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A REVIEW ON NEW DRUG DEVELOPMENT AND TREATMENT REGIMEN OF TUBERCULOSIS

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ABSTRACT

Tuberculosis (TB) is an infectious disease usually caused mycobacterium tuberculosis bacteria (MTB). TB generally affects the lungs, but can also affect other part of the body. TB is spread through the air when people who have active TB in their lungs cough, spit, speaks or sneeze. Tuberculosis has been a leading cause of death for more than a century. Treatment is long and difficult, commonly used drug for TB are; A 4-month chemotherapy regimen using a combination of 4 drug (rifampicin, isoniazid, ethambutol and pyrzinamide for 2 months, followed rifampicin and isoniazd for 4 months) with cure rates of approximately 90% in human. But there is some problems related to above treatment. isoniazid has very serious liver disease increased in people who are 35 years and older, who use alcohol or illegal injection drugs, rifampicin has a problem of immune-allergic reaction, ethambutol cause ocular toxicity and pyrazinamide has only substantial side effect.

Because of these problems, there are new drugs and treatment regimens are developed.

1) Bedaquiline-inhibiting mycobacterium ATP Synthase.
2) Nitroimidazoles-potent activity against drug sensitive and drug resistant TB.
3) Sequella-block cell wall synthesis.
4) Oxazolidinones-protein synthesis inhibitor.

Novel combination are being tested together rather than each drug sequencially, with the goal of dramatically shortening the time and expense associated with development of new regimens. New TB drugs are needed because of the complexity and toxicity of the current TB drug regimens so there is an urgent need for new TB drug.

INDRODUCTION

Tuberculosis(TB) is an infectious disease characterized by the growth of nodules(tubercles) in the tissue, especially the lungs. TB is caused by a type of bacterium called myctobacterium tuberculosis. TB commonly presents as a disease of the lungs. This means that you can develop tuberculosis in the pleura(the covering of the lungs), in the bones, the urinary tract and sexual organs, the infection can spread via blood from the lungs to other organs in the body.[1]

Tuberculosis(TB) is an important public health problem world wide. In industrialized countries, the numbers of reported cases leveled out in the mid to late 1980s and then started increasing. This increasing also occurred in countries across all countinents, l eading the world health organization (WHO) to declare tuberculosis is aglobal emergency in 1993.

Additonal concern regarding the increase in multidrug-resistant tuberculosis, with outbreaks in different parts of the world this has been attributed to both human immunodeficiency virus(HIV) infection and inappropriate or inadequate treatment.

Adequate and effective treatment is essential, both clinically for patients and to control the spread of tuberculosis. The success of this depends on close collaboration between clinical and public health teams, Current treatment of tuberculosis (TB) is based on drugs that are more than 40 years old. Despite a demonstrated high efficacy in clinical trials[2], standardized short-course chemotherapy (SCC) of active drug-susceptible TB requires direct supervision to assure good adherence and prevent drug resistance.[3] Drugs that are active against resistant forms of TB are less potent, more toxic, and need to be taken for a long time (18 months). The recent emergence of virtually untreatable extensively drug-resistant TB (XDR-TB) poses a new threat to TB control worldwide. Furthermore, effective treatment of TB in persons coinfected with HIV is complicated due to drug–drug interactions. Shorter and simpler regimens that are safe, well tolerated, effective against drug-susceptible and drug-resistant TB, appropriate for joint HIV–TB treatment, and amenable to routine programmatic conditions are needed urgently. In the present paper, I review the problems related to current

