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A Review on: Antituberculosis Agents

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ABSTRACT:

Tuberculosis is today amongst the worldwide health threats. In present study we reported current antituberculosis regimen and compounds under clinical trials, compounds under clinical trials, mechanisms of action of antituberculosis drugs or Antimycobacterials, effects of tuberculosis on pregnancy, first-line drug, second- line drugs, anti-tuberculosis drugs related hepatotoxicity, tuberculosis small intestine, tuberculosis lymphadenitis, multi-drug resistant and extensively drug resistant TB in India, prevention of MDR-TB and XDR-TB, diagnosis of MDR-TB, Current status in the development of the new anti-tuberculosis drugs. In future our review will helpful for researcher to find out novel antitubercular drugs.

KEYWORDS: Antituberculosis, First-line drugs, Second-line drugs.

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Introduction:

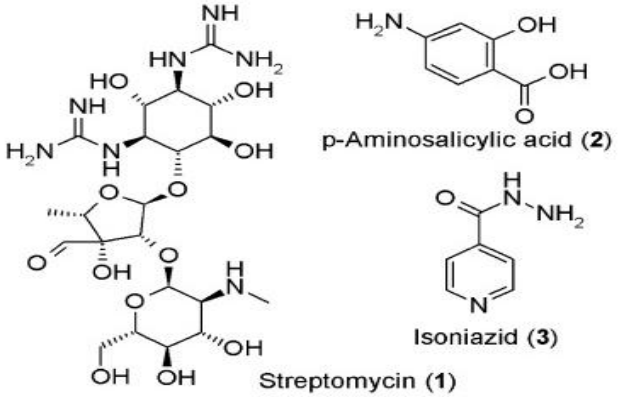
Tuberculosis (TB) is a disease of antiquity which is thought to have evolved sometime between the seventh and sixth millennia BC[1]. Current estimates suggest that one third of the world's population are infected resulting in some 2 million deaths per year**.** The introduction of the first drugs for TB treatment some 50 years ago - streptomycin, para-aminosalicylic acid, isoniazid - led to optimism that the disease could be controlled if not eradicated[2, 3]. These medicaments, coupled with generally increasing standards of health care, caused a rapid decline of tuberculosis in many industrialized countries which produced a climate of indifference to the need for fresh drugs. As a result of this apathy and the perception by the pharmaceutical industry that such agents would be unlikely to generate a suitable return on investment, few new drugs have been introduced in the last 30 years[4]. However, since the 1980's the disease has been undergoing a resurgence driven by a variety of changes in social, medical and economic factors. Thus, a dramatic increase in immuno-suppressed individuals due mainly to AIDS (but also to cancer chemotherapy and organ-transplant practices), coupled with increasing urbanization and poverty in developing countries, has compromised primary health care structures and led to large increases in TB incidence. Concomitant with the resurgence of TB has been the occurrence of multidrug- resistant disease which has exposed the frailties of the current drug armamentarium[5, 6].

In conjunction with the spread of HIV infection, tuberculosis is today amongst the worldwide health threats. As resistant strains of Mycobacterium tuberculosis have slowly emerged, treatment failure is too often a fact, especially in countries lacking the necessary health care organisation to provide the long and costly treatment adapted to patients. Because of lack of treatment or lack of adapted treatment, at least two million people will die of tuberculosis this year. From the mid-1990s, this infectious disease was the focus of renewed scientific interest. In the last 10 years,

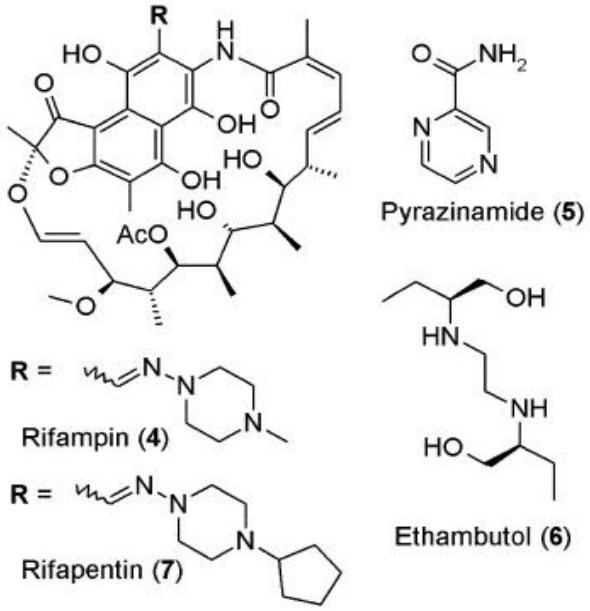
the research on M. tuberculosis, the causative agent of tuberculosis, has undergone much progress. Regimens were optimized along with the implementation of the directly observed therapy short course (DOTS) initiative. At the laboratory level, the genome of M. tuberculosis was unravelled and much work provided insights into the mechanisms of action of the antituberculosis drugs currently used[7].

