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Review Article

A Review on Tuberculosis combinational Treatment and Drug Regimens.

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ABSTRACT

A conventional drug delivery system to treatment on tuberculosis by combining action of drugs with synergic effect. Such an association is the one between Ethambutol hydrochloride and Isoniazid. The combination therapy of these drugs provides short term treatment for the tuberculosis. The other first line drugs like Pyrazinamide and Rifampicin in combinational pack with second line drugs to reduce the drug therapy. This combinational system eliminates or minimizes side effects. Short-course chemotherapy is highly efficacious in treating tuberculosis (TB). However, the length (≥6 months) and complexity (three or four different drugs) of the treatment makes adherence difficult.MDR and XDR tuberculosis are major challenges to tuberculosis control, but are not yet being sufficiently addressed. Emergence of 'multidrug resistant' TB of which over 0.4 million cases are occurring globally every year, is threatening the whole future of current antitubercular chemotherapy.

KEYWORDS

Tuberculosis, History first line drug, Combinational Drug Therapy and rationale, Multidrug resistance, Recent trends and Future trends and prospects.

1. INTRODUCTION

Tuberculosis is an air transmitted infectious disease treated with combination therapeutic regimens. Continuity to long-term antituberculosis therapy is important for maintaining sufficient blood drug level. The emergence and spread of drug-resistant Mycobacterium tuberculosis strains are mainly favored by the insufficient medical management of the patients. The therapeutic approach for drug-resistant tuberculosis is bulky because of the poor, expensive, less-effective, and toxic alternatives to the first-line drugs. New research and development activities should be implemented urgently. Public health policies are required to preserve the new and old therapeutic options. [1-13, 17, 54-59]

Tuberculosis is a chronic granulomatous disease and a major health problem in worldwide developing countries. About 1 /3rd of the world's population is infected with Mycobacterium tuberculosis. As per WHO estimate, 9 million people globally develop active TB and 1.7 million die of it annually. In India, it is estimated that nearly 2 million people develop active disease every year and about 0.5 million die from it. A new dimension got added in the 1980s due to spread of HIV with high prevalence of tuberculosis and Mycobacterium Avium Complex (MAC) infection among these patients. India has a large burden of HIV infected subjects, and these patients are especially unprotected to severe forms of tubercular /MAC infection. While lately, the increase TB case rate associated with HIV infection has been halted in the USA, no such trend is apparent in India

Medical treatment of tuberculosis, together with correct diagnosis, represents a cornerstone in the management and control of tuberculosis. It is relevant from a clinical and public health perspective, as tuberculosis is a serious contagious airborne disease. Antibiotic treatment, reducing the bacterial load in the lungs can be helpful to reduce the probability of transmission, along with other public health measures, such as isolation and cough etiquette.

The dramatic change of the epidemiological scenario during the last two decades is a consequence of the increased incidence of the tuberculosis/ HIV (human immunodeficiency virus) infection and the drug-resistant forms of tuberculosis however significantly complicated the clinical and public health management of the patients and of their contacts. Currently clinicians and public health specialists are facing daily problems related to the prescription of less effective and toxic second line drugs, with frequent pharmacological interactions with antiretroviral drugs or medicines used to treat other co-morbidities.

1.1. Tuberculosis Therapy: History and Rationale [1-13,17,29-32,46,54-59]

Tuberculosis is an ancient disease; nevertheless, effective drugs were not available for centuries. The pre-antibiotic therapy was initially represented by isolation in sanatorium to reduce the probability of Mycobacterium tuberculosis transmission to healthy contacts, with rest, adequate nutrition, and sunlight exposure. Then, the surgical approach represented the gold standard after Carlo Forlanini's discovery of the beneficial effects of the artificially induced pneumo-thoraxin 1927.

Only after the discovery of the etiological agent by Robert Koch in 1882 and the identification of the antibacterial activity of penicillin by Alexander Fleming did new experimental activities

focused on the evaluation of the efficacy of natural and chemical compounds in animals start (Goldsworthy and McFarlane 2002; Daniel 2006).

The first experimental evidence of the potential efficacy of new Anti-tuberculosis drugs was obtained in 1940 when a dapsone-derivative compound, known as promin, was administered to a sample of guinea pigs. However, that sulfonamide was never given to humans. A different destiny awaited, Streptomycin a natural substance isolated from *Streptomyces griseus* which proved its efficacy in animals and then in humans.

In 1944, Schatz and Waksman stated that the drug could be prescribed for the treatment of tuberculosis as a consequence of its bactericidal activity.

In 1946, the United Kingdom Medical Research Council Tuberculosis Unit showed its short-term 6-month efficacy in terms of mortality reduction (i.e., from 27% to 7%). However after 5 years no differences were found between those exposed and not exposed to streptomycin as a consequence of the acquired antibiotic. Four years later after the discovery of streptomycin, a new synthetic drug, called

Para-amino Salicylic acid (PAS) was presented as an alternative drug for the treatment of tuberculosis. Following the poor results of the monotherapy in 1952 the first regimen based on the combination of Streptomycin, PAS, and Isoniazid was proposed. Sir John Crofton with the "Edinburgh method" characterized by the prescription of at least two drugs, showed the efficacy of the combination therapy.

