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Previously licensed anti-mycobacterial drugs: a re-appraisal

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Abstract

The discovery of antimycobacterial agent was the outcome of intensive efforts made between 1930 and 1970 to identify antimicrobial drugs. Sulfonamides (1930s), Streptomycin (1944) and Rifampicin (1965) are first and the last of the anti-mycobacterial drugs currently in use. Despite the availability of effective anti-tuberculosis chemotherapy, significant morbidity and mortality due to this disease continue to occur. The emergence and spread of multi-drug resistant (MDR) and extensively-drug resistant (XDR) strains of *Mycobacterium tuberculosis* has more complicated the problem of tuberculosis (TB) control and reduced the effectiveness of the current anti-TB drug. The present situation clearly demonstrates the need for a re-evaluation of our knowledge to treating TB and the current TB drugs. One of the highest achievements of modern medicine has been the development of antibiotics for the treatment of lethal infections. Unfortunately, the progress for new drugs against tuberculosis has been very inadequate over the past four decades. In the fight against emerging MDR and XDR resistance we can no longer rely completely on the finding of new antibiotics; we must also follow rational approaches to the use of older antibiotics such as sulfonamide. This review provides a concise historical of previously licensed drugs for treatment of tuberculosis and the targets and their mode of action of these drugs are briefly discussed.

1- Introduction

It is about 133 years since Robert Koch discovered the tubercle bacillus and was an important event in the history of medicine ***[1]*** and ***[2]***. Tuberculosis (TB) is still the greatest single infectious causing mortality worldwide. Despite the availability of effective chemotherapy for tuberculosis, TB remains a major global health problem and significant mortality and morbidity due to this disease continue to occur ***[3]***. TB is the second leading cause of death from infectious disease, after acquired immunodeficiency syndrome (AIDS) ***[4]***. The incidence cases of TB were an estimated 9 million globally. Despite the first anti-tuberculosis drugs being discovered more than 60 years ago, TB today still kills an estimated 1.5 million people around the world including 360000 death among people HIV- positive, in 2013 ***[5]***. The emergence and spread of multi-drug resistant (MDR) *M. tuberculosis* strains and extensively drug resistant (XDR) *M. tuberculosis* strains complicates the control of the disease ***[6]***. Multi-drug-resistant tuberculosis (MDR-TB) is defined as TB that is resistant at least to isoniazid and rifampicin, the two most potent first-line anti-TB drugs whereas XDR-TB is defined as being resistant to rifampin, isoniazid, to any fluoroquinolone, and one or additional of three injectable anti-TB antibiotics (capreomycin, kanamycin, and amikacin) ***[7]***. MDR and XDR make this form of TB especially inapt to treat with available drugs (rifampicin or isoniazid). The current situation clearly demonstrates the need for a re-evaluation of our knowledge to treating TB and the current TB drugs. One of the greatest achievements of current medicine has been the development of antibiotics for the treatment of lethal infections. Unfortunately, there has been no new drug licensed and development to fight tuberculosis for more than 40 years ***[8]***. In the fight against emerging MDR and XDR resistance we can no longer rely completely on the discovery of novel antibiotics; we must also follow rational approaches to the use of older antibiotics such as sulfonamide. One of the strategies to find new therapies against particular infections is to reposition, Re-appraisal or find new uses for drugs that are previously used for other indications. This method has the advantage of decreasing the cost and shortening the time of drug development ***[9]***. Recent studies have supported the potential use of previously licensed anti-mycobacterial drugs to treat infections caused by *M. tuberculosis* strains. In recent report from USA shows impressive results, using co-trimoxazole [combination of trimethoprim (TMP) and sulfamethoxazole (SMX)] in patient with tuberculosis, two specimens of sputum taken 6 and 12 days after the TMP-SMX course were negative for tuberculosis by stain and culture ***[10]***. Also for other bacterial resistance many resolutions and recommendations have been propounded, and numerous reports have been written to use older antibiotic. Markowitz *et al*. showed that TMP-SMX can be used as an alternative to vancomycin to treat infections due to Methicillin-resistant S*taphylococcus aureus* (MRSA) ***[11]***. In a recent report from France, Stein and Raoult used colistin, an old drug rarely used today to treat patients who had infections associated with their orthopedic devices caused by *Pseudomonas aeruginosa* with resistance to all antibiotics tested except colistin ***[12]***. Over the years, antimicrobials have saved the lives and significantly eased the suffering of millions of people but antibiotic-resistant is one of the most significant threats to patient safety. Anti-mycobacterial resistance, are not a new phenomenon. Following the introduction of anti-tuberculosis drugs, streptomycin (STR), para-aminosalicylic acid (PAS), isoniazid (INH) resistance to these drugs was detected in clinical isolates of *M.tuberculosis* ***[13]*** and ***[14]***. To attain global control of this epidemic, there is an urgent need for development TB drugs, which can: shorten treatment period, target MDR or XDR strains, reduce dosing frequency and be co-participant with HIV medication.

2- History of anti-tuberculosis drugs

The development of present therapy for the treatment of tuberculosis and its success is an outcome of the effort of clinical trials. The antimicrobial era began in 1930 with the introduction of sulphonamides into the therapy of many infections ***[15]*** and ***[16]***. The first active antimycobacterial agents were the sulphonamides, followed by streptomycin, para-aminosalicylic acid, and isoniazid ***[17]***.

2.1- Broad spectrum (anti-mycobacterial) agents

It refers to an antibiotic with activity against mycobacteria and a wide range of disease-causing bacteria ***[18]***.

