

Medical Treatment of Pulmonary Multidrug-Resistant Tuberculosis

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Treatment of multidrug-resistant tuberculosis (MDR-TB) is challenging because of the high toxicity of second-line drugs and the longer treatment duration required compared with drug-susceptible TB. The efficacy of treatment for MDR-TB is poorer than that for drug-susceptible TB. The selection of drugs in MDR-TB is based on previous treatment history, drug susceptibility results, and TB drug resistance patterns in the each region. Recent World Health Organization guidelines recommend the use of least 4 second-line drugs (a newer fluoroquinolone, an injectable agent, prothionamide, and cycloserine or para-aminosalicylic acid) in addition to pyrazinamide. The kanamycin is the initial choice of injectable drugs, and newer fluoroquinolones include levofloxacin and moxifloxacin. For MDR-TB, especially cases that are extensively drug-resistant, group 5 drugs such as linezolid, clofazimine, and amoxicillin/clavulanate need to be included. New agents with novel mechanisms of action that can be given for shorter durations (9-12 months) for MDR-TB are under investigation.

Key Words: Tuberculosis, Multidrug-resistant, Therapeutics, Extensively drug-resistant tuberculosis

Introduction

After the introduction of anti-tubercular drugs, pulmonary tuberculosis (TB) became a medical disease. The treatment outcomes for drug-susceptible pulmonary TB are highly favorable if drug compliance is good. However, the incidence and degree of TB drug resistance are increasing worldwide. Recently, a definition of extensively drug-resistant TB (XDR-TB) was formally adopted, and XDR-TB patients have been found across the globe. The drugs used to treat drug-resistant TB, particularly multidrug-resistant tuberculosis (MDR-TB),

are highly toxic, costly, and require treatment durations of up to 2 years. Significantly, these treatments often lead to disappointing outcomes.

In order to increase treatment success rates, the availability of second-line drugs and education and social support systems are important. To further increase success rates, a rapid and accurate diagnostic method for drug-resistant TB is needed, along with the development of new drugs with novel mechanisms of action that can be given over shorter durations. In this review, we discuss the current state of medical treatment for pulmonary MDR-TB.

Received: September 29, 2013

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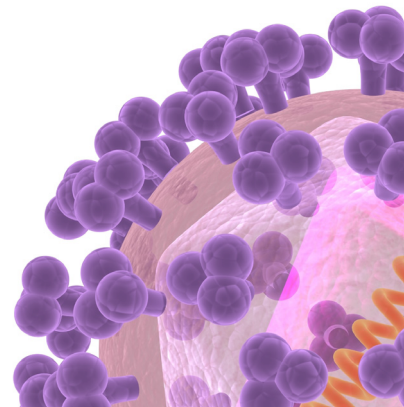
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Hierarchy of anti-TB drugs

Anti-TB agents have traditionally been classified as first- or second-line drugs. However, as the incidence of MDR-TB has increased, these agents have been categorized into 5 groups to assist with drug selection for MDR-TB [1].

Group 1 includes first-line oral drugs such as rifabutin. Group 2 comprises injectable agents including streptomycin (traditionally included as a first-line drug) and kanamycin, capreomycin, and amikacin (previously regarded as second-line drugs). Group 3 consists of fluoroquinolones. However, among these agents, ciprofloxacin is no longer considered to be an anti-TB drug and gatifloxacin is no longer used because of the risk of dysglycemic adverse events. Moxifloxacin and levofloxacin are the newer fluoroquinolones in this group. In an earlier retrospective analysis of 106 patients with MDR-TB, the treatment success rate was higher for the levofloxacin-containing regimen (90.0%) than the ofloxacin-containing regimen (79.7%) [2]. In another retrospective comparison of levofloxacin and moxifloxacin in MDR-TB, both drugs showed equivalent efficacy [3]. In a prospective study of these agents, the choice of levofloxacin or moxifloxacin for the treatment of MDR-TB did not affect sputum culture conversion rates after 3 months of treatment [4]. Group 4 drugs include the conventional second-line anti-TB drugs: prothionamide, cycloserine, and para-aminosalicylic acid. Group 5 includes drugs with unproven efficacy in MDR-TB. These drugs can be used only for patients for whom a regimen with confirmed anti-TB activity is not available.