In 1954 Pyrazinamide was discovered but at the prescribed dosages the rate of hepatic toxicity was significantly high.

Ethambutol and Rifampicin were introduced in 1961 and 1963 respectively. The duration of therapy varied from 1 to 2 year.

In 1970 trials on drug regimens including first line drug Rifampicin shows that good results with a therapy of 9 month whereas in later 1974 trials on regimens incorporation of Rifampicin and Pyrazinamide at low dosages demonstrated that the good efficacy of a 6 month treatment.

Table 1. Historical steps of the anti-tuberculosis treatment.

Year	Historical steps
1940	Use of dapsone derivative in guinea pigs
1944–1946	Discovery of Streptomycin
1948	Discovery of Para-amino Salicylic acid
1952	Streptomycin þ Para-amino Salicylic acid þ Isoniazid
1954	Discovery of Pyrazinamide
1956	Madras study
1961	Discovery of Ethambutol
1963	Discovery of Rifampicin
1970	9-month Rifampicin-containing regimens

1974	6-month Rifampicin- and Pyrazinamidecontaining regimens
2012	Food and Drug Administration approval of Bedaquiline
2013	Approval of Delamanid by European Regulatory authorities

1.2. Combinational Drug Therapy[35-49, 53,57-59]

The efficacy of the combination regimens described above will determine in addition to bacteriological conversion a subjective improvement of the patient's clinical conditions. The latter feature may anticipate the microbiological conversion and could be paradoxically dangerous from an individual and a public health perspective. Patients feeling better might decide to interrupt their treatment.

Several approaches have been proposed to increase patient's adherence. One of the most important is the so-called DOT (i.e. Directly Observed Therapy). The patient takes the prescribed therapy in the presence of a healthcare worker (physician or nurse), a social worker, or another person involved in agreement with the local tuberculosis program. The direct observation avoids all the problems associated with self-administration including compliance with the dosages and time of administration affecting the pharmacokinetic curve of the drugs. In addition, DOT allows rapid management of adverse events related to the drug intake.

Another important tool to enhance adherence is represented by the fixed-dose combination of the anti tuberculosis drugs. They were introduced in clinical practice at the end of the 1980s and several advantages were immediately recognized.

Easy management for the national tuberculosis program and for health staff not fully familiar with anti tuberculosis drugs and reduced probability of emergence of drug resistances because of the improved patient's adherence.

The main disadvantages intrinsically related to the fixed dose are the risk of a non adequate blood level (rare and limited to patients characterized by a poor intestinal absorption or by a rapid metabolism) and the difficulty in attributing an adverse event to a specific drug.

Another strategic therapeutic approach to improve adherence is represented by the intermittent regimens whose efficacy was shown in 1964 in Chennai, India.

Anti tuberculosis drugs are administered at intervals of 1 day. The relapse rate is 8% after a follow-up of 2 year (World Health Organization 2004).

An important role to increase adherence can be played by incentives and enablers (money, food, incentives for transportation, etc.) particularly in resource-limited countries. Poor patients living in rural areas can lose their job and their daily salary because of the medical visits in far urban settings.

National tuberculosis programs should identify the geographical areas or the social groups where these nonmedical interventions could be crucial in improving adherence (Tuberculosis Coalition for Technical Assistance 2009). Last but not least when health education is adequately provided by health services to the patients and their families' adherence tends to improve.

Adherence with drug treatment is a major determinant of the outcome of treatment. As an aid to adherence combination tablets of three drugs (Rifampicin, Isoniazid and Pyrazinamide) are available for use in the two-month initial phase of treatment and of two drugs (Rifampicin and Isoniazid) in the four-month continuation phase of treatment. The other potential advantage of combination tablets is that they prevent accidental or inadvertent single drug therapy which can lead to acquired drug resistance within weeks in active tuberculosis disease. Care is however needed in the prescribing and dispensing of anti tuberculosis drugs in the UK, because of the similarities in names between several drugs.

Drug combinations are selected to maximize the above actions together with considerations of cost, convenience and feasibility.

The general principles of anti tubercular chemotherapy are:

Use of any single drug in tuberculosis results in the emergence of resistant organisms and relapse in almost 3/4th patients. A combination of two or more drugs must be used. The rationale is the incidence of resistant bacilli to most drugs ranges from $10^8$to 10^6. Because an average patient of pulmonary tuberculosisharbours10^8 to 10^{10} bacilli, the number of organisms that will not respond to a single drug is high and cannot be dealt by the host defense. During protracted treatment, these bacilli multiply and become dominant in 3 to 4 months. Because insensitivity to one drug is independent to another, i.e. incidence of H resistance among bacilli resistant to R will be 10^{-6} and vice versa; only few bacilli will be resistant to both; these can be handled by host defense. By the same rationality, massive infection ($>10^{10}$ organisms) has to be treated by at least 3 drugs, a single drug is sufficient for prophylaxis because the number of bacilli is small.