2.1.1-Sulfonamides

Sulfonamides are one of the oldest groups of antimicrobial compounds still in use today. They have been in clinical use for over 60 years. Sulfanilamide was synthesized by Gelmo in 1908 and 1917 at the Rockefeller Institute this compound was added to quinine derivatives to increase bactericidal activity ***[19]*** and ***[20]***. The discovery of Sulfanilamide introduces a new epoch in chemotherapy. In 1927 by a research team at the Bayer Laboratories of the I.G. Farben-industries in Germany, Prontosil (Sulfonamide-containing dye) was developed under the direction of Dr. Gerhard Domagk.In 1932, he announced that the Prontosil (Figure 1) is active against streptococcal infection in mice and human ***[20]*** and ***[21]***. The discovery of these drugs was a major breakthrough, and they were the only active drugs until penicillin became obtainable in the early 1940s. The sulfonamides are chronologically the first of the modern synthetic anti-tuberculosis. Sulfonamides and salfones were discovered in the 1930s and have been used until the beginning of the 1950s as a single drug for treating tuberculosis ***[22]*** and ***[23]***. Because of streptomycin and isoniazid were proved to be more efficient than sulfamides in the treatment of tuberculosis ***[24]*** and because of the toxicity of latter antibiotics ***[25]*** their use as antituberculous antibiotics was mainly forgotten. There is extensive data on the effect of old sulfonamide compounds in the management of *M. tuberculosis in-vitro* and *in-vivo* in experimental animals and humans ***[26]***. The modern age chemotherapeutic treatment of tuberculosis had its beginning in sulfonamide developed by Domagk ***[27]***. In 1948, Anderson reported that 23 patient with pulmonary tuberculosis showed improvement after a period of sulphetrone therapy ***[28]***. As previously reported by Madigan *et al.* ***[29]*** 6 cases of tuberculosis have been treated with sulphetrone by mouth and streptomycin parenterally. Chang and Goetz, who gave trimethoprim and sulfamethoxazole to an adult patient with pulmonary *Mycobacterium avium* complex (MAC) disease, found that this patient successfully treated from infection ***[30]***. Breakpoints for trimethoprim-sulfamethoxazole have not been addressed by the Clinical and Laboratory Standards Institute (CLSI), yet for *M. tuberculosis* but the interpretive criteria for resistance to rapidly growing mycobacteria such as *M. kansasii* and *M. marinum* to sulfamethoxazole and trimethoprim were defined as MICs of ≥38.2 mg/L and ≥2.0 mg/L, respectively ***[31]***. In the modern epoch, there are few reports have looked at the susceptibility of *M. tuberculosis* to SMX-TMP and various methodologies have been applied. In a study published in the USA, 98% of their 44 isolates were susceptible to the trimethoprim/sulfamethoxazole combination at an MIC of ≤1/19 mg/L. ***[10]***. Ong *et.al.* found that all clinical isolates of *M. tuberculosis* (n=12) were susceptible to SMX at a concentration ≤38 µg/mL, using the Mycobacterium Growth Indicator Tube [MGIT; Becton Dickinson (BD)]. ***[32]***. Haung et al. using the agar dilution method with Middlebrook 7H11 agar, found that Sulfamethoxazole inhibited 80% growth of all 117 isolates at an MIC_{90} of 9.5 mg/L. ***[33]***.

2.1.2- Streptomycin

Streptomycin(figure 1), one of the first aminoglycoside antibiotics and effective against a wide range of gram-negative and some gram-positive bacteria ***[34]*** and it is an old drug used in the treatment of tuberculosis ***[35***] and ***[36]***. Selman A. Waksman (From 1914 to 1939) a soil microbiologist, who screened systematically soil bacteria and fungi in an effort to discover an antibiotic for tuberculosis ***[37]*** and ***[38]***. In January 1944, Schatz, Bugie, and Waksman were able to isolate Streptomycin from a soil actinomycete (*Streptomyces griseus*) ***[39]***. Since the discovery of streptomycin, antibiotics have revolutionized the treatment of bacterial and some other diseases and it's a real turning point in the therapy of tuberculosis disease. The effectiveness of streptomycin against experimental infection in animals and human tuberculosis has been confirmed soon after of its discovery ***[40]***. Thirty-six guinea pigs were divided into three groups in experimental work, group I - twelve untreated

controls, group II - twelve treated for 14 weeks from date of infection with a human strain of *M. tuberculosis* and group III - twelve treated for 11 weeks, starting 24 days after infection. Groups II and III received four subcutaneous doses of 2,500 units streptomycin daily at 8.30 a.m., 11.30 a.m., 2.30 p.m., and 5.30 p.m. Six of the nine guinea-pigs treated from the date of infection (group II) and two of the eight which did not receive treatment until 24 days after infection (group III) showed no macroscopic evidence of TB infection ***[41]***. Streptomycin was used in 1946 by Hinshaw and his colleagues for treatment more than 100 cases of tuberculosis of various types at the Mayo Clinic (Rochester, Minnesota, USA). The patient received 1-3 g. of streptomycin by intramuscularly injection every 4 to 6 hours, and this regimen has been continued for three to six months ***[42]***. The MIC breakpoint of streptomycin recommended by Clinical and Laboratory Standards Institute for *Mycobacterium tuberculosis* is 2µg/mL ***[31]***. Streptomycin is bactericidal against tubercle bacillus *in-vitro* ***[43]***. It is considered poorly active or not active against intracellular *Mycobacterium tuberculosis* ***[44]*** and ***[43]***. The combination of streptomycin with other antituberculosis drugs such as Para-aminosalicylic acid (PAS) has been proven to be more active than either alone in treating tuberculosis, and reduced the development of resistance ***[45]*** and ***[46]***.

2.1.3- Rifampicins

Rifampicin (Rif) is a semi-synthetic derivative of the natural product rifamycin, produced by fermentation of a strain *Streptomyces mediterranei* ***[47]*** and ***[48]***. Lepetit Research Laboratories in Milan developed rifampicin part of an extensive program of chemical modification of the rifamycins (figure 1) ***[49]***. Rifampicin is considered one of the most powerful antimycobacterial compounds was first recognized in 1965 ***[49]*** and ***[17]***. It introduced into TB therapy in Italy and was approved by the United States Food and Drug Administration (FDA) in 1971 ***[49]***. The introduction of rifampicin in combination with other anti-tuberculosis such as isoniazid provided the breakthrough in reducing the length of treatment necessary from 18-24 months to 6-9 months ***[44]*** and ***[50]***. Studies in both animals and human have clearly established the potentiality of rifampicin in the treatment of tuberculosis infections. Rifampin was used in 1972 by Davidson *et al.* for treatment 136 patients, 112 had infections with *M. tuberculosis*, 13 with *M. kansasii*, and 11 with Group 3 Battey avian organisms. Eighty-eight of cases *M. tuberculosis* with the drug-resistant disease were successfully treated with rifampin, and Twenty patients failed to respond. Twelve patients with *M. kansasii* infections were positively treated, and only three of 11 patients with Group 3 infections were successfully treated ***[51]***. Rifampicin has a minimum inhibitory concentration (MIC) 0.5 µg/mL for *M. tuberculosis* with achievable serum levels from 6-32 µg/mL and a serum peak activity at around 3hrs ***[52]***.