Regimens for MDR-TB

Updated guidelines now recommend that 4 or more drugs with definite or highly-probable effectiveness against TB should be included in treatment regimens [5]. The selection of TB drugs is structured such that treatment options proceed from group 1 through to group 5. Among the group 1 drugs, pyrazinamide or ethambutol can be selected for MDR-TB cases. However, the World Health Organization (WHO) does not recommend ethambutol, citing its limited efficacy against MDR-TB [5]. The efficacy of rifabutin for MDR-TB is unclear, and this agent is thus not routinely included in MDR-TB regimens.

Having selected the group 1 drugs, 1 injectable group 2 drug should then be selected as part of the regimen. The concomitant use of 2 or more injectable drugs is not recommended. In addition, the WHO does not recommend streptomycin for

MDR-TB because streptomycin-resistance rates are high, as is the frequency of ototoxicity, compared with other injectable drugs [5]. Capreomycin is not available in Korea and can only be purchased from the Korea Orphan Drug Center. Capreomycin is also very expensive. Kanamycin and amikacin have nearly 100% cross-resistance. Amikacin is usually injected intravenously (even though intramuscular injection is possible), and therefore kanamycin is the drug of choice for MDR-TB in Korea. The WHO recommends kanamycin as the first injectable drug for MDR-TB [5].

Among group 3 drugs, the newer fluoroquinolones are recommended for MDR-TB, with moxifloxacin or high-dose levofloxacin typically being the drugs of choice. A recent Korean randomized study has revealed that moxifloxacin and levofloxacin have comparable efficacy in terms of 3-month culture conversion rates and adverse events [4]. The concomitant use of 2 or more fluoroquinolones is not recommended.

At this stage in the regimen design, only 3 or fewer agents have been selected (pyrazinamide, 1 injectable drug or one fluoroquinolone). Hence, group 4 drugs should also be included in the regimen. In Korea, the available group 4 drugs include prothionamide, cycloserine, and para-aminosalicylic acid. These can be selected on the basis of drug susceptibility results, previous treatment history, and the resistance pattern in the region. Prothionamide is the preferred choice, followed by cycloserine then para-aminosalicylic acid [5]. The WHO has recommended an empirical regimen for MDR-TB comprising pyrazinamide, 1 injectable agent (kanamycin), 1 fluoroquinolone (moxifloxacin or levofloxacin), prothionamide, and either cycloserine or para-aminosalicylic acid (if cycloserine cannot be used). Ethambutol maybe used but is not included in the count of effective drugs [5].

An appropriate regimen cannot be formulated for some MDR-TB patients on the basis of previous anti-TB treatment history, drug susceptibility results, and drug adverse events. In these cases, group 5 drugs should be included in the regimen. Because the efficacy of group 5 drugs is unclear, more than 2 of these agents can be included.

The most important and effective second-line drugs for MDR-TB are the fluoroquinolones, and the most potent and well-known group 5 drug, linezolid, is therefore recommended in cases of fluoroquinolone-resistant MDR-TB or XDR-TB.

Rapid susceptibility testing and selection of drugs

Traditionally, when solid media have been used for culture

and drug susceptibility tests (DST), the DST results only became available 3–4 months after anti-TB treatment initiation. In Korea, DST panels include both first- and second-line drugs. Hence, clinicians can select anti-TB drugs according to DST results as well as the previous anti-TB treatment history. However, the WHO has recently recommended the use of commercial line probe assays for the rapid detection of MDR-TB [6], and clinicians can therefore obtain the DST results for isoniazid and rifampicin within 2–3 days without knowing the results for second-line drugs. In this situation, clinicians should formulate an anti-TB regimen on the basis of previous history of anti-TB treatment, the local area DST pattern, or the index case DST pattern. If the previous history of anti-TB treatment is not available, the empirical regimen should comprise pyrazinamide, 1 newer fluoroquinolone, 1 second-line injectable drug, prothionamide, and cycloserine or para-aminosalicylic acid. In cases of rifampicin mono-resistance detected using a rapid molecular test, the chance of MDR-TB development still exists (because the sensitivity of isoniazid resistance detection by molecular testing is lower than that of rifampicin resistance detection). Thus, rifampicin mono-resistant cases should be regarded as MDR-TB. In these instances, clinicians can add isoniazid to the regimen, but it should not be counted as an effective drug.