Current antituberculosis regimen and compounds under clinical trials[7]

As described recently, the chemotherapy of tuberculosis has much evolved along the years since it started with the introduction of streptomycin (1) in 1946. By 1955, the combination of streptomycin (1), p-aminosalicylic acid (2) and isoniazid (3) was adopted as a standard treatment by the western world. The minutes of a congress held in 1968 illustrate quite well what the clinical research concerns were at that time.

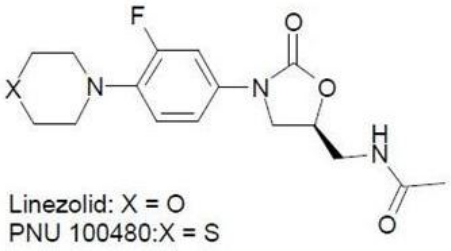


It will never be emphasized enough that the full observance of the treatment is probably at least as important as the level of efficiency of the drugs administered for a proper cure. Even worse, the lack of treatment observance is likely to become the main cause of the occurrence and spread of multi drug resistant strains of M. tuberculosis. Two regimens emerged from the many trials and involve first a two-month long treatment with four drugs; either: streptomycin (1), isoniazid (3), rifampin (4) and pyrazinamide (5) or: isoniazid (3), rifampin (4), pyrazinamide (5) and ethambutol (6). This is then followed by four months of isoniazid (3) and rifampin (4). Side effects, especially hepatotoxicity, are an issue which in some cases forces an untimely treatment termination. Patients following this regimen become non-infectious after the first few weeks but the remaining months are crucial to eradicate a slow growing fraction of the bacilli and also to allow time for the host immune system action to achieve a clinical cure. The 14th edition of the Merck index lists 30 different tuberculostatics. Many of them are analogues or prodrugs of the first line drugs mentioned above and others fell out of use.



Compounds under clinical trials[7]

Aside from some of the above-mentioned fluoroquinolones which are still in the process of being established as second line antituberculosis drugs, the oxazolidinone class of antibiotics is under study.



The first antibiotic of this class approved, linezolid (26), was also studied for the treatment of MDR tuberculosis. A clinical study in which, for some cases, went well beyond the recommended 28 days-long treatment took place under a compassionate- use programme. Among the side effects reported three cases of peripheral neuropathy were mentioned.

Later reports, including two focused on long MDR antituberculosis treatment, demonstrated an antituberculosis effect on patients but also consistently mentioned peripheral neuropathies that remain to be studied more thoroughly, especially its reversibility.

MECHANISMS OF ACTION OF ANTITUBERCULOSIS DRUGS OR ANTIMYCOBACTERIALS[7]

The determination of the biochemical processes targeted by antituberculosis drugs is still undergoing and has been reviewed in the recent past. This is one of the many fascinating facets of this field as many antituberculosis drugs have been used for decades with little or no knowledge of

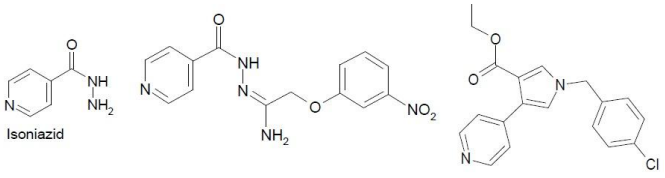
their mechanism of action. This 'deorphaning' of antituberculosis drugs is today of prime importance, as it can lead to the identification of already validated biological targets of M. tuberculosis. These targets can then be used for the search of better inhibitors (long lasting or overcoming the resistance of mutated strains) starting with the use of modern fast screening of chemical libraries. In many instances the classification of these mechanisms of action was difficult as no clear cut pictures were yet available. For instance, isoniazid (3) is, so far, likely to inhibit three NADH-using enzymes involved in fatty acid biosynthesis; but will the latter aspect hold true in some years? We strove to provide an overall view of the past and present studies which are sometime in contradiction. In this regard, the following is probably missing a table or two, although, we believe this would oversimplify the sum of the investigations reviewed and would ignore many antimycobacterials of interest. Moreover, our suggested biochemical targets for some compounds described below are sometimes only based on structural similarities and must be taken with the proverbial grain of salt.