Isoniazid and Rifampicin are the most efficacious drugs, their combination is definitely synergistic. Duration of therapy is shortened from > 12 months to 9 months. Addition of Z for the initial 2 months further reduces duration of treatment to 6 months. A single daily dose of all first line anti tubercular drugs is preferred.

The 'directly observed treatment short course' (DOTS) was recommended by the WHO in 1995. Response is fast in the first few weeks as the fast dividing bacilli are eliminated rapidly. Symptomatic relief is evident within 2-4 weeks. The rate of bacteriological, radiological and clinical improvement declines subsequently as the slow multiplying organisms respond gradually. Bacteriological cure takes much longer. The adequacy of any regimen is decided by observing sputum conversion rates and 2-5 year relapse rates after completion of treatment.

Conventional regimens consist of H + E with or without S (for initial 2 months) and require 12-18 months therapy. Failure rates are high, compliance is poor-therefore not recommended now.

Table 2. Commonly confused generic and brand names.

Drug(s)	Brand name
Rifampicin (called Rifampin in USA)	Rimactane, Rifadin
Rifabutin	Mycobutin
Rifampicin + Isoniazid	Rifinah, Rimactazid
Rifampicin + Isoniazid + Pyrazinamide	Rifater

Isoniazid	Rimifon (not marketed in UK)
Ibuprofen	Rimafen

FDC containing two drugs have been used for approximately over 2 decades.
A recent survey by WHO (Norval et al 1999, Level 8) found that a quarter of the notified TB cases worldwide are treated with Rifampicin and Isoniazid containing 2 drugs FDC (Rifampicin/ Isoniazid). Later on a 3rd drug FDC for daily and intermittent was introduced but their share of market has been low being used for 5% of all notified cases (Norval et al 1999, Level 8). A large number of FDC are being offered in the market with India being the biggest producer and consumer of medications. Dose concentrations are not standardized in most cases, which has led to confusion in the global market as which preparations to procure.
Therefore WHO has issued guidelines publications on standardized formulations in the Model List for Essential Drugs (EDL). WHO's current Model List of Essential Drugs, 1999 (Table 1) contains 12 different anti tuberculosis FDC, of which nine contain Rifampicin.
This schedule includes a 4 drug FDC for daily use i.e. a formulation containing all four oral first line anti tuberculosis drugs in a single tablet. Dispersible FDC for the treatment of TB in children have also been introduced. WHO recommends that only FDC complying with the EDL should ultimately be used by national health programmes.

Table 3. The recommended strengths of fixed dose combination formulations of essential anti-tuberculosis drugs (WHO Model List of Essential Drugs, 1999).

Drugs	**Forms**	**Strengths**
For Daily use		
RHZE	Tablet	R150mg + H5 mg + Z 400mg + E 275mg
RHZ	Tablet	R 150mg + H 75 mg + Z 400mg; R 60mg + H 30 mg+ Z 150 mg(pediatric)*
RH	Tablet	R 300mg + E 150 mg; R 150 mg + H 75 mg; R 60 mg +H 30mg(pediatric)*
EH	Tablet	H 150 mg + E 400mg
TH	Tablet	T 50 mg +H 100mg ; T 150mg + H 300mg
TH	Tablet	
For Intermittent Use		
Thrice weekly		
RHZ	Tablet	R 150mg + H 150mg + Z 500mg
RH	Tablet	R 150mg + H 150 mg; R 60mg + H 60 mg (paediatric)*

E= Ethambutol, H=Isoniazid, R= Rifampicin, S=Streptomycin, T= Thioacetazone,
Z- Pyrazinamide

In FDC, the dose-to-body-weight relationships have been carefully balanced between all the drugs in the combination in order to ensure sufficient dose delivery of all drugs at all times. Current WHO-recommended FDC, however have been formulated in such a way that it satisfies both situations irrespective of whether the cut-off weight for changing from three to four tablets in the WHO proposed four-drug FDC is at 50 kg or 55 kg. The therapeutic efficacy is maintained because the mg/kg doses would be kept between the maximum and minimum recommended limits at all times, thus for the gigantic majority of adults the number of tablets for both the initial phase and the continuation phase would be the same. For the individuals weight below 50 kg or 55 kg (depending on the decision of local national tuberculosis programmes) the dose would be three tablets and four tablets for 50 kg and 55 kg respectively. For children weighing greater than or equal to 10 kg the dose would be one dispersible tablet per 5kg body weight. For lower body weights, the tablet dose *w*ould be halved and administered per 2.5 kg with increments as appropriate to patients.

1.3. Multidrug resistant (MDR) TB

It is defined as resistance to both H and R and may be any number of other anti-TB drugs. MDR-TB has a more rapid course (some die in 4-16 weeks). Treatment of these cases is difficult because one or more second line drugs are to be given for 12-24 months. The second line drugs are less efficacious, less convenient, more toxic and more expensive. The choice of drugs depends on the drugs used in the earlier regimen, dosage and regularity with which they were taken, presence of related disease like AIDS/Diabetes/Leukemia/Silicosis and whether sensitivity of the pathogen to various drugs is known (by in vitro testing) or unknown. If sensitivity of the TB bacilli is known the drug/drugs to which they are resistant are excluded and other first line drugs are prescribed along with 1-3 second line drugs. A total of 5-6 drugs are given. One of the FQ's is generally included.

