duration of action for RPT is much greater than those of other available rifamycin derivatives, owing to its high serum peak level and elimination half-life which allows for its extended dosing intervals in TB patients. In addition, INH in combination with RPT gives very long post antibiotic effect (PAE) (137 h) and this PAE is about 17 times that of INH plus MXFX. Adverse events of RPT may occur less frequently at the currently recommended 600-mg dose as compared with RIF. Although RPT induces CYP450 somewhat less than RIF, C_{max} and AUC of a HIV protease inhibitor indinavir are strongly reduced, when RPT is co-administered with indinavir. In any case, both RBT and RPT are now included in drug regimens for the treatment of TB and MAC infections, particularly in HIV patients.[18]

Rifametane

It is a new semi-synthetic rifamycin having bactericidal spectrum and potency similar to that of rifampicin with much better pharmacokinetic profile. This is evident from the fact that when pharmacokinetics of rifamentane was studied in comparison with known rifamycin derivatives, like rifampicin although MIC90 values of the two compounds were the same against 20 strains of *M. tuberculosis* in TB-infected mice, rifametane proved to be more effective orally. In healthy male volunteers, the pharmacokinetics and safety of a 300 mg single oral dose of rifametane in comparison to a 300 mg dose of rifampicin, clearly showed that the pharmacokinetic profile of rifametane is significantly more favourable than that of rifampicin. The elimination half-life for rifametane was 10.58 hours compared with 1.89 hours for rifampicin, and the mean residence time was 18.05 hours for rifametane and 3.93 hours for rifampicin. The drug was well tolerated and no changes clinically or statistically in laboratory parameters were found. In another Phase I trial carried out in collaboration with Glaxo India, a single oral dose of 150mg was administered and the half-life and area under curve (AUC) were some 6 or 7-fold that of rifampicin. Encouragingly, serum drug levels above the MIC for *M. tuberculosis* were maintained for up to 48 hours after drug administration.[19]

Rifalazil

Rifalazil, a new semi synthetic rifamycin, is characterized by a long half-life and is more active than rifampicin and rifabutin against *M. tuberculosis* both *in vitro* and *in vivo*. However, high level rifampicin–resistant strains present cross-resistance to all ryfamycins. Moreover, due to severe side-effects during Phase II trial, the development of rifalazil has been terminated.[20]

Mikasome

Amikacin is an aminoglycoside used as a second-line anti-TB drug. The anti-mycobacterial activity of liposome-encapsulated drug, Mikasome (Gilliad Sciences), has been found to be effective against *Mycobacterium avium* infections *in vitro* and in animal models. In preclinical studies, 48 hrs after delivery to the lungs via liposome, over half of the antibiotic remained in this tissue.[21] In animals, pharmacokinetic data showed that Mikasome produced 7-fold higher peak plasma levels compared to free drug (amikacin) administered intravenously. Additionally, the AUC was 150-fold higher with the liposomal material and a single dose of liposomal amikacin produced therapeutic levels of antibiotic for more than 72 hrs. In a preliminary clinical study, a patient with tuberculosis treated with Mikasome for 49 days exhibited negative culture. Once weekly dosing maintained constant amikacin dose levels. Pilot Phase II studies showed that Mikasome was able to resolve *M. tuberculosis* infections in adults and children who had failed conventional therapies.[22]

Aconiazide

Aconiazide is a pro-drug of isoniazid which was designed to be less toxic than the parent drug lacks carcinogenicity. Isoniazid is metabolized to hydrazine and acetylhydrazine, which are considered to be responsible in the toxicity of isoniazid. Since aconiazide is converted to isoniazid and 2-formylphenoxyacetic acid, it was expected that the acid would bind to the isoniazid metabolites and so lower toxicity. .In healthy patients it was found to produce proportionately lower levels of isoniazid in serum than the parent molecule itself. For some time, further progression of the compound was delayed due to problems with its commercial synthesis. However, additional toxicology data are now being submitted to the FDA by Lincoln Diagnostics in order to conduct clinical trials in tuberculosis patients, and the compound has been granted Orphan Drug status in the US.[23]