Effects of tuberculosis on pregnancy[8]

Maternal tuberculosis has been associated with an increased risk of spontaneous abortion, perinatal mortality, small for gestational age and low birth weight in some studies. Outcome is unfavourably influenced by delays in diagnosis or treatment, along with disease other than that in lymph nodes. Congenital tuberculosis is a rare complication of *in utero* tuberculosis infection as a result of maternal haematogenous spread. Congenital tuberculosis is difficult to diagnose as it is seldom distinguishable from other neonatal or congenital infections. Symptoms usually arise in the second or third weeks' post-partum. Hepatosplenomegaly, respiratory distress and fever are common, and chest radiography is almost universally abnormal.

FIRST-LINE DRUGS[8,9]

Isoniazid:.Recommended for use in pregnancy. As isoniazid may be associated with an increased risk of hepatotoxicity in pregnant women, symptoms should be assessed, and it is recommended by some that liver function tests be performed fortnightly during the first two months of treatment, and monthly thereafter.

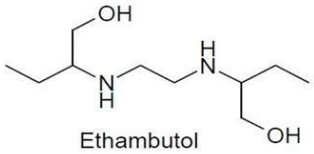


Isoniazid given for treatment of latent tuberculosis (chemoprophylaxis) is considered safe, and is recommended especially where the risk of developing disease is higher, such as with HIV co-infection or with a history of recent contact.

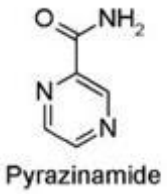
Pyridoxine: Pyridoxine supplementation is recommended for all pregnant women taking isoniazid as deficiency is more likely in pregnant women than in the general population. The Queensland Tuberculosis Control Centre recommends the routine use of pyridoxine in all patients taking isoniazid.

Rifampicin: Bleeding attributed to hypoprothrominaemia has been reported in infants and mothers following the use of rifampicin in late pregnancy. The use of rifampicin is indicated in pregnant women with tuberculosis, with the recommendation that vitamin K be given to both the mother and the infant postpartum if rifampicin is used in the last few weeks of pregnancy.

Ethambutol: Recommended for use in pregnancy.



Pyrazinamide: There are no reports of foetal malformations attributable to pyrazinamide, although there are additionally no animal or epidemiological studies reported to support the safety of this drug in pregnancy. The absence of such safety data is the reason that the CDC

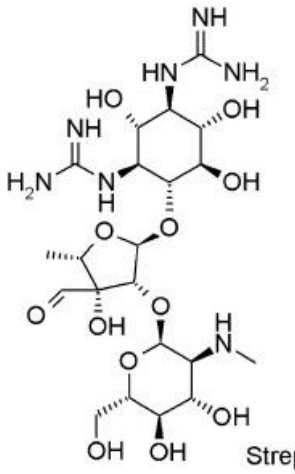


(USA) guidelines do not endorse pyrazinamide in pregnancy. Its use is supported by other tuberculosis authorities, including the IUATLD and the BTS. To date, there are no reports of significant adverse events from the use of this drug in the treatment of TB in pregnant women despite the fact that the drug is used as part of the standard regimen in many countries. However, additionally, insufficient data are available about the number of pregnant women treated for TB in these many settings. If the treating doctor elects not to use pyrazinamide, a nine-month regimen containing isoniazid and rifampicin throughout (supplemented by ethambutol until drug susceptibility results are available) is recommended.

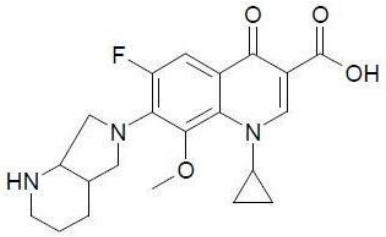
SECOND- LINE DRUGS[8,9]

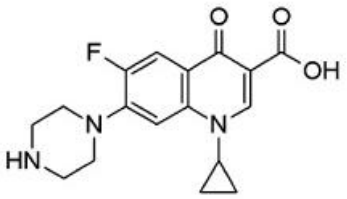
Streptomycin: Streptomycin has a well established association with foetal ototoxicity and is not recommended for the treatment of tuberculosis in pregnant women.