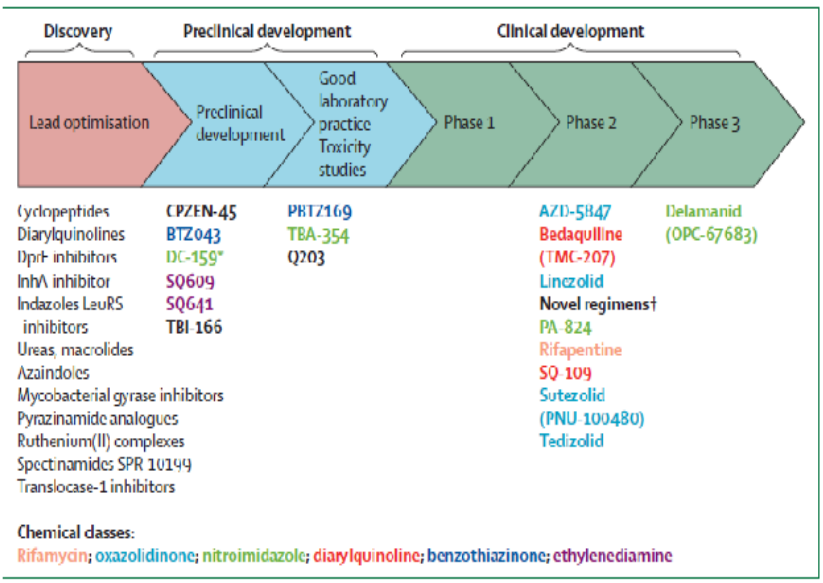
treatment of TB and its variants, and discuss recent advances in the development of new drugs and new regimens for the treatment of drug-susceptible and drug-resistant TB.

The number of new cases of multidrug-resistant(MDR) tuberculosis(caused by mycobacterium tuberculosis strains resistant to atleast rifampicin and isoniazid) and of extensively drug-resistant (XDR) tuberculosis (defined by resistance to rifampicin, isoniazid, plus fluoroquilonone and atleast one of the three injectable second-line tuberculosis drugs, amikacin, kanamycin and capreomycin) continue to increase.[4] An estimated 480000 new cases of MDR tuberculosis occurred in 2013, making up 3.5% of the estimated 9 million people who developed tuberculosis that year, only 97000 started treatment and 39000 were on waiting lists, thus leaving a huge number of people untreated. Treatment succecc rates for MDR tuberculosis regimens are still low for both individualized and standard regimens, resulting in high death rates.[5] MDR and XDR tuberculosis now greatly complicated patient management, particularly in resource-poor national tuberculosis programmes.[6]

The dismal treatment outcomes of MDR and XDR Tuberculosis highlight the urgent need for development of new anti tuberculosis drugs, treatment regiments and other adjunct treatment approaches to improve treatment outcomes.[7]

The review is the latest WHO guidelines and global recommendations for treatment and management of drug-sensitive and drug-resistant tuberculosis.

METHODS



Drug development and treatment trials

New drugs

Figure 2 shows the present tuberculosis drug developmental pipeline. For the fi rst time in more than 50 years, two new tuberculosis drugs, delamanid and bedaquiline,[8-12] have been approved by the US and European regulatory authorities and are now recommended by WHO for use as part of combination therapy for MDR tuberculosis. In 2013, the European Medicines Agency (EMA) approved conditional marketing authorisation for use of delamanid in adults with MDR tuberculosis as an addition to a background treatment regimen designed as per WHO recommendations.[13,14] In 2014, the EMA granted conditional marketing authorisation for bedaquiline on the same principles. WHO have put in place policy guidance for safe and rational use of bedaquiline and delamanid to treat MDR tuberculosis.6 The fi rst evidence on the eff ectiveness of delamanid was provided by Gler and colleagues, 30 who showed that this new drug, in combination with a background regimen developed according to WHO guidelines, 3,5 is associated with an increased sputum culture conversion at 2 months in patients with MDR tuberculosis. Another study31 showed effi cacy of delamanid in MDR cases and its ability to reduce mortality in these diffi cult-to-treat cases, and more recently the drug was used to treat XDR tuberculosis in a child.33 The efficacy and safety of bedaquiline was assessed in a phase 2b trial with a 2-year follow-up of 47 patients with MDR disease. 34 The proportion of adverse events was low, with the only exception being nausea.