In case Streptomycin is not being given the one drug out of Kanamycin or Amikacin or Capreomycin should be added because they are tuberculocidal.

• For H resistance-RZE given for 12 months is recommended.

• For H + R resistance-ZE+S or Kanamycin or Amikacin or Ciprofloxacin or Ofloxacin + Ethambutol could be used. The actual regimen is devised according to the features of the individual patient.

Emergence of 'multidrug resistant' TB of which over 0.4 million cases are occurring globally every year is threatening the whole future of current anti tubercular chemotherapy.

1.3.1. Extensively drug resistant (XDR) TB

Recently the WHO and COC (USA) have identified TB cases that are 'extensively drug resistant'. This term has been applied to bacilli that are resistant to at least

4 most effective bactericidal drugs i.e. cases resistant to H, R, a FQ, one of Kanamycin or Amikacin or Capreomycin with or without any number of other drugs.

The global survey for the period 2002-2004 has found 20% TB isolates to be MDR out of which 2% were XDR. The XDRTB is virtually untreatable the mortality is high particularly among HIV positive patients.

"Responding to drug-resistant tuberculosis is possibly one of the deepest challenges facing global health."

The past 20 years have seen the worldwide appearance of multidrug-resistant (MDR) tuberculosis followed by extensively drug-resistant (XDR) tuberculosis,

6 to 9 and, most recently, strains that are resistant to all anti tuberculosis drugs. MDR tuberculosis is caused by Mycobacterium tuberculosis that is resistant at least to Isoniazid and Rifampicin and XDR tuberculosis by mycobacterial resistant to Rifampicin and Isoniazid any fluoroquinolone and one of the among three injectable drugs like Capreomycin, Kanamycin and Amikacin. Drug resistance severely threatens tuberculosis control since it raises the possibility of are turn to an era in which drugs are no longer effective. Progress is being made in global control of drug susceptible tuberculosis as presented by Lonnroth and colleagues in the first report in this Series. In 2008, 5·7 million (61%) of the estimated 9·4 million new and relapsed tuberculosis cases were identified and treated on the basis of the WHO Stop-TB Strategy. Partly as a result of these efforts, worldwide incidence of tuberculosis has been slowly falling since 2004-15.

1.4. Prevention and control[1-59]

Efforts to address the epidemic of MDR and XDR tuberculosis have to prevent both acquired and primary resistance. Prevention of acquired resistance relies on early case finding and effective treatment, encapsulated in the directly observed therapy, short course DOTS and Stop-TB strategies, 131 which aim to improve treatment cure and completion rates and reduce failure and default. By contrast, prevention of transmission of drug-resistant strains needs not only early identification and initiation of treatment but also infection control. Transmission of tuberculosis occurs through droplet nuclei, aerosolized by patients with infectious pulmonary tuberculosis and inhaled by another individual. Probability of infection depends on site of disease and bacillary burden in the infectious patient duration and proximity of contact surrounding air volume and speed of replacement of air through ventilation. The principles are the same for drug-susceptible and drug-resistant strains.

1.5. Treatment of Drug-Resistant Tuberculosis[1-59]

The clinical and public health management of drug-resistant tuberculosis is complicated. The therapeutic approach as well as the prognosis, is significantly associated with the resistance pattern.

It has been clearly shown that the multidrug resistance could represent are relevant clinical issue because of the poor therapeutic armamentarium. The so called second and third lines anti tuberculosis drugs are less efficacious, more toxic and more expensive than the first-line drugs. It is straightforward that the adequate treatment of drug-resistant tuberculosis can prevent the emergence of new serious drug resistant forms which could have a worst prognosis and less alternative therapeutic options. Furthermore, another relevant feature of an adequate and early treatment is the low probability of transmission of drug-resistant mycobacterial strains in a

specific setting such as a hospital or a community. Nevertheless, to obtain a clinical and a microbiological cure, it is mandatory to treat individuals for a long period because of the lesser effectiveness of the second and third line drugs. The prolonged exposure to medicines characterized by a poor safety and tolerability profile reduces the adherence of the patient.

One of the most important points in the management of the drug-resistant strains is the prescription of an efficacious drug regimen which should be based on the results of the drug-susceptibility testing. The current availability of rapid molecular tests which can assess the resistances of mycobacterial strains to Isoniazid and Rifampicin can allow the administration of an early tailored anti tuberculosis regimen. In particular, the World Health Organization recently approved an automated nucleic acid amplification test to diagnose tuberculosis disease and to assess mycobacterial resistance to Rifampicin. The rapid identification of a multidrug resistant case can allow an immediate prescription of an empiric and specific anti tuberculosis drug regimen. This molecular method might avoid the administration of an inappropriate treatment and consequently, indirectly favor the clinical recovery of patients and the reduction of their infectiousness (World Health Organization2011a).