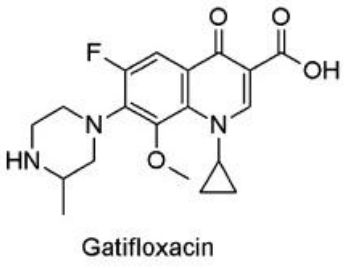
Fluoroquinolones: (Pregnancy Category B3 for Ciprofloxacin, Gatifloxacin, Moxifloxicin and Norfloxacin). There is no evidence of increased incidence of abnormalities in babies of mothers treated with fluoroquinolones. Animal studies of ciprofloxacin suggest that there is a risk of damage to articular cartilage and subsequent juvenile arthritis with short courses



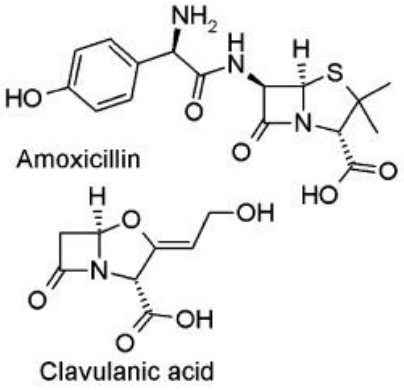
of treatment, and the possibility of joint damage with longer courses of treatment used for tuberculosis must be seriously considered. Fluoroquinolones should only be used in pregnant women with tuberculosis where the benefits of treatment are judged to outweigh the potential risks and the decision to use such drugs in this setting should only be made after discussion with clinicians experienced in the management of TB.





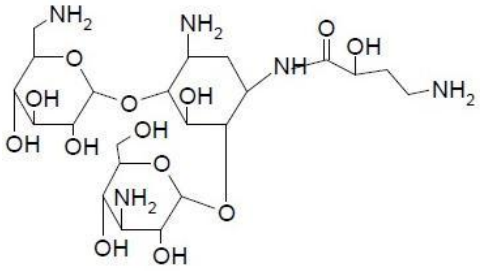


Amoxycillin/Clavulanic Acid: There is no evidence of teratogenicity in animal studies. Amoxycillin/clavulanic acid has been used in late pregnancy as prophylaxis in women with prolonged rupture of membranes without any problems documented, but there is limited experience with its use in the first trimester. There is only likely to be a minor role for amoxycillin/clavulanic acid in the treatment of pregnant women with MDR-TB where insufficient alternatives are available (Bothamley 2001). MDR-TB should only be treated after close consultation with clinicians experienced in the management of TB.



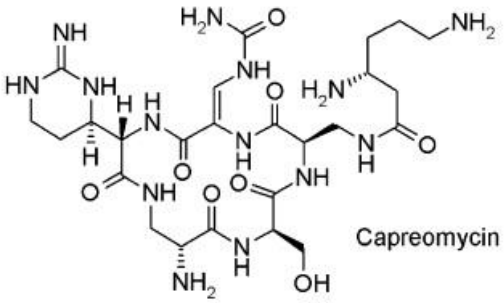
Para-Aminosalicylic Acid (PAS): There is insufficient animal and human safety data relating to the use of PAS in pregnancy. It has been associated with a slightly higher incidence of limb and ear abnormalities in one report involving 123 patients taking PAS with other anti-TB drugs. However, an increased risk of congenital defects has not been found in other studies. PAS should not be used to treat TB in pregnant women unless the benefit/risk ratio (after discussion with a clinician experienced in the management of difficult TB cases) is favourable.

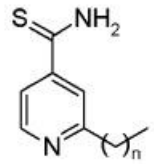
Amikacin: There is concern that all aminoglycosides are potentially nephrotoxic and ototoxic to the foetus and their use is not recommended in tuberculosis in pregnant women. Maternal drug levels do not appear to correlate with foetal safety. Use of aminoglycosides in pregnancy should only be as a last resort after due consideration of the risks and benefits (WHO 2003) and close discussion with experts in the clinical management of TB.



Capreomycin: There is evidence of teratogenicity in studies where capreomycin was given to pregnant rats. Capreomycin is generally contraindicated in pregnancy and should only be used following consideration of its risks and benefits (MIMS 2003, WHO 2003) in consultation with an expert in the clinical management of TB.

Ethionamide and Prothionamide: These drugs have been shown to be teratogenic in animal studies and their use is not recommended in pregnancy.

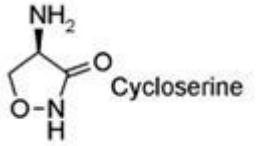




18a-b

n = 1: Ethionamide
n = 2: Prothionamide

Cycloserine: There is no evidence of teratogenicity in rats, but there is insufficient study in humans to confirm the safety of cycloserine in pregnancy. Its use should only be considered where the benefits outweigh the potential risks (MIMS 2003) after discussion with an expert in the clinical management of TB.



