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Review article

Recent Advances and Perspectives in Antitubercular Drug Design- A Review

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ABSTRACT

Tuberculosis is a chronic infectious disease caused by various strains of Mycobacterium tuberculosis which is an acid-fast aerobic bacillus. It is transmitted via the respiratory route. It mainly affects the lungs but can spread through blood stream and lymphatic system to the brain, bones, eyes and skin. It mainly affects the lungs and causes severe coughing, fever, and chest pains. With the rising prevalence of drug-resistant and inactive Tuberculosis, there is an essential need to discover more effective molecules capable of combating this heinous illness. The World Health Organization has recently approved a revision of the classification of new anti-TB drugs based on current evidence on each drug. The choice of drugs was based on efficacy and toxicity in a step-down manner. The World Health Organization has regularly evaluated new evidence on the use of specific drug compositions and combinations of regimens of different durations. Most recently, new evidence has resulted in a major breakthrough in the treatment that can be recommended for people with multidrug resistance tuberculosis and extremely drug resistance tuberculosis. Owing to the pressing need for more effective treatment regimens for people with multidrug resistance tuberculosis, various studies and initiatives to test more effective and novel treatment regimens, including newer and repurposed medicines. This article review the possible future evolutions in antitubercular drugs.

Key words: Antitubercular drugs, tuberculosis, muti drug resistance, infection.

Running Title: Recent Advances in Antitubercular drugs.

INTRODUCTION

Tuberculosis (TB) is an infectious disease caused by bacteria that most often affects the lungs. It spreads through the air when people with TB cough, sneeze or spit. Tuberculosis is preventable and curable. Those who are infected but free of disease cannot transmit it. TB disease is usually treated with antibiotics and can be fatal without treatment. The patient with active tuberculosis having symptoms such as cough that lasts more than three weeks, especially one that produces phlegm or blood, pain in the chest, unexplained weight loss, high temperature, sweating at night, feeling tired or exhausted, loss of appetite, firm, red, or purple swellings under the skin, rash on the face, legs, or other parts of the body, headache, especially if TB has spread to the brain, feeling confused, especially if TB has spread to the brain, back pain, especially if TB has spread to the spine, hoarseness, especially if TB has spread to the larynx, blood in the urine, especially if TB has spread to the kidney and dark or cloudy urine [1].

The WHO has recently updated the classification of new antituberculosis drugs which is based on a meta-analysis and expert panel recommendations [2]. The classification of antituberculosis drugs is important as it helps the clinician to build an appropriate antituberculosis regimen for multi drug resistant and extensively drug-resistant cases that do not fulfil the criteria for the shorter multi drug resistant tuberculosis regimen [3,4]. The aim of this viewpoint article is to describe the evolution in WHO TB and recent changes in WHO guidance, while commenting on the differences between them. The latest evidence on the ex-group 5 drugs is also discussed.

The rationale basis of antituberculosis treatment is that the historical principles, derived from randomized clinical trials are still valid which encompasses combining different effective drugs to prevent the selection of resistant mutants of mycobacterium tuberculosis; and also prolonging the treatment to sterilize the infected tissues and, therefore, prevent relapse [5,6,7]. At least four drugs likely to be effective compose the regimen, of which at least two are essential core drugs whereas two are companion drugs [8]. The core drugs are those with the capacity to kill mycobacterium tuberculosis in any of its metabolic phases. In contrast, the role of the companion drugs is to support the core ones, protecting their action and avoiding selection of further resistance. Whilst one of the core drugs should have a good bactericidal activity, the other should have a good sterilizing activity, and they need to be maintained for the entire duration of treatment. While bactericidal drugs efficiently reduce the bulk of the rapidly multiplying bacilli (decreasing infectiousness and avoiding the disease's progression), sterilizing drugs take care of the population of dormant and semi-dormant bacilli, allowing cure and preventing relapse.

The newer drugs/ regimen in needed as there are multiple problems associated with the current drug regimen such as drug resistance, drug interaction of anti-tubercular drugs with ART, long duration of antituberculosis treatment and long duration of treatment of latent tuberculosis. However, the newer drugs/regimen have novel mechanism of action, less drug interaction, more potent and better regimen. The classification of antituberculosis drugs as per WHO classification is mentioned in table 1, table 2 and table 3. The choice of drugs is based on their efficacy and toxicity. The newer drugs with includes

Table 1:-WHO 2011 TB Drugs classification.