With regard to the molecular line probe assay to detect second-line TB drug resistance, too few data on the direct testing of sputum specimens are available to develop policy guidance on its use. Hence, a WHO expert group concluded that because our knowledge of the degree of cross-resistance between second-line injectables for TB is incomplete, the MTB-DRsI assay (Hain Lifescience, Nehren, Germany) cannot be used to identify individual drugs to be used for treatment [7].

Controversial issues

1. Rifabutin treatment of MDR-TB

Although the level of cross-resistance between rifampicin and rifabutin has been reported to be approximately 90% [8, 9], cross-resistance is relatively low in South Korea, with as many as 20–30% of patients showing rifabutin-susceptible MDR-TB by in vitro tests [10, 11]. The rate of cross-resistance between these 2 drugs varies according to mutations in the *rpoB* gene. The rifampicin resistance-determining region, composed of 81-bp nucleoside-containing codons 507 through 533 of the *rpoB* gene, has been proposed as the most frequently mutated region. Among these *rpoB* codons, mutations at codons 526

and 531 are usually found in isolates of *M. tuberculosis* resistant to both rifampicin and rifabutin [12], while mutations at codons 516 and 522 are associated with resistance to rifampicin but susceptibility to rifabutin [13]. According to the findings of a retrospective report with a limited number of patients, rifabutin-containing regimens used for the treatment of patients with rifabutin-susceptible MDR-TB lead to higher success rates than those in control MDR-TB patients infected with TB with identical drug resistance patterns except for that against rifabutin [14]. In Korea, rifabutin is routinely included in the drug susceptibility panel and is usually administered at a dosage of 300 mg/day.

2. Newer fluoroquinolones in the treatment of MDR-TB resistant to older fluoroquinolones

Newer fluoroquinolones, such as levofloxacin and moxifloxacin, have longer serum half-lives, achieve higher peak levels, and have higher volumes of distribution than their older counterparts, such as ofloxacin. In addition, newer fluoroquinolones have lower minimum inhibitory concentrations (MICs) than older fluoroquinolones. Fluoroquinolone resistance mutations in *M. tuberculosis* most commonly occur in the *gyrA* and *gyrB* genes. The quinolone resistance-determining region (QRDR) of *gyrA* is conserved across bacterial species, and is the site at which fluoroquinolone resistance mutations frequently arise; the most common mutations occur at codons 90, 91, and 94 in *M. tuberculosis* [15]. Specific mutations in the QRDR of *gyrA*, particularly at codon 94, have also been associated with higher fluoroquinolone MICs [16, 17].

In an earlier Korean report, in vitro DST results revealed 35 moxifloxacin-susceptible isolates among 63 ofloxacin-resistant *M. tuberculosis* isolates (55.6%) [18]. However, the clinical efficacy of newer fluoroquinolones in the treatment of ofloxacin-resistant MDR-TB has not yet been determined. Regardless, WHO guidelines and other criteria recommend the use of newer fluoroquinolones in MDR-TB regimens [5], and even in patients infected with XDR-TB (fluoroquinolone-resistant) strains. Another recent Korean retrospective study has reported better treatment success rates for moxifloxacin-susceptible and ofloxacin-resistant MDR-TB than for moxifloxacin-resistant and ofloxacin-resistant MDR-TB (72.7% [16/22] vs. 41.7% [20/48], respectively, $P < 0.05$) [19]. To date, no commercial tests have been available to differentiate newer fluoroquinolone-susceptible or resistant TB isolates from ofloxacin-resistant isolates. Hence, in MDR-TB patients without an appropriate number of effective drugs and without a history of treatment failure with fluoroquinolones, newer fluoroquino-

lones may be included in the treatment regimen but should not be counted as effective drugs.