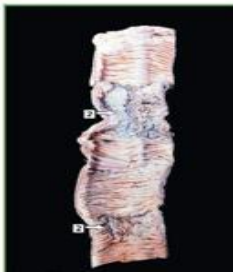
Anti-tuberculosis drugs related hepatotoxicity[10]

One third of the world population infected with *Mycobacterium tuberculosis* and tuberculosis (TB) in one of the main cause of morbidity and mortality in developing countries[11]. If diagnosed and treated properly with anti-TB drugs, TB is a curable disease. These drugs can cause severe adverse reactions including hepatotoxicity[12]. Hepatic transaminase elevation without clinical presentation is common and benign episode following anti-TB treatment, but symptomatic hepatotoxicity can be fatal without any intervention[13]. From the first line anti-TB drugs, isoniazid, rifampicin and pyrazinamide are potentially hepatotoxic. Based on hepatotoxicity diagnosis criteria and population under study, incidence of anti-TB related hepatotoxicity is reported from 2% to 28%. High alcohol intake, older age, pre-existing chronic liver disease, chronic viral infection due to hepatitis B (HBV) and hepatitis C viruses (HCV), human immunodeficiency virus (HIV) infection, advanced TB, Asianethnicity, female sex, concomitant administration of enzyme-inducers, inappropriate use of drugs and poor nutritional status increase the risk of anti-TB drug induced hepatitis. Hepatotoxicity due to anti-TB drugs has been evaluated as a a part of adverse drug reactions (ADR) assessment in previous studies and based on recent literature review, there is not any specific report of this reaction in Iranian TB patients[14,15].

Tuberculosis small intestine[16]

The small intestine is identified externally by absence of taenia coli band, appendices epiploicae and haustrations. Mesentry shows an enlarged lymph node in cut section having areas of caseation necrosis.

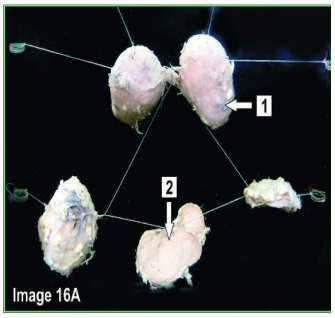
The lumen shows transverse ulcers and strictures (transverse to the long axis of intestine).



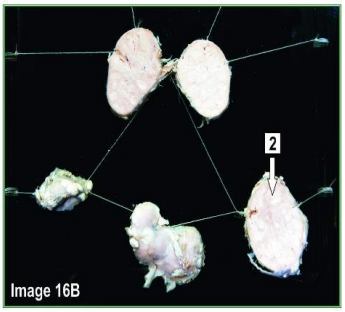
The intestinal wall in the strictrous areas is thickened and gray white and mucosa ulcerated. The mucosal surface in the intervening areas shows irregularity of mucosal folds.

Tuberculosis lymphadenitis[16]

Multiple lymph nodes are matted together and surrounded by fat.



Sectioned surface shows merging capsules of adjacent nodes and large areas of yellowish caseation necrosis.



Multi-drug resistant and extensively drug resistant TB in India[17]

MDR-TB is defined as resistance to isoniazid and rifampicin, with or without resistance to other anti-TB drugs. XDR-TB is defined as resistance to at least Isoniazid and Rifampicin (i.e. MDR-TB) plus resistance to any of the fluoroquinolones and any one of the second-line injectable drugs (amikacin, kanamycin, or capreomycin).

Prevention of MDR-TB and XDR-TB[17]

The use of inadequate regimens and the absence, or inappropriate application, of directly observed treatment can lead to the development of drug resistance and potentially to an increase in drug resistance levels amongst the community. The implementation of a good quality DOTS programme will prevent the emergence of MDR and XDR-TB in the community. Therefore the highest priority is to further improve the quality and reach of DOTS services in the country. For this, all health care providers managing TB patients need to be linked to RNTCP and operational challenges in implementing DOTS needs to be addressed. The proportion of TB patients being treated outside the DOTS strategy needs to be minimized. The International Standards of TB Care need to be used by RNTCP and professional medical associations as a tool to improve TB care in the country. The fluoroquinolone group of drugs are not as yet recognized, nor recommended, as first line anti-TB drugs, and their use should be restricted only to the treatment of confirmed MDR-TB cases. MDR-TB management to be preferably undertaken only at selected health institutions with experience, expertise and availability of required diagnostic and treatment facilities

Diagnosis of MDR-TB[17]

Drug resistance may be suspected based on history of prior treatment (e.g. smear positive case after repeated treatment courses, Cat II failure etc.) and/or close exposure to a possible source case confirmed to have drug-resistant TB For patients in whom drug resistance is suspected, diagnosis of MDR-TB should be done through culture and drug susceptibility testing from a quality-assured laboratory.