WHO 2011 TB Drugs classification	
Group 1 First-line oral antituberculosis drugs	Isoniazid Rifampicin Ethambutol Pyrazinamide Streptomycin Kanamycin Amikacin Capreomycin
Group 2 Injectable anti antituberculosis drugs (injectable or parenteral agents)	
Group 3 Fluoroquinolones	Levofloxacin Moxifloxacin Gatifloxacin Ofloxacin
Group 4 Oral bacteriostatic second-line anti antituberculosis drugs	Ethionamide Prothionamide Cycloserine Terizidone p-Aminosalicylic acid
Group 5 Anti antituberculosis drugs with limited data on efficacy and long-term safety in the treatment of drug-resistant TB	Linezolid Clofazimine Amoxicillin/clavulanate Imipenem/cilastatin Meropenem High-dose isoniazid Thioacetazone Clarithromycin

Table 2: WHO 2016 TB Drugs classification

WHO 2016 TB Drugs classification	
Group A Fluoroquinolones	Levofloxacin Moxifloxacin Gatifloxacin
Group B Second-line injectable agents	Amikacin Capreomycin Kanamycin Streptomycin
Group C Other core second-line agents	Ethionamide/ prothionamide Cycloserine/terizidone Linezolid

	Clofazimine
Group D Add on agents (not core MDR-TB Regimen components)	D1 Pyrazinamide Ethambutol High-dose isoniazid D2 Bedaquiline Delamanid D3 p-Aminosalicylic acid Imipenem–cilastatin Meropenem Amoxicillin–clavulanate Thioacetazone

Table 3: Possible future evolutions in antitubercular drugs

Possible future evolutions in antitubercular drugs	
Group A Fluoroquinolones	Levofloxacin Moxifloxacin Gatifloxacin
Group B Other core second-line agents	Bedaquiline Delamanid Ethionamide/ prothionamide Cycloserine/ terizidone Linezolid Clofazimine
Group C Second-line injectable agents	Amikacin Capreomycin Kanamycin Meropenem
Group D Add-on agents (not core MDR-TB Regimen components)	Pyrazinamide Ethambutol High-dose isoniazid p-Aminosalicylic acid Amoxicillin–clavulanate Rifabutin

Linezolid

Linezolid is a core oral drug. Increasing evidence on its efficacy is accumulating, including meta-analyses and random clinical trials in addition to observational studies. Unfortunately, the current cost and the documented toxicity [9,10] have been a barrier to its wider use. However, the cost of a generic, quality assured compound is decreasing and a recent report suggests that tolerability can be increased lowering the initial dose or adjusting it during treatment [11]. The recommended dosage of the drug is daily unsupervised therapy with linezolid (600mg od/bd), one injectable agent, one fluoroquinolone and two or more other drugs (median of six antimycobacterial agents). Besides linezolid, capreomycin, moxifloxacin, levofloxacin and amoxycillin-clavulanic acid were used in 41.4%, 58.6%, 41.4%, and 79.3% of patients.

Delamanid and bedaquiline

The information on a favourable safety and efficacy profile are accumulating for both delamanid and bedaquiline, including individual use as per existing recommendations, use beyond 6 months and in children and even combined use [12]. Bedaquiline is a core drug, targeting both actively replicating and dormant bacilli. The available evidence includes random clinical trials [13] and observational studies, including experiences from compassionate use programme as well. Bedaquiline accelerates bacteriological conversion while increasing the proportion of converters and the cure rates [13]. The main concern regarding safety of bedaquiline is the unexplained higher number of deaths in the bedaquiline arm of the random clinical trials, as its commonest adverse reaction is the QTc interval increase in the electrocardiogram [13]. Important to mention, its cross-resistance with clofazimine, although recent data seem to indicate it might be non-clinically relevant [14].

Delamanid because of its bactericidal and sterilizing activity, can also be considered a core drug. It does not show cross resistance with other anti-TB drugs and is effective in increasing both bacteriological conversion and treatment outcomes and does reduce mortality. As it also increases QTc, ECG monitoring is necessary likewise bedaquiline.

Recently anecdotal evidence has been provided that both drugs can be given for more than 6 months, that delamanid is safe in children and that the two drugs might be combined [15]. Which drugs might be upgraded Linezolid, bedaquiline and delamanid might be able to change the bleak prognosis of MDR-TB patients with resistance to fluoroquinolones. Linezolid, delamanid and bedaquiline might acquire a more prominent role in multi drug resistance tuberculosis treatment both in adults and in children, given their core drug profile. Under specific conditions delamanid and bedaquiline might be considered for combined use, although further random clinical trials evidence is necessary [16].