Macrolides

Clarithromycin (CAM) is effective against *M.tuberculi* only at very high concentrations *in vitro* (MIC50 and MIC90 are 64 and >128 mg/ml, respectively), which are significantly greater than its C_{max} values in the serum and lung tissue in humans and thus cannot be achieved clinically. However, a recent study by Bosne-David et al.[24] showed that the intrinsic resistance of *M.Tuberculi* to CAM is reversed when inhibitors of bacterial cell wall synthesis, especially bacitracin and vancomycin (at subinhibitory concentration) are co-administerwed with CAM. This indicates that the natural resistance of *M.tuberculi* to macrolides is attributable to the cell wall structures of *M.tuberculi* as a drug permeability barrier. They also found that Ethambutal (EMB) reversed CAM resistance in all of the test *M.tuberculi* strains regardless of their baseline susceptibility to CAM. It is also found that CAM or its metabolite, 14-hydroxyclarithromycin, when co-administered with anti tubercular drug like INH, RIF and EMB results in 4- to 32-fold reduction in MICs of these drugs and made drug-resistant strains susceptible. Thus CAM may be concurrently given with first line antitubercular drugs to improve the therapeutic efficaciousness of these drugs in treating MDR-TB.[25]

Clofazimine

A riminophenazine antimycobacterial agent, is mainly used for the treatment of leprosy. Clofazimine (CFZ) shows substantial activity against *M.tuberculi* both *in vitro* and *in vivo* in preclinical studies. The MICs of CFZ and its analogs (B4154; B4157) at which 90% of strains were inhibited were 0.25, 0.12, and < or = 1.0 microgram/ml, respectively. At a dose of 20 mg/kg of body weight, the activity of CFM was slightly superior to that of B4157; however, both compounds prevented mortality and caused a significant reduction in the numbers of CFU in the lungs and spleens. Because of the therapeutic efficacies of these compounds, it is often empirically included in regimens for treatment of MDR-MTB. However, oral CFZ was found inactive against intracellular M. when it was used alone or co-administered with other drugs (such as PZA plus EMB) for the treatment of MDR-TB. Long-term CFZ therapy is associated with dermal side effects like dark brown pigmentation, ceroid lipofuscinosis. Oral clofazimine exhibits a sometimes prolonged and variable lag-time and considerable variability in plasma concentrations. From the population analysis (one-compartment model), the mean oral clearance was 76.7 l/h (CV=74.2%) and mean apparent volume of distribution was 1470 l (CV=36.3%). The first-order absorption rate constant ranged from 0.716 to 1.33 h(-1) (pooled CV=61.7%). Thus, justification of the meaning of empirical use of CFZ in multidrug regimens for MDR-MTB requires more detailed and systematic experimentation in future. Novel riminophenazine like B746 and B4157 have shown better activity against *M.tuberculi* compared to CFZ *in vitro* studies and are devoid of side effects on skin.[26]

Capuramycin analogs

possess potent antimycobacterial activities *in vitro* and *in vivo* through the inhibition of enzyme phospho-MurNAc-pentapeptide translocase and thereby inhibit the peptidoglycan assembly of mycobacteria. Few of the potent cupuramycin analogues were not considered for further development owing to the lack of desirable pharmacokinetic characteristics. RS-118641 is one of the most potent anti-MTB capuramycin analogs, had MIC50 and MIC90 for drug susceptible M.tuberculi strains, 1 and 2 mg/ml respectively, while its MIC50 and MIC90 for MDR-MTB strains were 0.5 and 2 mg/ml, respectively. However, this agent had very poor solubility and was not considered suitable for further development. Other capuramycin analogs RS-112997 (Fig. 1R) and RS-124922 exhibited appreciable levels of therapeutic efficacy against MTB infection in mice, causing about 3-log unit-reductions of bacterial loads in the lungs, when given to mice at doses of 0.1 or 1 mg/mouse daily during the early phase of infection and the MIC50s against MDR-MTB strains were 16 and 4 mg/ml, respectively. Capuramycin analogs may be considered for further evaluation in the treatment of MDRTB patients, since these agents act on unique and selective targets in the cell wall synthesis of TB bacilli.[27]