2.1.4- Macrolides

Macrolides are among the oldest antibacterial agents and comprise a family of antibiotics ranging from erythromycin to many analogs synthesized more recently ***[53]*** and ***[54]***. *E*rythromycin, characterized by a 14-membered lactone ring, is a mixture of macrolides that isolated from *Streptomyces erythreus* in 1952, represents the first-generation ***[54]*** and ***[55]***. For over 50 years, the macrolides are a valuable class of antimicrobial agent and have been used successfully in the treatment of various infectious conditions. The second-generation macrolides in particularly clarithromycin (CAM) have been welcome additions in the treatment of several typical mycobacterial infections. CAM revolutionized the treatment of disseminated *M.avium* complex (MAC) infections in HIV patients ***[56]*** and ***[57]***. It was also found possess potent activity against *M. leprae* in axenic media ***[58]***, in mice ***[59]*** and at last in human ***[60]***. World Health Organization (WHO) recommended the use of CAM for treatment of leprosy in case of rifampin resistance ***[61]***. Nevertheless, they have little or no effect on *M. tuberculosis* complex ***[62]*** and ***[63]***. A comparative study of the anti-mycobacterial activity of clarithromycin versus HMR 3647 (telithromycin) and HMR 3004 showed the superior activity of clarithromycin for both the moderately clarithromycin-susceptible mycobacteria and the clarithromycin-resistant mycobacteria ***[62]***. The

roles of macrolides in the treatment of tuberculosis remain controversial because modern studies have described synergy of macrolides in paired with other antibiotics or antituberculosis ***[64]*** and ***[65]***.

2.1.5- Fluoroquinolones (FQ)

Fluoroquinolones are fluorine-containing derivatives of older quinolones and characterized by broad-spectrum antimicrobial activity ***[66]***. Flumequine was the first fluoroquinolone compound that was patented in 1973. After that several fluoroquinolones have been licensed and are still used today, including pefloxacin (1979), enoxacin (1980), fleroxacin (1981), ciprofloxacin (1981) and ofloxacin (1982) ***[67]***. Fluoroquinolones are recommended and widely used for the treatment of bacterial infection of the respiratory, gastrointestinal and urinary tracts ***[68]*** and ***[69]***. The antimycobacterial activity of fluoroquinolones was described in 1984 ***[70]***. Recent research has highlighted the activity of fluoroquinolones (sparfloxacin, ofloxacin, levofloxacin, moxifloxacin, and gatifloxacin) against *M. tuberculosis* ***[71]*** and ***[72].*** They are currently part of the recommended regimen as second-line drugs for treating drug-resistant tuberculosis or as a substitute for first-line drugs in cases of intolerance ***[73]*** and ***[74]***. The most efficient newer fluoroquinolones against *M. tuberculosis* are moxifloxacin and gatifloxacin and have lower minimum inhibitory concentrations (MIC) than the older levofloxacin, ciprofloxacin and ofloxacin ***[69]*** and ***[75]***. In a report from India suggested the potential usefulness of ofloxacin for shortening the length of treatment of drug-susceptible tuberculosis from six months to five or even four months ***[76].*** Nueremberger *et al*. in 2004 found that the combination of rifampicin, pyrazinamide and moxifloxacin in animals has greater sterilizing power than the standard regime and opens up the possibility that the drug might reduce the duration of treatment ***[77]***. Lubasch *et al*. showed that Sparfloxacin (SPX) was an active and harmless alternative agent in the treatment of complicated tuberculosis and the appropriate alternative drug for some cases of MDR tuberculosis ***[78]***. An in vivo comparison, Alvirez-Freites *et al*. found that gatifloxacin (GAT) has sufficient action alone and in paired with ethanomide with or without pyrazinamide for treatment of tuberculosis***[79]***.

2.1.6- Cycloserine

The cycloserine (figure 1) is broad-spectrum antibiotics with a broad range of activity against both Gram-positive and Gram-negative bacteria including mycobacteria ***[80]*** and ***[81]*** and was first isolated by Harned and the staff of the Commercial Solvents Corporation in 1954 from *Streptomyces orchidaceus* ***[82]***. Eli Lilly and Co. has collaborated in its study and their trade name for it is "seromycin." ***[83]***. Cycloserine is a structural analogue of D-alanine amino acid, which is essential components of all bacterial cell walls thus inhibiting cell wall synthesis, including those of mycobacteria ***[84]*** D-cycloserine possesses activity against a wide range of bacteria and *inhibits M. tuberculosis* at the concentrations of 5–20 µg/mL ***[54]*** and ***[85]***. The peak serum level of cycloserine is 10 to 50 mg/L following administration of 0.75 g -1 g after 0.5 to 4 hours ***[86]***. In 1959, Murdoch showed that cycloserine concentration levels in the plasma considerably below those required for effective *in-vitro* inhibition ***[82]***. Clinically validated criteria for drug resistance testing on Löwenstein Jensen (L-J) using the proportion method have been determined almost 50 years ago, for D-cycloserine and other antituberculosis ***[87]*** and ***[88]***. Cycloserine is principally employed as a second-line agent for management of MDR-TB ***[18], [81]*** and ***[89]***. It *has been* reported to be active both *in-vitro* and *in vivo against* tubercle bacilli ***[90]*** and ***[84]***. Cycloserine was found to have good *in-vitro* activity: 50 µg/mL of cycloserine resulted in killing <1 log (80%) of the initial inoculum when tested against *M. tuberculosis* in macrophages ***[90]***. Cycloserine exhibited synergistic activity with an experimental drug b-chloro-d-alanine that reduced the MIC (from 50 to 2.5 µg/mL) ***[84]***. Cohen and his colleague had treated 37 pulmonary tuberculosis by cycloserine which was given in doses that began with 250 mg twice daily and increased gradually by 250 mg daily each week for two weeks and then every 2 weeks until a total daily dose of 2 grams was achieved. In these large doses, it was established that cycloserine was a moderately effective antituberculosis drug, causing the decline of tubercle bacilli in the sputum in most cases ***[91]***.