Carbapenems

Recently new evidence has been made available on carbapenems, with the profile of a companion drug. Imipenem/cilastatin and meropenem, combined with clavulanic acid, seem to have a promising activity, while being well tolerated [17,18]. In the direct comparison meropenem performs better than imipenem. Initial clinical experience with ertapenem suggests that it can be a valid drug for the home care phase of multi drug resistance tuberculosis treatment, as it can be administered intramuscularly once a day [19]. Important to note that recent evidence suggests this category of drugs might have, in view of its bactericidal activity, the role of a core drug [20].

Shorter regimes of Antituberculosis drugs:

Rifapentine

Rifapentine is known as a rifamycin antibiotic. It works by stopping the growth of bacteria. This antibiotic treats only bacterial infections. It will not work for viral infections. Using any antibiotic when it is not needed can cause it to not work for future infections. This medication is used with other medications to treat active tuberculosis of the lungs. It may also be used with another medication (isoniazid) to prevent active tuberculosis infections in people who are infected with the bacteria (people with positive tuberculosis skin test). The side effects of the drug includes **s**tomach upset, nausea, vomiting, loss of appetite, or headache. If any of these effects last or get worse, the consultation with doctor is recommended. This medication may also cause urine, sweat, saliva, or tears to turn reddish. This effect is harmless and will disappear when the medication is stopped. The recommended dosage is once weekly dosing: Half-life of rifapentine (active metabolite) vs rifampicin is 13to 24 hours vs 2-3 hours [21].

Moxi/Gatifloxacin

Moxifloxacin is active in patients with pulmonary tuberculosis with positive sputum smears. In various studies the authors believed that moxifloxacin was significantly less active than isoniazid when the time to reduce the viable bacillus count by 50%. This drug has faster culture conversion rates compared to conventional regimes in animal studies and human pilot studies. Early bactericidal activity of moxifloxacin was comparable to that of isoniazid [22,23].

Pyrazinamide

Pyrazinamide is a bio-isomer of nicotinamide. Use: It is a secondary tuberculostatic agent used in combination with other antitubercular drugs. It is an essential component of combination therapy. Pyrazinamide is a first-line tuberculosis therapy that shortens prophylactic duration from twelve to six months. The majority of presently used tuberculosis medications were found by a mix of serendipity and innovative chemical alterations of an existing lead drug. Given that the majority of these discoveries occurred years ago, there is a definite need to use fresh methodologies and technology for discovery to meet the grave danger posed by tuberculosis and the rise of treatment resistance strains [24].

Ethambutol Hydrochloride

Ethambutol is 200 to 500 fold more active than its enatiomer. It is used as a tuberculostatic drug that is effective against tubercle bacilli resistant to isoniazid or streptomycin. However, due to the high toxicity of the drug, it is less choice of preference by the clinician [25].

Ethionamide

Ethionamide is an important second line antituberculosis drug used for the treatment of patients infected with multidrug-resistant Mycobacterium. Although ethionamide is a structural analogue of isoniazid, both are pro-drugs that need to be activated by mycobacterial enzymes to exert their antimicrobial activity. Ethionamide mechanism of action is thought to be identical to isoniazid although the pathway of activation is distinct from that of isoniazid. Ethionamide is activated by an EthA enzyme, leading to the formation of an Soxide metabolite that has considerably better activity than the parent drug. The drug is less potent and more toxic than isoniazid, so its general use should be avoided. It should be used only when the usual combination of Streptomycin, and isoniazid are ineffective or cannot be tolerated [26].

Cycloserine

It is an antibiotic, isolated from *Streptomyces* species. The compound slowly dimerizes on standing or in solution. It is useful in the therapy of tuberculosis resistant to other drugs. It is always combined with another anti-tubercular drug. Limited pharmacokinetic/pharmacodynamic (PK/PD) data exist on cycloserine in tuberculosis patients [27].

Future scenarios

Further studies are also necessary to establish if high dose moxifloxacin, and rifabutin, might play a future role multi drug resistance tuberculosis in the armamentarium. We hope that further evidence will be accompanied by decreasing

costs of these compounds; the recent inclusion of both of them in the Global Drug Facility list of prequalified drugs is encouraging.

CONCLUSION

In conclusion, the WHO has recently provided an important and useful evidence-based new classification of antituberculosis drugs, which is the present roadmap allowing clinicians to correctly design safer and more effective multidrug resistant and extensively drug resistance tuberculosis treatment regimens. As more evidence becomes available, further changes are likely to occur, particularly with the new drugs and some of the previous group drugs. It is hoped that ongoing random clinical trials will soon provide the necessary information to further improve the clinical and programmatic approach to the management of multidrug resistant and extensively drug resistance tuberculosis cases.

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