Linezolid

Linezolid an oxazolidinone which acts by inhibiting protein synthesis and is active against multi drug-resistant strains of mycobacterium tuberculosis. Linezolid inhibits ribosomal protein synthesis by interfering with initiation complex formation, resulting in inhibition of protein synthesis at a very early stage. The advantages are the lack of cross resistance to existing antimicrobial agents, a spectrum of activity that includes a number of important bacterial species, superior oral and parenteral bioavailability, low emergence rate of resistant mutants and there is no natural reservoir of resistance. Linezolid lacks cross resitance to other existing antimicrobial agents and it has been confirmed by recent studies using 117 clinical isolates of MTB, including organisms susceptible to first-line drugs, resistant to one first-line drug and resistant to multiple first-line drugs (MIC50=0.5 mg/ml, MIC90=0.5 to 1.0 mg/ml) and a total of 234 strains of drug-susceptible or MDR-MTB. Synergism was found between Linezolid and RIF in 30% of drug-susceptible MTB strains. In experimental studies with the murine model of tuberculosis, oxazolidinones- linezolid have shown an activity similar to isoniazid. However, clinical experience with linezolid in tuberculosis is scarce. In addition to the lack of information on the efficacy in the treatment of tuberculosis or toxicity is a matter of concern when the drug has to be used for long periods. Clinical trials have shown that linezolid (600 mg twice daily in adults) is safe and generally well tolerated for courses of therapy of <28 days, but long-term linezolid use has been associated with reversible haematopoietic suppression, primarily thrombocytopenia and neuropathy. Moreover reduction in dose of linezolid to half of the acceptable dose although does not interfere with its antimycobacterial activity but long-term use of the drug can cause side effects, such as peripheral and optic neuropathy.[28]

Phenothiazines

Phenothiazines are derivatives of methylene blue, which was described by Paul Ehrlich in the 19th century as rendering bacteria immobile. Since then, phenothiazines have been shown to be active against a wide variety of viruses, bacteria, mycobacteria and protozoa. The phenothiazines chlorpromazine (CPZ) and thioridazine (TZ) have equal in vitro activities against antibiotic-sensitive and resistant mycobacterium tuberculosis. Phenothiazines are calmodulin antagonist and antituberculous activity of these agents is due to presence of calmodulin-like protein in mycobacteria. These compounds have not been sufficiently explored for their antimycobacterial activity because their in vitro activities take place at concentrations which are beyond those that are clinically achievable. However pulmonary macrophages concentrate chlorpromazine 10-100 fold above the concentration found in plasma and has activity against mycobacteria that have been phagocytosed by these cells. Since chlorpromazine has antimycobacterial activity within the macrophage,it is likely that thioridazine exerts a similar activity with concentrations at the level of 1 mg/L. In comparison to CPZ ,TZ is the very mild anti-psychotic agent whose most common side effect is drowsiness, and its use for a limited period of 2–3 months should not produce side effects that are more severe than simple drowsiness. It has equal anti-tuberculosis properties in vitro to chlorpromazine. CPZ and TZ found to interacts synergistically with antimicrobial agents which include streptomycin, erythromycin, oleandomycin, spectinomycin, levofloxacin, azithromycin, and amoxicillin-clavulanic acid. The MICs of these antibiotics were reduced as much as 8,000-fold in the presence of the CPZ & TZ.[29] Hence human studies are required to evaluate efficacy of CPZ & TZ as alternative/adjuvant in treatment of tuberculosis.

5-Nitroimidazole

In many individuals, M. tuberculosis infection takes the form of a latent disease state. At some time the disease may reactivate and give rise to an active and often fatal infection. In some patients, this may occur even after the individual has been given prolonged chemotherapy. A key problem in TB control is the persistence of organism. Significantly the dormant form of the mycobacterium was found to be resistant to the standard anti-mycobacterial agents like isoniazide and rifampicin. M. tubercle is an obligate aerobe that is capable of long-term persistence under conditions of low oxygen tension. Mycobacteria encounter hypoxic environments invivo which cause it to shift down from active replication to dormancy i.e. nonreplicating (NR) state. Metronidazole is the ûrst drug which has shown activity against dormant tubercle. Metronidazole acts as a pro-drug as it undergoes reduction at low redox potential in susceptible micro-organism to form intermediate nitro-group which in turn damages DNA and cause sub-sequent cell death. Significant synergistic activity was observed in combination with rifampin and metronidazole. In the single blind study, patients receiving metronidazole showed clinical improvements on the basis of improved rates of reduction of sputum quantity and greater radiographic improvements. Thus, it may be valuable to carry out further clinical trials of metronidazole.[30]