2.2- Narrow spectrum (antimycobacterial) agents

Narrow-spectrum agents are those whose activity is only restricted to mycobacteria, or even to mycobacterial individual species ***[18]***.

2.2.1- Clofazimine

Clofazimine (figure 1) is a lipophilic riminophenazine derivative ***[92]*** and ***[93]***. It is initially known as B663 and developed in 1957 by Barry *et al*. to be used specifically for the treatment of tuberculosis ***[94]*** and ***[95]***. The first clinically developed riminophenazine compound was clofazimine ***[93]***. It has both antimicrobial and anti-inflammatory activity ***[96]*** and has found active against diverse mycobacteria such as *M. leprae* ***[97]*** and ***[98]***, *M. tuberculosis* ***[18]*** , ***[99]*** and ***[100]*** , *M. avium intracellulare complex* ***[101]*** and *M. bovis* ***[102]***. Clofazimine has been used to treat leprosy since 1960 ***[103]***. In 1981, WHO first recommended the use of multidrug regimens, including dapsone (DDS), rifampin, and clofazimine, to prevent the emergence of drug-resistant strains of *M. leprae* and to effectively shorten the duration of chemotherapy ***[104]***. Recent studies showed that clofazimine had good activity against *M. tuberculosis*, including multidrug-resistant strains *in vitro* and in animal studies ***[98]***. Nevertheless its first use as an anti-leprosy drug, clofazimine has been used with limited success in the treatment of MDR and XDR TB as a category five agent ***[105]***. Mitnick *et al.* presented the most affirmative treatment results, proposing that patients with XDR-TB treated in a community-based setting in Peru had a 60% cure rate ***[99]***. Treatment of a small group of five human tuberculosis patients with clofazimine in combination with linezolid and other drugs has been described ***[106]***. Clofazimine also showed efficacy in combination, for the treatment of disseminated *M. avium* complex infection in HIV disease ***[107]*** and ***[108]***.

2.2.2- Dapsone.

Dapsone, (4, 4'-diaminodiphenyl sulfone), (figure 1) is a synthetic sulfone which exerts weakly bactericidal activity against acid-fast bacteria and especially *M. leprae* ***[109]*** and ***[110]***. Dapsone was first synthesized on 15 June 1908 by Eric Fromm and J. Wittmann, chemists at the University of Freiburg ***[111]*** and ***[112]***. The antibacterial action of dapsone was discovered in 1937 ***[113]***, since then, a diverse group of diseases has been treated with dapsone, including leprosy, tuberculosis, malaria, toxoplasmosis, acne and AIDS-related pneumonia ***[111]***. *In-vivo* sulfone research was initiated in 1937, when Buttle *et al.* in England treated experimental streptococcal infections in mice with dapsone ***[111]***. The first breakthrough to obtain an active antileprosy agent occurred in the 1940s with the development of the drug dapsone, which stopped the disease and has been principal drug in chemotherapy regimen suggested by the WHO for the treatment of leprosy disease ***[114]***. Until the early 1980s, the drug treatment of leprosy consisted of using dapsone monotherapy for the control of the disease, when the emergence of dapsone-resistant *M. leprae* the WHO expert committee recommended multi-drug therapy (MDT) for leprosy with a combination of dapsone, rifampicin, and clofazimine ***[115]*** and ***[116].*** Dapsone-resistant strains of *M. leprae* have already been reported worldwide, and the first dapsone-resistant strain was reported in 1964 ***[117]***. The anti-tuberculosis chemotherapy, in the modern sense, date from 1939. During that period, Rist, Bloch, and Hamon demonstrated for the first time the in vitro and *in-vivo* efficacy of 4-4-diaminodiphenylsulfone against tubercle bacillus ***[118]***. The MIC dapsone against *M. tuberculosis* and *M. avium* complex (MAC) are 50-250mg/l and 2-100mg/l respectively. Nevertheless, at a concentration as low as 1.5 µg/mL dapsone significantly inhibited the growth of MAC bacteria when used in paired with additional drugs particularly acting at the mycobacterial cell wall ***[119]***. Dapsone is highly active against *Mycobacterium leprae* with MICs as low as 0.01/µg/mL ***[120]*** and ***[119]***. George and Balakrishnan conducted a study to determine the amount of dapsone (DDS) in the blood of leprosy patients by giving acedapsone (intramuscular injection of 225mg), on the 75 day,

the DDS level reaches the minimum value of 14.76 *ng* /mL which was still about 5 times more than MIC level of DDS against *M. leprae* ***[121]***.

2.2.3- Ethambutol (EMB)

In 1961, Wilkinson and his colleague from Lederle research laboratories first reported the synthesis and activity of ethambutol (figure 1) ***[122]*** and ***[123]***. It is one of the essential first-line drugs in the treatment of tuberculosis ***[73]***. Also, it is commonly employed as part of a combination regimen in the treatment of *M. avium* complex (MAC) and *M. kansasi* infections in patients with or without associated infection with human immunodeficiency virus ***[124]*** and ***[125]***. It has been used since 1966 as a primary drug in tuberculosis therapy ***[126]***. In 1966s ethambutol was shown to be an effective replacement for para-aminosalicylic acid (PAS) ***[127]***. Ethambutol has demonstrated excellent activity against intracellular and extracellular *M. tuberculosis* ***[128]*** and ***[129]***. It has been found that the MIC of EMB is different in different media for the same strains of *M. tuberculosis*, the MIC breakpoint recommended by Clinical and Laboratory Standards Institute for *M. tuberculosis* is 5 µg/mL in Middlebrook 7H10 agar and 7.5 µg/mL in Middlebrook 7H11agar ***[31]***. Several studies have shown that ethambutol is effective against *M. tuberculosis* in vitro and *in-vivo*; the MIC of EMB against the standard strain of *M. tuberculosis* H37Rv is 0.5 µg/mL ***[90]***. Treatment of *M. tuberculosis* H37Rv-infected macrophage with EMB, the log CFUs at 3 days were as follows: 3 µg/mL = 4.32; 6 µg/mL = 4.17; control value = 4.8. The MICs for *M. avium* (MTCC1723) and *M. smegmatis* (MTCC 6) were 15 and 0.18 µg/mL, respectively ***[130]***. The usual daily doses of EMB recommended by WHO and American Thoracic Society is 15–20 mg/kg ***[73]***. Based on human studies, Serum concentrations of ethambutol have been determined in ten normal volunteers, peak levels of 3 to 5 µg /mL have been achieved 2 to 4 h after oral administration of 20 to 30 mg of EMB per kg. There was expected serum concentration were proportional to the dose ***[131]***. In EMB-treated mice infected with wild-type H37Rv, Plinke *et al*. found relationships between dose and reduction in bacterial multiplication. Lower doses (6.25 and 12.5 mg/kg/day) of EMB treatment had no significant effect on the growth of H37Rv in the lung, liver, and spleen compared to the untreated mice. In opposite, mice treated with the intermediate-dose (25 mg/kg/day) and high dose (50 mg/kg/day) EMB therapy exhibited a significant reduction in CFU counts in the lung compared to the untreated mice ***[1312]***.