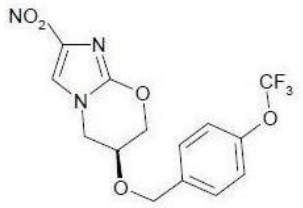
Current status in the development of the new anti-tuberculosis drugs[18]

It is expected that development of the new effective anti-TB drug will bring us various outcomes such as shortening the total duration treatment, improvement of the treatment completion ratio, prevention and treatment of the multiple drug resistant tuberculosis (MDR-TB) and reducing the total medical expenditure.

A new anti-TB drug needs to show the well phrmacokinetic distribution and permeation into lung tissue and cells. Furthermore, it is also desired that the novel candidate exhibits the potent bactericidal activity both against exponential and stable phase of M. tuberculosis in vivo.

In addition, it is ideal that the novel agent possesses narrow anti-microbial spectrum specialized only against Mycobacterial species.

Nitroimidazopyran is the center of attention in the world today as a most potent novel drug candidate for TB.



PA 824

Its leading compound PA-824 is being developed at the stage of the first clinical trial phase I. PA-824 possesses two types of mechanism; inhibitions of the biosynthesis of protein and cell wall lipid of M. tuberculosis. PA-824 exhibits bactericidal activity against both replicating and static M. tuberculosis. It also shows potent bactericidal activity against MDR-M. Tuberculosis[18].

Among the new rifamycin derivatives, rifalazil (KRM-1648) is the most promising drug candidate. The development of rifalazil is in progress at the stage of the clinical trial phase II. Rifalazil demonstrates potent long-acting oral activity against M. tuberculosis both in animal models and in humans.

Rifalazil

Gatifloxacin (GFLX) and moxifloxacin (MXFX) are the 8-methoxy-fluoro- quinolone representatives. They show bactericidal activity against replicating M. tuberculosis both in vitro and in murine tuberculosis models[18].

ABT-773 and HMR-3647 are the ketolide compound representatives; they possess a potential bactericidal activity against M. avium-intracellulare complex (MAC) in vitro, but these ketolide compounds are ineffective against macrolide resistant MAC strains.

Caprazamycin-B (CPZ-B) is the promising novel antibiotic recently developed in Japan, which was isolated from Streptomyces species. In contrast to current anti-TB drugs,

CPZ-B with a novel chemical structure possesses specific bactericidal activity only against Mycobacterial species especially M. tuberculosis including MDR strains and MAC isolates. CPZ-B inhibits the biosynthesis of the cell wall of Mycobacteria, and exhibits moderate therapeutic efficacy that is dose size dependent in pulmonary tuberculosis model induced in mice. Any cyto-toxicity is not observed in the preceding animal experiments.

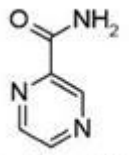
"The Global Alliance for TB Drug Development (GATB)", recently formed organization under WHO initiative started funding pharmaceutical companies to develop the novel agents for TB. GATB has recently set up a new project called "Aerosolized new drug in DDS". It has a potentially promising scope for developing new ant-TB drugs and the management of chemotherapy as well.

1st line antiTB table[19]:

Rifabutin with soft-gel saquinavir and nevirapine, because data regarding the use of rifabutin with soft-gel saquinavir and nevirapine are limited. If nelfinavir, indinavir, amprenavir, or ritonavir is administered with RFB, blood concentrations of the PIs decrease. Thus, when RFB is used concurrently with any of these drugs, the daily dose of RFB is reduced from 300 mg to 150 mg when used with nelfinavir, indinavir, or amprenavir; and to 150 mg two or three times a week when used with ritonavir. If efavirenz is administered with RFB, blood concentrations of RFB decrease. Thus, when RFB is used with efavirenz, the daily dose of RFB should be increased from 300 mg to 450 mg or 600 mg. No maximum dosages for EMB but in obese patients dosage should be calculated on lean body weight.

Preventive measures againstdrug -induced ocular toxicity during anti-tuberculosis treatment[20]

Ethambutol (EMB) is one of the important first line drugs in the treatment of tuberculosis (TB). It is also commonly employed in the treatment of non-tuberculous mycobacterial infection. EMB may occasionally cause ocular toxicity but evidence suggests that it is as safe as or safer than the other standard anti-TB drugs provided proper precautions are taken when prescribing the drug. It has been reported to compare favourably to isoniazid (INH), rifampicin (RMP) and pyrazinamide (PZA).