The World Health Organization suggests the prescription of at least four active drugs during the intensive phase. In particular, the backbone of the administered regimen should include Pyrazinamide one of the injectable second-line drugs (Amikacin, Capreomycin or Kanamycin) a new-generation fluoroquinolone, Ethionamide (or Prothionamide) and Cycloserine (or PAS). Other drugs should be prescribed in case of resistances to one or more of the backbone drugs. The duration of the first phase of the treatment should depend on the culture conversion but it should last at least 8month whereas the duration of the second phase should be longer than 20 months.

The World Health Organization guidelines is used in 2011 (WHO2011b) showed significant differences if compared with those issued in2008, in particular, the suggested duration of the intensive phase is longer (i.e. 8 vs. 6 month) as well as the total duration of therapy (i.e. at least 20 month). If feasible, Pyrazinamide should be added up to a backbone regimen of four second line anti tuberculosis drugs, in which Ethionamide and new-generation fluoroquinolones are the preferred medicines. Further more; monthly monitoring of the culture conversion is relevant to assess the efficacy of the prescribed therapy (World Health Organization 2008).

Table 4. Dosing Regimens of Anti tuberculosis drugs.

Drugs	Mean daily dosage
Isoniazid	5 mg/kg
Rifampicin	10 mg/kg
Ethambutol	15–25 mg/kg
Pyrazinamide	30–40 mg/kg
Streptomycin	15–20 mg/kg
Amikacin	15–20 mg/kg
Kanamycin	15–20 mg/kg

Capreomycin	15–20 mg/kg
Ofloxacin	800mg
Ciprofloxacin	1000 mg
Gatifloxacin	400mg
Moxifloxacin	400mg
Levofloxacin	1000mg
Ethionamide	15–20 mg/kg
Prothionamide	15–20 mg/kg
Cycloserine	500–1000 mg
Para-aminosalicylic acid	150 mg/kg
Linezolid	600 mg
Clofazimine	200–300 mg
Clarithromycin	1000 mg
Terizidone	600–900 mg
Thiacetazone	150 mg
Thioridazine	75 mg
Bedaquiline	400 mg (for 2 wk.) or200 mg TIW (for 22 wk.)
Delamanid	200 mg
Amoxicillin Clavulanate	875/125 mg BID or500/125 mg TID

BID, twice a day; TID, thrice a day; TIW, thrice a week.

1.6. Current trends in Anti TB drug development and its future aspects[54-63]

TB treatment is generally consists of 2 months with isoniazid, rifampicin, ethambutol and pyrazinamide (the intensive phase), followed by four additional months of isoniazid and rifampicin therapy (the continuation phase). Unfortunately, lack of adherence to prescribed treatment procedures and inefficient healthcare structures have contributed to the development of multidrug- resistant TB (MDR-TB, defined as resistance to at least isoniazid and rifampicin, two front-line drugs used for the treatment of TB) that requires at least 20 months of treatment with second-line drugs comprised of capreomycin, kanamycin, amikacin and fluoroquinolones; these are more toxic and less efficient, with cure rates in the range of 60–75%

In patients affected by XDR-TB, the chances of successful treatment are quite low, underpinning the need for urgent discovery of novel compounds with activity against MTB strains resistant to second- line drugs. Recently, a few reports have claimed that the emergence of a 'totally drug-resistant TB' strain with a limited chance of successful TB therapy.

1.6.1. Current Trends[54-63]

After a long period of inactivity, the last few years have seen an increase in the number of new anti-TB drugs in the pipe- line. As shown in figure, there are currently

adequate numbers of drug candidates in the lead optimization stage, preclinical development, phase II and phase III clinical trials. However, there is a worrying gap within phase I that needs to be filled to have a constant delivery of molecules in case of failure of advanced drug candidates. Many molecules carried under the clinical evaluation, such as fluoroquinolones, were developed to treatment other infectious diseases and have now been repurposed for TB treatment and this call for increased efforts towards discovery of new tubercular compounds against different physiological states of tubercle bacilli.

Bedaquiline, a diarylquinoline, was approved by the FDA (Food and Drug Administration) in December 2012 as part of the combination therapy for the treatment of adult patients affected by MDR-TB, and it is now in phase III of clinical development. Bedaquiline can be considered to be the first major drug approved by the FDA for TB therapy in the last 40 years. It came out following a phenotypic screening of compounds against MTB, while the corresponding target was identified through the whole-genome sequencing of MTB and Mycobacterium segments is spontaneous mutants that were resistant to chemical molecules. Interestingly, the resistant mutants showed missense mutations in the atpE gene (encoding the c subunit of ATP synthase). Bedaquiline acts by inhibiting ATP synthase and has activity against active and dormant Mycobacterium TB strains. Currently, it is well known that TB patients with pulmonary TB can have both active and dormant tubercle bacilli, the latter being difficult to eliminate with the currently used anti-TB drugs, hence favoring the development of resistant strains and latent Tubercular infection.

Delamanid and pretomanid- moxifloxacin– pyrazinamide combination are two new imidazooxazoles in phase III clinical development.These both molecules are prodrugs whose activation depends on a F420- deazaflavin-dependent nitroreductase (Ddn) which is present in MTB. Delamanid inhibits mycolic acid biosynthesis and has been associated with increased sputum-culture conversion in MDR-TB patients. In addition, Delamanid has been shown to be effective with admissible toxicity when combined with other anti-TB drugs in an MDR-TB regimen.