2.2.4- Isoniazid (Nydrazid)

Isoniazid is one of the most active early anti-tuberculosis drugs, also called Isonicotinic acid hydrazide (INH). In 1945 its antituberculosis properties were discovered. Comprising of a pyridine ring and a hydrazide group (Figure 1), INH is a nicotinamide analog, structurally related to the antimycobacterial agents ethionamide and pyrazinamide ***[133]***. The synthesis of INH was first reported in 1912 by Meyer and Mally ***[134]***. INH has been the cornerstone in the treatment of tuberculosis for almost half a century since its discovery as an effective anti-tuberculosis agent in 1952 [***135]***. Clinical trials were started in June 1951 by Selikoff and Robitzek of the Sea View Hospital, Staten Island, New York ***[136]***.It has been recommended for use in latent tuberculosis treatment ***[137]*** and can reduce the risk of disease in contacts of infectious TB patients when taken for 6–9 months ***[138]***. The treatment of latent TB infection with INH offers an opportunity to minimize the harm carried by TB/HIV coinfection ***[139]***. INH is highly active against the *M. tuberculosis* complex pathogens (*M. tuberculosis, M. bovis, M. africanum, and M. microti*) with very low MICs (0.02- 0.06 µg /mL) ***[140]***. After oral administration of 300 mg (approximately 5 mg/kg body weight) of INH, peak serum concentrations are well above the MIC ***[141]*** and ***[142]***. Isoniazid has potent bactericidal activity against *M. tuberculosis* grown in vitro and animal models of tuberculosis. Clinical studies with isoniazid and associated compounds have exhibited the anti-mycobacterial activity of high magnitude and thus confirmed results of *in-vitro* and *in-vivo* investigations. Mainly significant are the evaluations recorded by Selikoff, Robitzek, and Ornstein in 1952 on 166 patients with pulmonary and

extrapulmonary tuberculosis treated with isoniazid or iproniazid alone ***[143]***. In 1979, Mitchison noticed that the effectiveness of a fixed total dose of INH in infected guinea pig was similar whether it was given daily, every 2 days, or every 4 days over a period of 6 weeks. Thus, the efficacy of INH is dependent on the dose size and not the regimen ***[144]***.

2.2.5- Isoxyl (ISO)

Isoxyl (Thiocarlide) (Figure 2) is a thiourea derivative that was synthesized in 1953 by Buu-Hoi an Xuong ***[145]***. It is an anti-tubercular agent that has been in clinical use since the 1960s ***[146]***. Recently, ISO was shown to have a potentially efficient anti-tuberculosis drug for treatment of the MDR strains in monotherapy or in a combined regimen. *In-vitro* studies exhibited that ISO have strong anti-tubercular activity with minimum inhibitory concentration (MIC) of 2.5 µg/mL for *M. tuberculosis* H37Rv and MIC of 1–10 µg/mL for several clinical isolates of strains resistant to rifampicin and isoniazid ***[147]***. Pharmacokinetic features of ISO revealed the maximum serum levels (10-13.2µg/mL) greatly exceed the MIC that needed to inhibit bacterial growth ***[148]***. ISO mono-therapy showed modest efficacy in cases of untreated pulmonary tuberculosis of various degrees of difficulty ***[149]***.In 1970, Schmid concluded that combined INH and ISO were more active than monotherapy with either drug. It had been noted in the early 1950s that ISO showed strong anti-tubercular activity *in vitro* ***[150]***. In 1971, Winder *et al*. reported that ISO inhibits the synthesis of mycolic acids and free fatty acids in *M. bovis* BCG during six hours of exposure which is similar to isoniazid and ethionamide, two other predominant anti-mycobacterial agents ***[151]***. Bhowruth and his colleagues have synthesized symmetrical and unsymmetrical analogues of ISO and determined their activity against *M. tuberculosis* H37Rv and *M. bovis*. ISO showed activity against *M. tuberculosis*, with MIC 2.0 µg/mL. Some of the synthesized analogues had similar or better inhibitory activities relative to ISO ***[152]***.

2.2.6- p-aminosalicylic acid (PAS)

PAS formed a part of the standard treatment for tuberculosis prior to the introduction of rifampin and pyrazinamide. The anti-mycobacterial activity of PAS (figure 2) was first discovered by Lehmann in 1946 ***[153]*** on the basis of the previous observations of Bernheim ***[154]*** that the oxygen consumption of the tubercle bacillus Increased under the influence of benzoates and salicylates. Still 1955, PAS was regarded as a first-line drug in a combination regimen with isoniazid and streptomycin ***[84]***. The earliest clinical reports were by Lehman in 1946, who demonstrate that tuberculous abscesses after thoracoplasty showed healing after several months of daily local-injections of a 10% solution of PAS, even though the abscess cavities had remained unaffected for 3-6 months before treatment ***[153]***. In 1948, Erdei reported on five patients treated over a period of 60 days and one patient treated for four weeks with PAS administered orally. All the patients were given 12 gm. of PAS daily in divided doses three-hourly. The most astonishing effect of the drug was the great improvement in the patients' general condition that occurred about the third day, especially in toxic, anorexic and apathetic patients. Also he observed the considerable decrease in body temperature and E.S.R., a reduction in cough, stop of night sweats, an improvement in weight and appetite, and a very great reduction in the number of tubercle bacilli present in the sputum ***[155]***. Youmans and his colleagues found that PAS is highly bacteriostatic in vitro for virulent tubercle bacilli in human infections, also in experimental tuberculosis in mice they observed the addition of 2 percent concentration of PAS in the diet prolonged the average survival time of mice infected with 0.1 mg of H37Rv to 27.9 days as compared with the average survival time of 20.2 days for the control series. ***[156]***. PAS is effective against *M. tuberculosis* with MIC 1 µg/mL ***[84]***. Following twice-daily dosing administration of 4 g of granular PAS in 40 patients, the maximum serum concentrations remain above the typical minimum inhibitory concentration of *M. tuberculosis* over the entire dosing interval ***[142]***.