Pyrazinamide

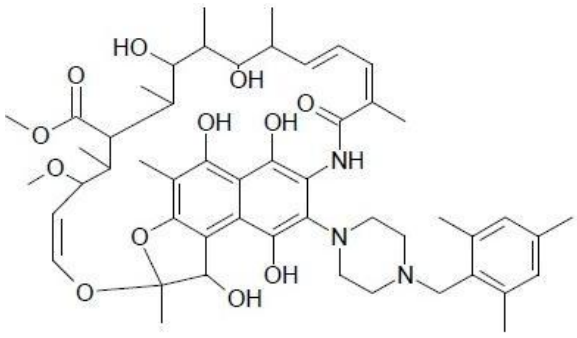
The ocular side effects of EMB therapy were first described by Carr and Henkind in 1962. Retrobulbar neuritis is the most important potential side effect from EMB. It is reversible in most cases and is related to the dose and duration of treatment, but may occasionally become irreversible resulting in permanent visual disability especially in the older population. It has been said that there is no so-called "safe-dosage" for EMB. The reported incidence of retrobulbar neuritis when EMB is taken for more than 2 months is 18% in subjects receiving greater than 35 mg/kg/day, 5-6% with 25 mg/kg/day, and less than 1% with 15 mg/kg/day.

Treatment of latent TB infection[21]

TB remains a common and preventable opportunistic infection in HIV-infected patients. Test people with HIV infection for latent TB infection (LTBI) as soon as possible after diagnosis of HIV infection and at least once a year thereafter. The 9-month isoniazid regimen may be administered concurrently with any antiretroviral regimen used to treat HIV infection. Isoniazid is prescribed daily if on self-administered therapy and twice a week if given by DOT. Rifampin or rifabutin for 4 months can be used with selected antiretroviral drugs as an alternative. Because of reports of severe liver injury associated with its use, a regimen of two months of rifampin and pyrazinamide is not recommended and should generally not be offered to persons with LTBI. HIV-positive persons who have had recent close contact with an active TB patient should have a medical evaluation and chest x-ray. Once active TB is ruled out, they should receive treatment for LTBI regardless of age, results of tests for TB infection, or history of previous treatment for LTBI.

HIV-positive individuals with a history of prior untreated or inadequately treated TB disease should be re-evaluated for active disease regardless of age or results of tests for TB infection. If active TB disease is ruled out, patients should still receive treatment for old, healed TB, or for LTBI.

Evaluate liver function in all HIV-positive individuals before starting treatment for LTBI. Obtain baseline CBC with platelets if a rifamycin will be given. Monitor all patients monthly with a directed clinical exam and hepatic enzymes.



Rifamycin

Many patients started on treatment of LTBI do not complete the prescribed regimen. Adherence should be rigorously promoted for this life saving intervention. Directly observed treatment (DOT) for LTBI is available for all HIVinfected patients with LTBI. Contact the TB hotline (212-788-4162) to arrange DOT for your patient. If interruptions of fewer than

Three months in treatment occur, patients can be given 2 to 3 additional months to complete the regimen.

The new TB drug pipeline[22]

Drug development for tuberculosis and other neglected diseases has been at a standstill for decades. Today however, thanks also to the work of the Global Alliance for TB Drug Development (TB Alliance), the TB drug pipeline is richer than it has been in the last forty years. Created in 2000 and largely funded by the Bill & Melinda Gates Foundation, the TB Alliance is a product development partnership (PDP) that focuses on both pre-clinical and clinical development of candidate compounds for TB chemotherapy.

In order to analyse the pipeline it is useful to group drug candidates currently in two main categories:

1) Novel chemical entities

2) Compounds originating from existing families of drugs, where innovative chemistry is used to optimise the compounds.

Novel chemical entities

1 Diarylquinoline TMC207 (Johnson & Johnson)

2 Nitroimidazole PA-824 (Chiron Corp.-TB Alliance)

3 Nitroimidazole OPC-67683 (Otsuka Pharmaceuticals, Japan)

4 Pyrrole LL- 3858 (Lupin Limited, India)

5 Pleuromutilins (GlaxoSmithKline-TB Alliance Partnership)

6 Dipiperidine SQ-609 (Sequella Inc.)

7 ATP Synthase Inhibitor FAS20013 (FASgene)

8 Translocase I Inhibitor (Sequella Inc.)

9 InhA Inhibitors (GlaxoSmithKline-TB Alliance)

10 Isocitrate Lyase Inhibitors (GlaxoSmithKline-TB Alliance)

Compounds originating from existing families of drugs

1 New Quinolones

2 Non-fluorinated quinolones

3 Diamine SQ-109

4 Macrolides

5 Thiolactomycin analogs

6 Nitrofuranylamides

7 Nitroimidazole Analogs

8 New rifamycin derivatives

9 Oxazolidinones (Linezolid)

DISCUSSION

At the bench level, many M. tuberculosis biochemical transformations have been identified as potential targets for original antituberculosis treatment today. In view of this wealth, it seems, to our probably biased chemist point of view, that the current limiting factor at our level is not anymore the availability of new biochemical targets but may well be the access to original (i.e., untested) chemical compounds[7]. ADR including hepatotoxicity can be one of the main reasons for poor adherence with Anti-TB treatment in tuberculosis patients[23].