Rifapentine, is a semi-synthetic cyclopentyl rifamycin derivative, it acts by binding the b-subunit of the RNA polymerase in MTB, a mechanism of action that is also utilized by rifampicin. It is more effective than rifampicin against MTB. Both rifamycin and rifapentine exhibit cross resistance. The United States Food and Drug Administration (US FDA) in 1998 approved rifapentine at a dosage rate of 10 mg/kg (oral administration) once or twice weekly for the therapy of active and latent Tuberculosis Treatment. There is good clinical evidence that supports the use of rifapentine plus isoniazid for 3 months (once-weekly regimen) against latent TB, but quite different for the treatment of active TB, where it is approved by the FDA at a dose of 600 mg orally, twice weekly during the intensive phase of TB treatment (2 months), and then once weekly during the continuation phase (4 months). Recently, animal studies have suggested that more frequent administration of rifapentine might cure both active and latent TB

in 3 months and less, how- ever; the observed findings could not be reproduced in clinical trials involving human subjects.

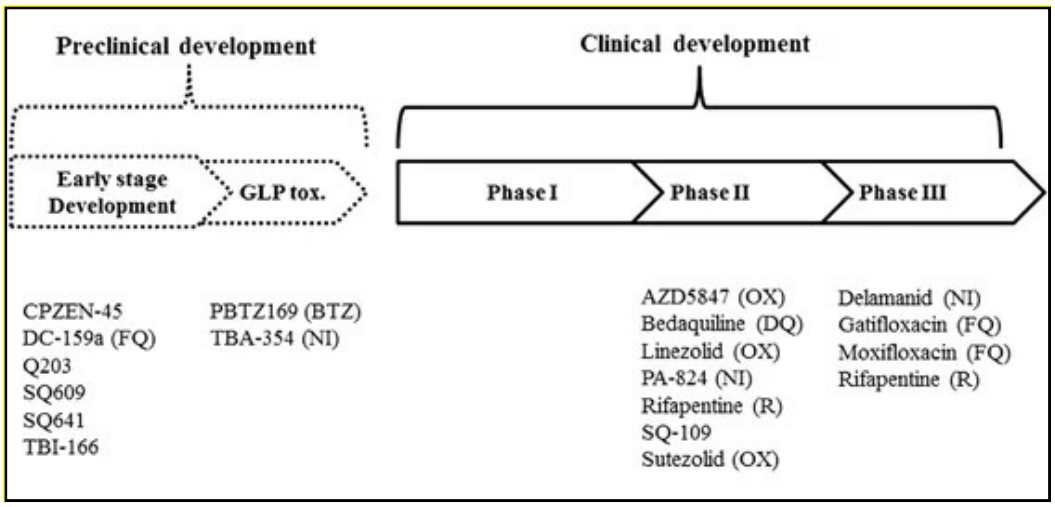

Fig. 1. Current Global Drug Pipeline.

SQ109, a 1,2-ethylenediamine, 7-dimethylocta-2,6-dienyl]ethane-1,2-diamine} is in phase II clinical trials . SQ109 is active against sensitive MTB, MDR-TB and XDR-TB strains

Interestingly, both ethambutol (EMB) and SQ109 have different chemical structures and different mechanisms of action, with SQ109 targeting MmpL3 (an essential membrane trans- porter belonging to the resistance, nodulation and division [RND] family), whose main function (MmpL3) in MTB is to transport the trehalose monomycolate into the envelope thus interfering with mycolic acid synthesis in the mycobacterial cell. Currently, MmpL3 is considered as one of the hottest targets in drug discovery against MTB, as several other com- pounds under preclinical investigation have also been reported to inhibit the transporter, such as the urease in lead optimization stage.

Other compounds have recently moved from phase I to phase II clinical trials. These include PNU-100480 (Sutezolid), a close analog of linezolid and AZD5847 a member of the oxazolidinone class as shown in fig. 1.

1.7. The need for tuberculosis drug development

The current needs, challenges and recent advances towards development of novel chemical molecules against TB have been reviewed recently. Approximately 2 billion people of the world's population are latently infected with Mycobacterium TB and are at risk of reactivation to active disease. Even though an inexpensive and effective quadruple drug therapy regimen comprising isoniazid, rifampicin, ethambutol and pyrazi- namide was introduced 40 years ago, TB continues to spread in every corner of the globe. TB remains a global emergency according to the seventeenth World Health Organization (WHO) report on the worldwide incidence of the disease. Globally, there are approximately 8 million new cases and 2 million deaths yearly associated with TB; hence, the disease is responsible for more human mortality than any other

single microbial infection. A major break- through in TB therapy came after the introduction of streptomycin, followed by p-aminosalicylic acid (1949), isoniazid (1952), pyrazinamide (1954), cycloserine (1955), ethambutol (1962) and rifampin (1963) over 40 years ago. The current treatment regimen has several drawbacks, including prolonged treatment time to completely eradicate or demolish the bacterial growth (sterilization). This increases the opportunity for development of Mycobacterium TB-resistant strains documented in almost every country where the disease is prevalent. These obstacles, in addition to an increasing prevalence of MDR, XDR and currently TDR strains, call for an urgent need to search for and develop novel agents against TB. A number of challenges, including the lack of economic incentive due to the predominance of the disease in the developing world, have continued to face drug discovery towards TB. These efforts have recently culminated in the approval of two new drugs: delamanid and bedaquiline for the treatment of MDR strains of MTB (Mycobacterium Tuberculosis)