2.2.7- Pyrazinamide

Pyrazinamide (PZA), is a synthetic derivative of nicotinic acid (figure 2), was first described by Dalmer and Walter in 1936 ***[157]*** and has been used as an anti-tuberculosis drug since 1952 ***[84]***. It is an important first line anti-tuberculosis drug that helps to shorten the duration of current chemotherapy regimens from previously 9–12 months to 6 months, presumably due to its ability to kill 'semi-dormant' bacilli that are not killed by other anti-tuberculosis agents ***[158]***. PZA is active only against *M. tuberculosis* complex organisms (*M. tuberculosis, M. africanum* and *M. microti*), but not against *M. bovis* and *M. leprae* ***[159]***, also has an important role in the treatment of both drug-susceptible and drug-resistant tuberculosis ***[160]***. In an acid environment (pH of 5.5), the MIC of PZA for *M. tuberculosis* is 6.25-50.0 µg/mL ***[84]***. A significant event in the development of TB therapy was the discovery in the early 1970s that combining isoniazid, pyrazinamide and rifampicin in a 2-month initial phase regimen, followed by fewer drugs in the continuation phase, led to patients being recovered in as short a time as 6 months ***[161]***. The early experimental study using the mouse model of TB infection was elegantly demonstrated in 1950s by McCune *et al*. ***[162]*** and McCune and Tompsett ***[163]***. The average peak plasma level of Pyrazinamide was 30.9 mg/L, which exceed the MIC that required for inhibition of growth of *Mycobacterium tuberculosis* ***[164]***.

2.2.8- Thiacetazone (TAC)

Thiacetazone (figure 2), is one of the earliest antimycobacterial agents, which exhibit bacteriostatic action on *M. tuberculosis.* It was developed in 1946 by Domagk *et al*. at the Bayer Laboratories ***[165]***, after investigations on sulphonamides had revealed that thiazoles and thiadiazole derivatives had antituberculosis activity. Thiacetazone has an MIC 0.4 µg/mL for *M. tuberculosis* with achievable serum levels from 3.2 µg/mL ***[166]***. In East African, thiacetazone has been found to be an effective drug for treatment of pulmonary tuberculosis when administered in combination with isoniazid ***[167]***. In a study reported by Heifets *et al*., 65 of 68 *M. avium* strains were susceptible to the thiacetazone with MICs ranging from 0.02 to 0.15 µg/mL while the MICs for 14 wild drug-susceptible *M. tuberculosis* strains ranged from 0.08 to1.2 µg/mL ***[168]***. In a study performed in the UK, the response to treatment with thiacetazone of guinea-pigs and mice infected with resistant and sensitive TB strains belong to the East African, no definite response was found at any dose level in the animals infected with the resistant strains while the survival groups of treated animals infected with the sensitive strains was prolonged with a dosage of 100–250 mg/kg ***[169]***. In 1954, Barry and his colleague reported the good results obtained with a combination of isoniazid and thiacetazone (amithiozone) in experimental tuberculosis, the ability of the thiacetazone to delay the emergence of isoniazid resistance strains, and the great susceptibility of isoniazid-resistant bacilli to thiacetazone ***[170]***. Previously thiacetazone has been widely used as a front-line therapeutic in poor countries. However, because of the prevalence of HIV infection among tuberculosis cases and the severe side-effects caused by the drug in TB/HIV co-infected patients, the use of thiacetazone was restricted ***[171]***.

2.2.9- Capreomycin (CAP)

Capreomycin (figure 2) is a bactericidal agent of the polypeptide antibiotic and was first isolated from *Streptomyces capreolus* in 1960 by Herr and collaborators at the Lilly Research Laboratories ***[172]***. It is active against several species of mycobacteria, including *M. tuberculosis* ***[173]***. The MICs of capreomycin were within the range of 1.25–2.5 µg/ml in either liquid or solid (7H11 agar) medium against actively multiplying *M. tuberculosis* ***[173]*** and ***[174]***. Black *et al*. (1960s) measured the pharmacokinetics of CAP in humans.The serum concentrations of CAP have been determined in ten healthy adult male volunteers, the average peak serum concentrations of 32.7 µg/ml have been achieved in one to two hours following a single one gram intramuscular injection ***[175]***. CAP has recently attracted attention due to their demonstrated efficacy against resistant strains of *M .tuberculosis* ***[90]***. Popplewell, *et al*. found that CAP is an active agent for treating previously untreated

pulmonary tuberculosis. Although x-ray improvement appeared when CAP was used in a 120-day regimen with PAS and the 90-day regimen with INH and produced similar results as a control group receiving INH and PAS ***[176]***. Mouse model studies of tuberculosis infection show that CAP (150 mg/kg) reduced cell counts in spleens and lungs compared with mouse control ***[177]***. Up to now, the studies on cross-resistance to CAP in *M. tuberculosis* isolates have been opposing. There are reports of cross-resistance to CAP and Kanamycin, CAP and Viomycin ***[178]***. However, there are reports of drug-resistant isolates that do not show these cross-resistance relationships ***[179]***.