In this trial, 34 bedaquiline added to the background regimen reduced the median time to culture conversion, compared with placebo, from 125 days to 83 days (hazard ratio in the bedaquiline group, 2 · 44; 95% CI 1 · 57–3 · 80, p<0 · 001 by Cox regression analysis) and increased the rate of culture conversion at 24 weeks (79% vs 58%, p=0 · 008) and at 120 weeks (62% vs 44%, p=0 · 04). The overall incidence of adverse events was similar in the two groups, with ten deaths in the bedaquiline group and two in the placebo group, with no identifi ed relation with the study drug.34

In terms of new regimens, Diacon and colleagues32,35 assessed the 14-day early bactericidal activity of a regimen composed of pretomanid (previously known as Pa-824), moxifl oxacin, and pyrazinamide, which proved to be signifi cantly higher than that of bedaquiline alone, bedaquiline plus pyrazinamide, bedaquiline plus pretomanid, but not to pretomanid plus pyrazinamide and comparable to that of the standard treatment regimen (isoniazid,

rifampicin, and pyrazinamide with streptomycin or ethambutol). An additional, important fi nding of the study is that the addition of pyrazinamide increased the activity of both bedaquiline and pretomanid.

This innovative method, which is able to test several drugs at the same time, opened the way to a new approach in antituberculosis treatment, proposing a universal regimen that would be equally eff ective on drug-susceptible and MDR strains.33 Because rifampicin was not part of the regimen, interactions with antiretroviral drugs are not expected, which solves one of the major clinical problems in treatment of individuals with both HIV and tuberculosis.

A phase 2b trial36 compared the bactericidal activity of an 8-week regimen composed of moxifl oxacin, pretomanid, and pyrazinamide (MPa100Z or MPa200Z) with the standard antituberculosis regimen for drug-susceptible tuberculosis in sputum smear-positive patients with drugsusceptible and drug-resistant tuberculosis.

The bactericidal activity in drug-susceptible cases was significantly higher compared with that of the WHOrecommended regimen after 2 months of treatment. The experimental treatment was well tolerated and no cardiotoxicity episode of QT interval exceeding 500 ms was identifi ed.36 Bedaquiline is associated with sudden unexpected death and mortality data appear in the product label including a boxed warning. The use of bedaquiline is therefore limited to patients with MDR tuberculosis for whom resistance to several other drugs necessitates the inclusion of bedaquiline in the treatment regimen.

Search strategy

A computerized search identified peer-reviewed primary research studies reporting fluoroquinolone-resistant or fluoroquinolone-susceptible isolates of M. tuberculosis in which mutations in DNA gyrase geneswere identified. The search was limited to studies in English published between 1 January 1990 and 30 June 2010. Figure S1 (available as Supplementary data at JAC Online) illustrates the study selection methodology. Full text articles were screened using the Medical Literature Analysis and Retrieval System Online (MEDLINE) using the keywords ‘fluoroquinolone resistance’, ‘M. tuberculosis’, ‘gyrA’, ‘gyrB’, ‘DNA gyrase’, ‘mutations’, ‘drug resistance’, ‘fluoroquinolone susceptibility’, ‘second-line drug resistance’, ‘quinolone resistant’ and ‘ofloxacin resistance’ in different combinations. The inclusion criteria consisted of (i) publications in which genotypic susceptibility methods were compared with a solid or liquid-based phenotypic resistance reference standard and (ii) DNA

gyrase gene mutations were identified in M. tuberculosis isolates obtained from human clinical specimens.

Papers were excluded if they were reviews, letters, duplicates or if the title indicated that the studywas not relevant to our study. The online database http://www.tbdreamdb.[15] com was excluded because it is a compilation of mutations previously reported in the literature rather than a primary source document.

Abstracts of the remaining papers were reviewed and studies with irrelevant content were excluded. If the abstract did not provide enough information to include or exclude the article, the entire article was reviewed. Articles were also excluded if they lacked data on amino acid changes or phenotypic susceptibility testing. The bibliographies of the included publications were reviewed, and additional articles not previously identified were added as appropriate.