1.8. Drug discovery against TB from natural products

The urgent need for the development of new drugs from natural products to help reduce the global burden of TB. Uplekar et al. [54] points out that in order to attain the WHO's ambitious targets of 95% reduction in TB deaths and 90% reduction in TB incidence by 2035, the need for better and safer drug regimens to shorten treatment is key.

Mdluli et al.[64] highlights some recent notable examples of natural product compounds that may prove to be useful leads for TB drug discovery. A number of medicinal plants with very good activity against TB have recently been reported. Anti-mycobacterial bioactive chemical molecules have been found from many natural products like skeletons, mainly from plant biodiversity, but also from other organisms, such as fungi and marine/sea organisms.

The classic pathway towards anti-TB drug discovery from natural products and indeed other infectious diseases must be able to overcome a number of challenges in tuberculosis treatment.

***1.9. Future Trends and Aspects*.**[64-74]

For looking towards the future treatment to TB the following point focused to challenges issue identified.

1.10. Shorter treatment.

Figure represents a meta-analysis of treatment trials involving regimens of varying duration. The "shoulder" of the sigmoid curve is between 4.5 and 6 months of therapy. Assuming that an appropriate objective for performance of a regimen is 95% cure rates, steps that can be taken to "shift the curve to the left" should be considered. Conceptually, this might be accomplished by strengthening either the early bactericidal activity (EBA) or the late sterilizing effects of the regimen.

Future issues in tuberculosis (TB) therapy

Can the duration of curative chemotherapy be shortened?

Can the periodicity (days between doses) of therapy be increased?

Can new drugs be developed?

What is optimal therapy of TB in persons with AIDS?

Can chemotherapy be supplemented with immunomodulation to shorten treatment or overcome drug resistance?

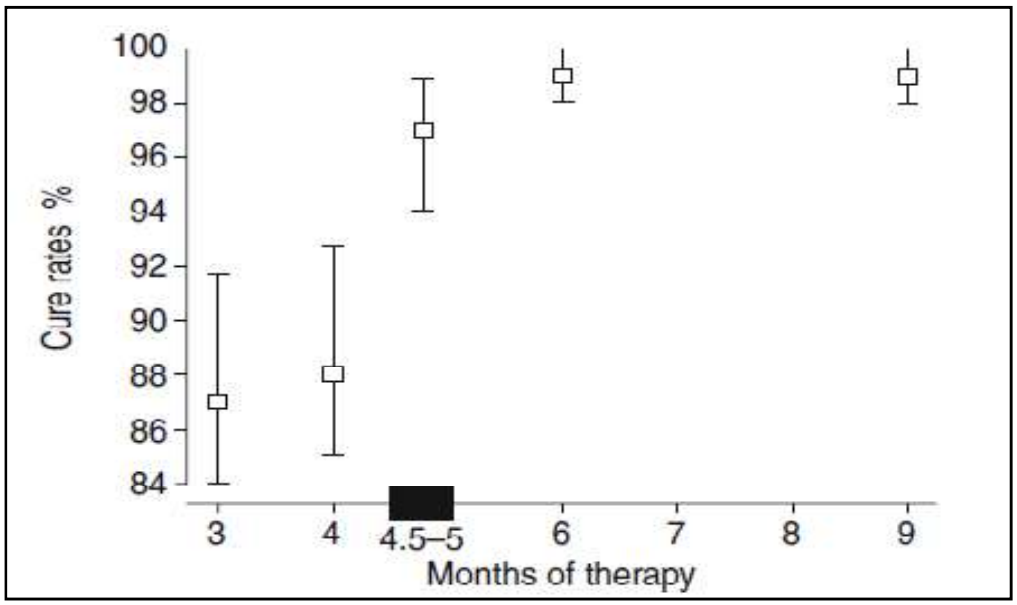

Fig. 2. Meat Analytical representation of cure rates for tuberculosis regimens of varying duration and constituents.

Early mycobacterial death has been shown by to primarily be the product of Isoniazid, Rifamycin and Pyrazinamide. Although INH had the most prominent EBA as a single agent in a BMRC study, the dramatic killing effect seen in the first week seems not to be vital to curative therapy. Thus, attention shifts to the rifamycins and PZA, and consideration must be given to novel compounds that might be enhance either the Early Bacterial Activity or sterilizing phase.

RIF is the standard rifamycin. It is typically given to adults in daily or particular intervals schedules at 600 mg dosage (or 450 mg for those weighing v50 kg). Increasing the dose in daily therapy is not like to yield the improved results, in a USA trial, 750 mg daily did not have a greater effect than 600 mg. In intermittent regimens, increasing the dose above 600 mg resulted in increased toxicity of drug. Other rifamycins currently in use include rifabutin and rifapentine. Both of these agents have significantly longer half-lives than RIF, but they have significantly different pharmacokinetics and toxicity.