Nitroimidazopyran PA-824

PA-824, a lead compound of series of nitroimidazopyrans synthesized on the basis of 5-nitroimidazole CGI 17341 is highly active against MDR-MTB and exhibits bactericidal action against dormant MTB. In addition, PA- 824 has much reduced mutagenicity compared to that of CGI 17341. Nitroimidazole antibiotics show potent microbicidal activity against MTB mainly due to its inhibitory activity against both protein and lipid synthesis by MTB organisms after activation by a mechanism dependent on MTB F-420 cofactor.[31] Notably, in contrast to current antituberculous drugs, nitroimidazopyrans exhibited bactericidal activity against both replicating and static MTB .It lack the cross resistance to other first line antitubercular drugs.

Diarylquinoline TMC207 (Johnson & Johnson)

Diarylquinoline TMC207 is currently in phase IIa clinical trials and has shown promising therapeutic activity against mycobacterium tuberculi in preclinical studies. In preclinical studies it has showed potential for reduction of treatment duration.Diarylquinoline TMC207 is most active compound with unique spectrum and specificity to mycobacteria with minimum inhibitory concentration below 0.5 g/ml. Antimicrobial activity of TMC207 was confirmed in vivo.[32] Pharmacokinetic and pharmacodynamic studies in mice showed long plasma half-life, high tissue penetration and long tissue half-life. These are all attributes that are valuable for treatment of chronic infections and may also be important for development of simpler dosing regimens. The target and mechanism of action of diarylquinoline TMC207 is different from those of other anti-TB agents it acts by inhibiting the ATP synthase, leading to ATP depletion and pH imbalance implying low probability of cross-resistance with existing-TB drugs.[33] This is further suggested by the fact that diarylquinoline TMC207 is able to inhibit bacterial growth when tested on MDR-TB isolates.TMC207 has potent early bactericidal activity matching or exceeding that of isoniazid. When diarylquinoline TMC07 is used as substitution for drug used in existing first line drug combination to treat TB it is observed that culture conversion occurs after 2 months of treatment in some combinations. In particular, the diarylquinoline-isoniazid-pyrazinamide and diarylquinoline-rifampicin-pyrazinamide combinations cleared the lungs of TB in all the mice after two months. When diarylquinoline TMC207 was tested in various combination with the second line drugs amikacin, pyrazinamide, moxifloxacin and ethionamide in mice (infected with the drug-susceptible virulent M. tuberculosis strain H37Rv) the diarylquinoline containing regimen was found to be more active than the current recommended regimen for MDR-TB . The diarylquinoline containing regimen attains the culture negativity of the both lungs and spleens after 2 months of treatment in almost every case.[34]

Pyrrole LL- 3858 (Lupin Limited, India)

Lupin Limited reported the identification of a Pyrrole derivative (LL-3858) that showed antimycobacterial activity in preclinical studies. When pyrrol LL-3858 was administered as monotherapy in infected mice it was found to be more active than Isoniazid. Combination of LL-3858 with currently existing first line drugs isoniazid-rifampicin, pyrazinamide sterilized the lungs of all infected mice within the period of less than 2 months. Experiments conducted in mice and dogs showed that the compound is well absorbed, with levels in serum above the MIC and better half-life and Cmax than those showed by isoniazid.[35] No information is available concerning the molecular mechanisms that mediate LL-3858's bactericidal activity Pyrrole LL3858 is currently in Phase I Clinical Trials.

Pleuromutilins

Pleuromutilins have been shown to inhibit the growth of M. tuberculosis and acts by interfering with mycobacterial protein synthesis by binding to the 23S r RNA and thus inhibits the peptide bond formation. However the current studies revealed that there exists the cross resistance among the pleromutilins and oxazolidinones.[36] Pleuromutilins is derived from natural source and represents noval class of antibiotic. Currently GSK-TB Alliance is working on Pleuromutilins for the identification of pleuromutilins derivative that is active against MDR-TB and efficient enough in shortening the duration of existing duration of tubercular treatment .