3-Targets and mode of action of TB drug

According to their mode of action, first and second-line antituberculosis drugs have been divided as cell wall inhibitors (isoniazid, ethambutol, cycloserine), nucleic acid synthesis inhibitors (rifampicin, quinolones), protein synthesis inhibitors (streptomycin) and inhibitors of membrane energy metabolism (pyrazinamide). The antituberculosis drugs can also be classified as bacteriostatic (EMB and PAS) and bactericidal drugs (INH, RIF, SM, and FQ) ***[43]***. The disparity between bacteriostatic and bactericidal drugs is proportional because some bacteriostatic agents can be bactericidal under particular situations (such as with higher drug concentrations, smaller inoculums, or change in bacterial physiological status). For example, PZA is actively bactericidal against small numbers of non-replicating bacilli at acid pH but mainly exhibits static activity for growing bacilli with active metabolism ***[180]***. It is well known that antituberculosis drugs act on specific targets in the genome of the tubercle bacillus to which they or their derivatives bind. For instance, the primary target of INH is inhibition the cell wall mycolic acid synthesis pathway (inhA), EMB inhibits cell wall biosynthesis (EmbA, and EmbB), while RMP binds strongly to β-subunit of bacterial DNA- dependent RNA polymerase and thereby inhibit RNA synthesis (RpoB) and SM inhibits protein formation at the ribosome (RpsL and 16S rRNA). As we shall see, the two drugs responsible for the main sterilizing activity of standard therapy are RMP and PZA ***[43]***. The origins, mechanisms of action and targets of inhibition for the first-line and second line of anti-tuberculosis drug are summarized in Table 1.

Conclusions

It very concerns that the resistance of TB to available drugs continues to grow, increasingly restricted our ability to control this serious disease. The revisiting of older drugs may help meet therapeutic needs more quickly than new drug development. Some old anti-tuberculosis drugs have the potential and offer the advantage of extensive clinical experience in TB therapy and may be alternative weapons in the fight against drug-resistant TB strains.

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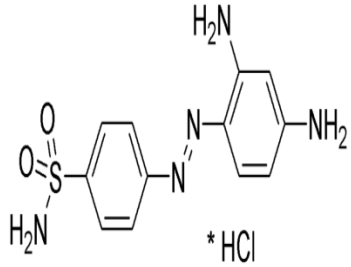
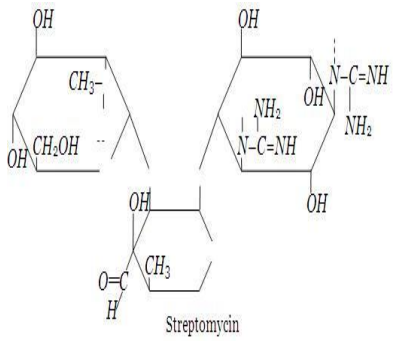
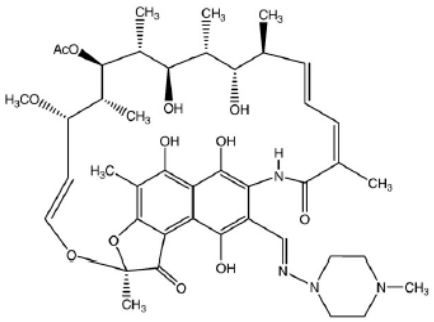


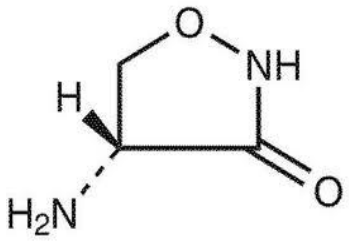
Prontosil ***[186]***



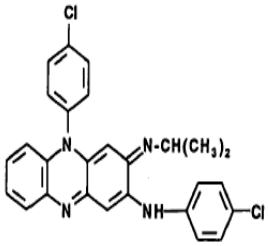
streptomycin ***[85]***.



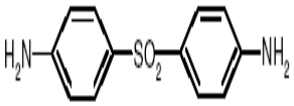
Rifampicin ***[46]***



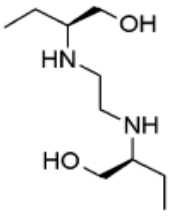
cycloserine ***[185]***



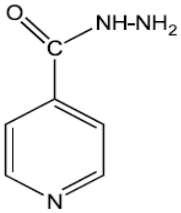
Clofazimine ***[182]***



Dapsone ***[183]***

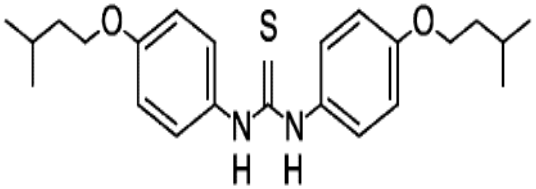


Ethambutol ***[184]***

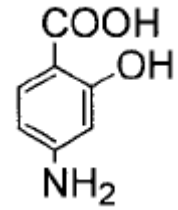


Isoniazid ***[134]***

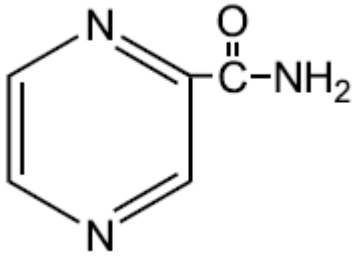
Figure 1 : Chemical structure of Prontosil, streptomycin, Rifampicin, Cycloserine, Clofazimine, Dapsone, Ethambutol and Isoniazid.



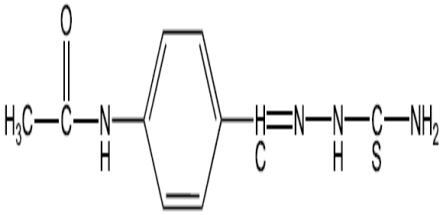
Isoxyl ***[187]***



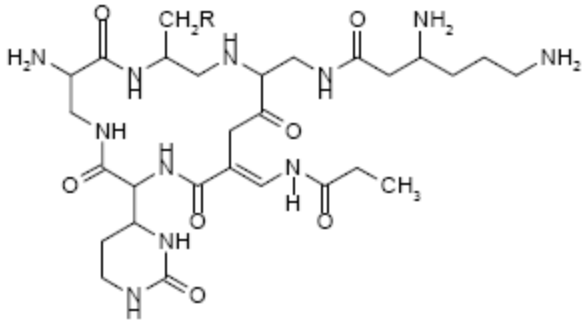
p- aminisalicylic acid ***[18]***



Pyrazinamide ***[162]***



Thiacetazone ***[18]***



Capreomycin ***[188]***

Figure 2: Chemical structure of Isoxyl, p- aminisalicylic acid, Pyrazinamide, Thiacetazone and Capreomycin.