Group 5 drugs

Among the group 5 drugs, linezolid and clofazimine are worthy of mention. Linezolid is a member of the oxazolidinone family of antibiotics and inhibits protein synthesis [20]. It is active against a variety of gram-positive organisms, anaerobes, and atypical microbes. Linezolid has also been found to be active against *M. tuberculosis* in vitro, in animal studies, and in some clinical trials. The usual effective anti-bacterial dose of linezolid is 600 mg twice daily over a maximum recommended duration of 28 days. The problem with its use in anti-TB treatment is the risk of the development of long-term adverse events: the most frequent is peripheral neuropathy, with optic neuropathy and cytopenia also being reported. A recent prospective trial has shown that linezolid is effective for achieving culture conversion among patients with treatment-refractory XDR-TB [21]. Most patients (34 of 39 [87%]) in that study had a negative sputum culture within 6 months of linezolid being included in their treatment regimen. However, of the 38 patients who received linezolid, 31 (82%) had clinically significant adverse events that were possibly or probably related to this antibiotic, and 3 patients discontinued therapy as a result. Patients in this earlier study cohort who received a 300 mg/day linezolid dose after a second randomization had fewer adverse events than those who continued with the 600 mg/day schedule [21]. In another report, treatment of intractable MDR/XDR-TB with linezolid at a daily dose of 300 mg was found to be effective (favorable treatment outcomes, in-

cluding treatment successor still on treatment after culture conversion, occurred in 78% of cases), and was associated with fewer neuropathic side effects than daily dosages of 600 mg/day or 1200 mg/day [22].

Clofazimine is a fat-soluble ruminophenazine dye used in the treatment of leprosy [23]. However, even though clofazimine is listed as a group 5 drug for MDR-TB, its efficacy against this disease is uncertain. In a murine model of MDR-TB, a clofazimine-containing regimen achieved a higher degree of culture conversion after 5 months of second-line drug treatment than a control regimen [24]. Furthermore, in a report from Bangladesh, short-course regimens containing clofazimine showed high efficacy in the treatment of MDR-TB [25]. Skin discoloration is the principal adverse event associated with this antibiotic, and this reaction recovers very slowly owing to clofazimine's long half-life (approximately 70 days) [26]. The optimal dose of clofazimine is not yet established, but in previous clinical studies, it has been used at 100 mg/day in the majority of patients (84.1%). In a Korean study, 32 patients with MDR-TB and additional resistance to ofloxacin (11 with XDR-TB) were treated with clofazimine-containing regimens [27]. The treatment success rate in this series was 48.4% (15/31), and multivariate analysis revealed that both male sex and linezolid use were significant indicators of treatment success. Only 4 patients in this cohort achieved treatment success without linezolid or surgical resection. Nine patients stopped receiving clofazimine owing to adverse events, including skin discoloration (n = 3), hepatotoxicity (n = 3), and gastrointestinal disturbance (n = 3). The authors of that study concluded that clofazimine may be an effective treatment for MDR-TB but that concurrent or subsequent use of linezolid may contribute to treatment success.

Table 1. Group 5 MDR-TB drugs (optimal doses have not been established) [1]

Drugs	Usual doses
Clofazimine	Usual adult dose is 100 mg to 300 mg daily. Some clinicians begin at 300 mg daily and decrease to 100 mg after 4 to 6 weeks.
Linezolid	Usual adult dose is 600 mg twice daily. Most reduce the dose to 600 mg once a day after 4 to 6 weeks to decrease adverse effects.
Amoxicillin/Clavulanate	Dosages for DR-TB not well defined. Normal adult dose 875/125 mg twice a day or 500/125 mg three times a day. Dosages of 1,000/250 have been used but adverse side-effects may limit this dosing.
Thioacetazone	Usual adult dose is 150 mg.
Imipenem/cilastatin	Usual adult dose is 150-1,000 mg IV every 6 hours.
Clarithromycin	Usual adult dose is 500 mg twice daily.
High-dose isoniazid	16-20 mg/kg daily.