In addition to another agents like as the rifamycin which are primarily effective in killing organisms undergoing routine metabolism, mediation is being focused on compounds that are active against tubercle bacilli in a non-multiplying, semi dormant state.

1.11. Increased periodicity

To accessibility Direct Observed Treatment, once-weekly treatment schedules have been studied employing rifapentine. Three major studies have been performed in Hong Kong, South Africa/USA and USA/Canad, employing slightly different protocols. All trials concluded with

the 4 months of once-weekly rifapentine and INH, compared to twice-weekly or thrice-weekly RIF and INH. In all three trials, the RIF arms modestly outperformed the rifapentine arms. However, for patients in the Centres for Disease Control and Prevention (CDC) whose sputum cultures became negative after 2 months of treatment, outcomes were comparable.

An alternative approach would be to employ rifapentine throughout the therapy, including the twice- weekly in continuation phase treatment. The current author believes that the sustained high-level exposure to a rifamycin, which would be realised with twice- weekly rifapentine might reduce the duration required to assure 95% cure rates to the range of 4–4.5 months.

1.12. New drugs

While recent studies suggest that moxifloxacinis particularly active, the long-term tolerability and safety of third-generation FQNs like moxifloxacin or gatifloxacin have not been established as they have for ofloxacin and levofloxacin, and given the unanticipated toxicity of such agents as temafloxacin, trovafloxacin, sparfloxacin, and grepafloxacin, this should not be regarded lightly. Although, these drugs merit careful study both as agents to accumulate conventional therapy and as major drugs for MDR-TB. The oxazolidinones are a novel group of anti- microbials. One member of the family, linezolid, has been introduced into clinical medicine primarily for the treatment of drug-resistant Gram-positive coccal infections.

Compounds that have potential activity versus non-multiplying bacilli include relative of metronidazole and isocitrate lyase inhibitors. Nitroimidazo- pyrans have been shown to be active compared to static M. tuberculosis populations, and replicate bacilli. Metronidazole itself has limited activity against non-replicating bacilli, but analogues may be more active. Research is underway to find agents capable of disruption of this system under the premise that this might dramatically improve "sterilization".

2. CONCLUSION

All available evidence indicates that FDC does not produce more adverse reactions then of equivalent combinations of single drug formulation and adverse reactions serious enough to warrant withdrawal of treatment is rare. There is some evidence suggesting that FDC are effective in the treatment of tuberculosis however these studies are looking at different FDC combinations and dosages from what have been recommended by WHO Essential Drug List 1999. As far as organizational aspects are concerned if FDC is introduced as a national policy then there will be a need for appropriate planning and dissemination of information to service providers procurement departments and local regulatory authorities.

The current therapeutic management of drug-susceptible and drug-resistant strains needs to be further improved. The available regimens are characterized by a relevant pill burden, long duration, variable efficacy, safety and tolerability.

The overall treatment success rate is below the recommended World Health Organization proportion of 85% and consequently, the drug resistance level increases. The World Health

Organization estimates that a suboptimal proportion of multidrug-resistant cases is presently diagnosed and treated.

In 2010, 48% of the detected multidrug-resistant tuberculosis cases were successfully treated. Only 34 countries obtained a treatment success rate 75% (World Health Organization2013a). Even in tuberculosis reference centers, the proportion of treatment success in multidrug-resistant cases does not exceed 50%.

Although the adherence, efficacy, safety and tolerability profile of the newly available drugs (Delamanid and Bedaquiline) in particular appear to be promising, we cannot predict as of today their long-term efficacy and the affordability f their use in resource-limited settings. Further research efforts are necessary to identify the potentialities of the new drugs and to understand better how to use them in combination regimens.

These new regimens are ideally able to treat tuberculosis sustained by both drug-susceptible and drug-resistant strains without interfering with antiretroviral drugs, thus allowing a more effective approach against HIV-infected cases.

The new approach adopted to test different drug combinations in parallel can improve the current situation, giving new insights in a shorter period of time.

MDR and XDR tuberculosis are major challenges to tuberculosis control but are not yet being sufficiently addressed. National governments have yet to make available adequate resources for control efforts. Unless countries invest substantially in management of MDR tuberculosis, the possibility remains that MDR strains could become the dominant form of tuberculosis.

Several new (and not so new) approaches are needed in health systems to address the causes and management of MDR and XDR tuberculosis. Every country needs a comprehensive framework for management and care of MDR and XDR tuberculosis.

New research and development activities are requested, along with a preservation of the current therapeutic options. Training and educational activities focused on the rationale use of the anti tuberculosis drugs are necessary to avoid the dramatic increase of the drug-resistant forms.

National and local public health programs should issue guidance based on the local epidemiology to prevent inappropriate management of the new and old antibiotics as to ensure that all cases of tuberculosis diagnosed and correctly treated complete their treatment. The risk is to loose the new drugs in much less than the time necessary to develop them.

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