Dipiperidine SQ-609 (Sequella Inc.)

Dipiperidine SQ-609 is a novel compound structurally unrelated to existing anti-TB drugs. It kills M. tuberculosis by interfering with cell wall biosynthesis (precise mechanism unknown). Anti microbial activity has been demonstrated in vivo in mouse models.[37] When tested in mice using a low-dose infection model of TB, SQ-109 at 1 mg/kg was as effective as ethambutol at 100mg/kg. However SQ-109 did not show improved effectiveness at higher doses (10mg/kg; 25mg/kg) and was clearly less effective than isoniazid (Protopopova et al., 2005).[38]

ATP Synthase Inhibitor FAS20013 (FASgene) FAS20013

It is a novel compound identified by Fasgen belonging to the class Sulphonylcarboxamides. In many preclinical studies the compounds have shown the therapeutic effectiveness against mycobacterium tuberculi. The compound is thought to act through inhibition of ATP synthase. The compound is very effective in killing MDR-TB organisms that are resistant to multiple drugs currently in use. The compound FAS20013 was proved to be superior in its ability to sterilize the TB lesions and kill latent TB compared to the all existing antitubercular drugs in a series of recent laboratory experiments. The compound has good pharmacokinetic characteristics and is 100% bioavailable on oral administration. To date no dose limiting toxicity has been encountered, even when doses 10 times the effective dose were administered.[39]

InhA Inhibitors (Glaxo-SmithKline-TB Alliance)

Isoniazid is considered to be first line drug in tuberculosis treatment. Isoniazid requires activation in which Inheritant protective enzyme of mycobacteria - Kat G plays vital role. Isoniazid resistance to tuberculosis develops primarily by mutations in Kat G. InhA, the enoyl reductase enzyme from Mycobacterium tuberculosis, catalyses the last step in the fatty acid biosynthesis pathway (FAS II). Active form of isoniazid inhibits this step. Consequently, InhA inhibitors that do not require activation by KatG are attractive candidates for drug discovery. The main purpose for this screen is therefore to bypass the activation step and directly inhibit InhA. A possible limitation for this kind of compounds is that cross-resistance with isoniazid may easily occur. Indeed, mutations in InhA encoding gene have been already identified in INH-resistance strains even if they occur less frequently than KatG mutations.[40]

CONCLUSION

The current antitubercular drugs offer treatment which demands continuous administration of drugs for six months. The patient nonadherance along with HIV co- infection, emergence of MDR-TB, XDR-TB and recalcitrance of mycobacterium has pushed alarm for the need of effective molecules with better therapeutic outcomes. Newer drugs are needed to shorten the total duration of treatment and/or significantly reduce the number of doses needed to be taken under DOT, improve the treatment of MDR-TB, provide a more effective treatment of latent TB infection, provide more effective treatment of TB associated with HIV with minimal or no interaction with antiretroviral drugs. Established in 2000 and largely funded by the Bill & Melinda Gates Foundation, the Global Alliance for TB Drug Development (TB Alliance) has played a critical role in changing the TB research and development (R&D) landscape. It is evident that although candidates in TB pipeline have shown therapeutic promise in reducing the treatment duration, the number available in the pipeline is very few.

Many of the candidates are analogues of drugs with known antitubercular activity hence possibility of cross resistance cannot be neglected. Better understanding of clinicopathogenesis of mycobacteria in human host is required in order to discover novel targets. The most promising novel drug candidates currently in clinical stage were identified serendipitously and were not designed originally for activity against M. tuberculosis. There is an urgent need to identify compounds acting on key targets that are essential for mycobacterium persistence. An example is the search for inhibitors of the isocitrate lyase, an enzyme that has been proven to be involved in the “dormancy” response. Compounds able to inhibit this enzyme are expected to kill persistent bacteria. It is necessary to re-think the traditional roles played by academia and pharmaceutical industry in drug discovery and development when it comes to drugs for diseases like TB that do not represent an interesting market. Without public sector engagement into translational research and implementation of rational drug design, fast progresses will be severely hampered.

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