Data acquisition

Data abstracted from journal articles that met the inclusion criteria were organized in three ways: (i) all mutations reported in gyrA, (ii) all mutations reported in gyrB and (iii) all combinations of mutations (in gyrA and/or gyrB) reported in a single M. tuberculosis isolate. Although substitutions Glu21Gln, Ser95Thr and Gly668Asp in GyrA result in amino acid changes, they were omitted from the summary tables because they are common polymorphisms that do not correlate with drug resistance.[16]

When more than one mutation was observed in one strain (doubl or triple mutation), we noted two scenarios: (i) either mutation was observed as a single mutation elsewhere or (ii) the mutations were never observed independent of one another. In both scenarios, the mutations were listed as single mutations and as multiple mutations. Mutations that were never observed independently of one another are noted in the tables. This process was designed to capture every mutation without undermining the potential effect that combinations of mutations may have on fluoroquinolone resistance. For this review, all of the substitutions in GyrB were standardized to the re-annotated genome numbering system of M. tuberculosis GyrB, where the QRDR of M. tuberculosis GyrB ranges from codon 461 to 499.[17] Regarding the QRDR of GyrA, some publications used the E. coli numbering system to describe substitution location.[18-21] In this systematic review, all substitution locations in GyrA were standardized to the genome M. tuberculosis numbering system, in which the QRDR of GyrA ranges from codon 74 to 113.

We reported the number of clinical isolates tested, the region sequenced (entire gyrA or gyrB genes or only the QRDRs of gyrA or gyrB), along with the genotypic and phenotypic susceptibility methods used to determine fluoroquinolone resistance for each study. The number of isolates containing a specific mutation was determined and the fluoroquinolone MIC associated with thismutation was included if available. Fluoroquinolone activity (measured as 50% inhibitory concentration) against M. tuberculosis with specific DNA gyrase mutants was also reviewed.

Quality Control

Two authors (F. M. and A. W. K.) independently reviewed and abstracted the data. The data were reviewed for accuracy and compared with particular attention to the numbering systems used. Two additional authors (Y. F. van der H. and A. A.) adjudicated differences between the authors and reviewed the data for accuracy.

RESULT AND DISCUSSION

Several new drugs for TB treatment are being evaluated in clinical trials.available data reveal different properties of the agent and provoke speculation about future direction. Higher doses of the rifamycins are promising and may be the first to be implemented in a regimen of shorter duration.

Moxifloxacin and gatifloxacin might shorten TB treatment,possibly in combination with rifamentine.coadministration of moxifloxacin and PA-824 could be active against latent TB.PA-824 and TMC 207 are candidates for arifampin free regimen for treatment of MDR and XDR TB.SQ109 on the other hand, could enhance activity of rifampin containing regimen.

Unfortunately, shorter treatment regimens based on the new agents discussed here are likely to take at least another decade to be fully developed and implemented in clinical practice. since not all new agents will succeed in clinicaly useful regimens, and since only a few drugs are currently in preclinical development,more new agents are needed.

However tretment of TB is long and difficult, the commonly used TB drug have cure rates of aoproximately 90% in human.But there is some problems related this treatment isoniazid has very serious liver disease increased in people who are 35 yr and older, Rifampicin has a

problem of immune-allergic reaction.Ethambutol cause ocular toxicity and pyrazinamide has substantial side effects.

Because of these problems,there are new drugs and treatment regimens are dveloped.

CONCLUSION

Present WHO global guidelines and recommendations are important and provide evidence based principles of TB care in the public an private sections world wide, and ensure that an accurate diagnosis is established and proven acceptable reatment regimens are used under supervision. with the failure of existing drug like flouroquinolone, isoniazid, rifampicin, ethambutol and pyrazinamide etc.

There is a need for shorter and better way of evaluating new TB drug and drug regimens. The history and evaluation of TB drug discovery, development and evaluation of TB drug discovery, development and evaluation has been fascinating over the past 10 years a major investment by scientist, funders and the WHO has led to a renalssance of activity in to new TB drug development and evaluation.

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