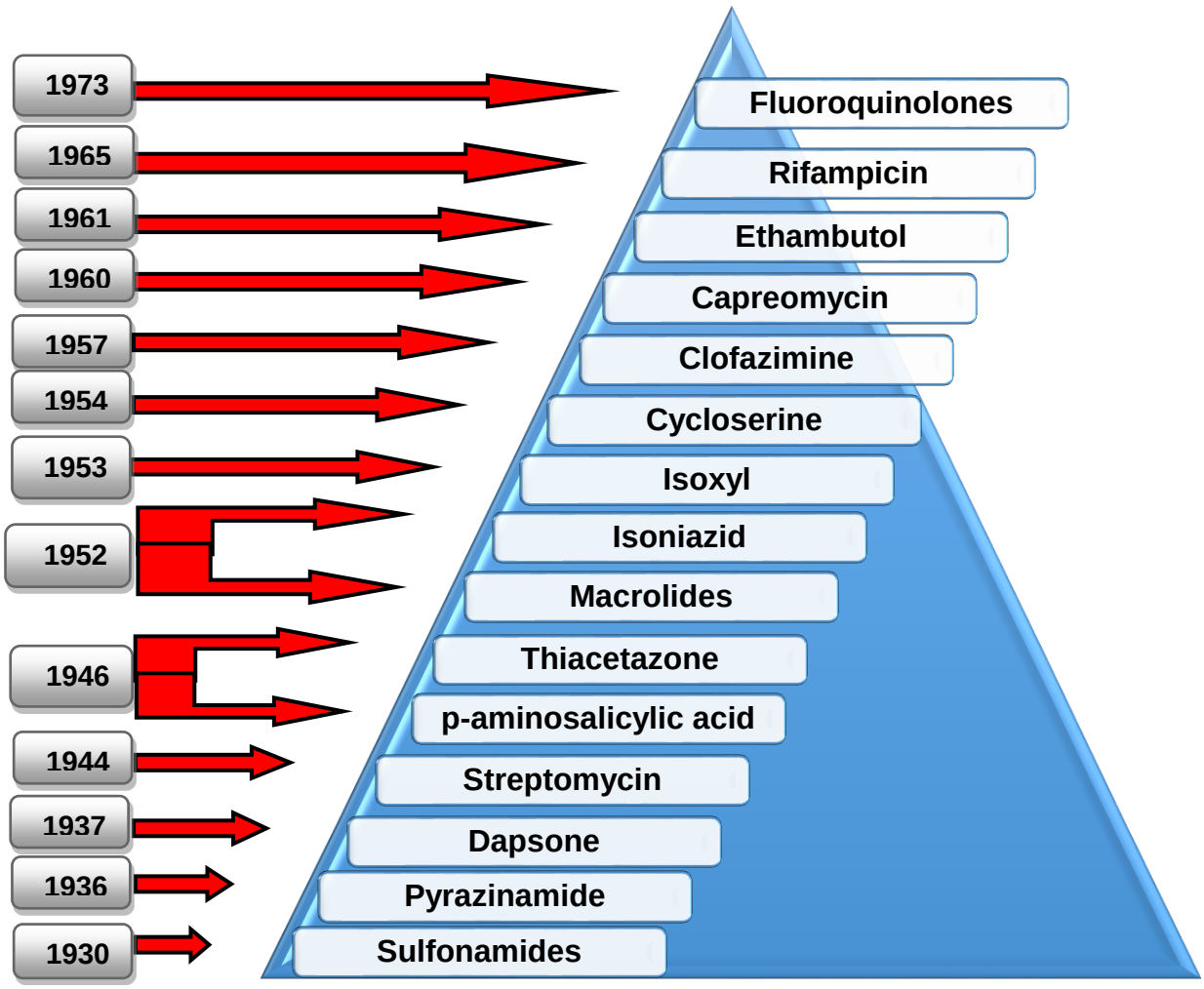


Figure 3: Timeline for Previously licensed anti-mycobacterial drug development.

Table 1.Previously licensed anti-tuberculosis agents and their targets

Drug	Source	Effect on bacterial cell	Mechanism of action	Targets	Gene involved in resistance
†Streptomycin	*Streptomyces griseus*	Bactericidal	Inhibition of protein synthesis	Ribosomal S12 protein and16S rRNA	*rpsL*, *rrs*
† Rifampicins	semi-synthetic	Bactericidal	Inhibition of RNA synthesis	RNA polymerase β subunit	*rpoB*
• Macrolides	actinomycetes / semi-synthetic	Bacteriostatic	Inhibition of protein synthesis	50S ribosomal subunit	*erm*
× luoroquinolones	synthetic	Bactericidal	Inhibits DNA synthesis	DNA gyrase	*gyrA, gyrB*
†Cycloserine	*Streptomyces orchidaceus*	Bacteriostatic	Inhibition of peptidoglycan synthesis	D-alanine racemase	*alrA, Ddl* [c]
‼ Clofazimine	Synthetic	Bacteriostatic	Binds to DNA and inhibition of RNA polymerase	Unknown	Unknown
† Ethambutol	Synthetic	Bacteriostatic	Inhibition of cell wall arabinogalactan synthesis	Arabinosyl transferase	e*mbCAB*
† Isoniazid	Synthetic	Bactericidal	Inhibition of cell wall mycolic acid synthesis and other multiple effects on DNA, lipids, carbohydrates and NAD metabolism	Multiple targets including acyl carrier protein reductase (InhA)	*katG*[b] *inhA* *ndh*
▼Isoxyl	Synthetic	Bactericidal	Inhibition of oleic and mycolic acids synthesis	Δ 9-stearoyl desaturase	*DesA3*
†p-aminosalicylic acid	Synthetic	Bacteriostatic	Inhibts folic acid synthesis and iron metabolism	Thymidylate synthase	*thyA*
† Pyrazinamide	Synthetic	Bacteriostatic/ Bactericidal (pH 5.5 or 6.0)	Disruption of membrane transport and energy depletion	Membrane energy metabolism	*pncA*[b]
» Thiacetazone	Synthetic	Bacteriostatic	Inhibits mycolic acid cyclopropanation	cyclopropane mycolic acid synthases	*mmaA4*
☼Capreomycin	*Streptomyces capreolus*	Bactericidal	Inhibition of protein synthesis	16S rRNA	rrs

[b]KatG and PncA are enzymes involved in the activation of prodrugs INH and PZA respectively.

[c] In fast growing *M. smegmatis*.

† : *[43]*, •: *[190]*, × : *[189]*

‼: *[18]*, ▼: *[191]*

»: *[181]*, ☼: *[192]*.