REFERENCES

1. A Hudson, T Imamura, W Gutteridge, T Kanyok, P Nunn. The current anti-TB drug research and development pipeline or http://whqlibdoc.who.int/hq/2003/TDR_PRD_TB_03.1W.pdf
2. Manchester K. Tuberculosis and leprosy in antiquity: an interpretation. *Medical History*, 1984, 28:162-173.
3. Dye C et al. Global burden of tuberculosis, estimated incidence, prevalence, and mortality by country. *Journal of the American Medical Association*, 1999, 282:677-686.
4. Centers for Disease Control and Prevention. Tuberculosis elimination revisited: obstacles, opportunities, and a renewed commitment. Advisory Council for the Elimination of Tuberculosis (ACET). *Morbidity and Mortality; weekly report*, 1999, 48(RR-9):1-13.
5. Weil DEC. Drug supply: meeting a global need. In: Porter JDH, McAdam KPWJ, eds. T*uberculosis: Back to the future*. Wiley and Sons Ltd., 1994:123-143.
6. Snider DE. Tuberculosis: the world situation. History of the disease and efforts to combat it. In: Porter JDH, McAdam KPWJ, eds. *Tuberculosis: Back to the future*. Wiley and Sons Ltd., 1994:14-31.
7. Y L Janin. Antituberculosis drugs: Ten years of research. Bioorg Med Chem. 2007, 15 (7), 2479-2513.
8. http://www.health.qld.gov.au/ph/documents/qtbcc/31044.pdf
9. Bothamley G. Drug Treatment for Tuberculosis during Pregnancy: Safety Considerations Drug Safety, 2001, 24(7):553-65
10. H Khalili, S Dashti-Khavidaki, M Rasoolinejad, L Rezaie, M Etminani. Anti-tuberculosis drugs related hepatotoxicity; incidence, risk factors, pattern of changes in liver enzymes and outcome. Daru, 2009;17 (3):163-167.
11. Brewer TF, Heymann SJ .To control and beyond: moving towards eliminating the global tuberculosis threat. J Epidemiol Community Health, 2004; 58:822-825.
12. Forget EJ, Menzies D. Adverse reactions to first-line anti-tuberculosis drugs. Expert Opin Drug Saf, 2006; 5:231-249.

13. Hussain Z, Kar P, Hussain SA. Antituberculosis drug-induced hepatitis: risk factors, prevention and management. Indian J Exp Biol, 2003;41:1226-1232.

14. Frieden TR, Sterling TR, Munsiff SS, Watt CJ, Dye C. Tuberculosis. Lancet, 2003; 362: 887-899.
15. Girling DJ. The hepatic toxicity of antituberculosis regimens containing isoniazid, rifampicin and pyrazinamide. Tubercle, 1978; 59: 13-32.
16. Harsh Mohan, textbook of pathology, 6th edition, Published by Jaypee Brothers Medical Publisher (P) Ltd., 149-155.
17. Multi-drug resistant and extensively drug resistant TB in India. Or http://www.tbcindia.org/pdfs/Consensus%20statement%20on%20MDR%20XDR%20TB%20-Final.pdf
18. Current status in the development of the new anti-tuberculosis drugs. Or http://www.jata.or.jp/rit/re/eproject7.pdf
19. http://www.ndhealth.gov/disease/tb/Documents/First%20Line%20TB%20drugs.pdf
20. Preventive measures against drug-induced ocular toxicity during anti-tuberculosis treatment or www.chp.gov.hk/files/.../grp-preventive-ocular toxicity-en-2004052100.pdf
21. S Munsiff, D Nilsen, S D Ahuja, J N Burzynski. Antiretroviral drugs and the treatment of tuberculosis. Or http://www.nyc.gov/html/doh/downloads/pdf/tb/tbanti.pdf
22. http://www.msf.or.jp/info/pressreport/pdf/TBpipeline_E.pdf
23. Khalili H, Dashti-khavidaki S, Sajadi S, Hajiabolbaghi M. Assessment of adherence to tuberculosis drug regimen. DARU, 2008; 16: 47-50.