Six drugs with antimicrobial activity (phenothiazine, metronidazole, doxycycline, disulfiram, tigecycline, and co-trimoxazole) are not included in the WHO guidelines for MDR-TB treatment but have been proposed as potential candidates for evaluation against *M. tuberculosis* [28]. The optimal doses are not yet known, however (Table 1) [1].

Treatment duration

Traditionally, the recommended treatment duration for MDR-TB has been 18 to 24 months, including a period of 12–18 months after culture conversion. According to a recent meta-analysis of 9,153 MDR-TB patients, an intensive phase of at least 8 months and a total duration of at least 20 months is recommended in patients without any previous MDR-TB treatment [5]. However, such durations present problems in terms of costs and adverse events. Recently, Van Deun et al [25], reported successful treatment outcomes in an MDR-TB cohort from Bangladesh using a 9-month regimen. In that study, 206 patients with MDR-TB who had not been treated previously with second-line drugs were enrolled. They received an intensive treatment phase of at least 4 months' duration involving gatifloxacin, clofazimine, ethambutol, pyrazinamide, kanamycin, and high-dose isoniazid, and a 5-month maintenance phase with gatifloxacin, clofazimine, ethambutol, and pyrazinamide. The relapse-free cure rate was 87.9% in this patient

series. Several subsequent studies have also reported successful treatment outcomes for MDR-TB with 9–12-month short-course treatments.

The STREAM trial (Standardized Treatment Regimen of Anti-TB drugs for patients with MDR-TB) has been initiated, and will test a 9-month MDR-TB treatment regimen. In the aforementioned Bangladesh study, the drug resistance rates for ofloxacin and kanamycin were 10.3% and 0%, respectively; the rates were slightly higher (16.6% and 13.3%, respectively) among 1,407 patients with MDR-TB in a Korean series [29]. Recent guidelines for MDR-TB therapy published by the International Union Against Tuberculosis and Lung Disease recommend the 9-month Bangladesh regimen for MDR-TB cases showing susceptibility to fluoroquinolones and injectable drugs [30].

Treatment of XDR-TB and beyond

Theoretically, patients with XDR-TB are resistant to at least 1 fluoroquinolone and 1 second-line injectable drug. However, our knowledge of the cross-resistance patterns between drugs in a given class is not complete. The acquisition of resistance to streptomycin and second-line injectable drugs is derived from different gene mutations. Streptomycin susceptibility was found to be an important predictor of favorable long-term survival in patients with pre-XDR-TB [31, 32]. Hence, other second-line injectable drugs or streptomycin could be select-

Table 2. Classes of drugs with anti-tuberculosis activity reported in clinical studies [37]

Class	Drug(s)	Mechanism of action
Diarylquinoline	Bedaquiline	Interferes with how bacterial cells make energy by targeting the proton pump adenosine triphosphate synthase.
Ethylenediamine	SQ109	Disrupts bacterial cell-wall construction by disturbing the assembly of mycolic acids, possibly by targeting the MmpL3 protein; in vitro activity has yet to be confirmed in humans.
Fluoroquinolone	Gatifloxacin, levofloxacin, moxifloxacin, ofloxacin	Disrupts bacterial replication by inhibiting the DNA gyrase enzyme, thus preventing bacterial DNA from unwinding and duplicating.
Nitroimidazole	Delamanid, PA-824, TBA354 (preclinical)	Destabilizes the bacterial cell membrane by blocking the synthesis of mycolic acids; poisons the bacterial cell by releasing nitric oxide when metabolized.
Oxazolidinone	AZD5847, linezolid, sutezolid, tedizolid (for MRSA)	Blocks protein synthesis (translation) by inhibiting the initiation step at the ribosome.
Rifamycin	Rifabutin, rifampicin, rifapentine	Blocks messenger RNA synthesis (transcription) by inhibiting the bacterial DNA-dependent RNA polymerase.
Riminophenazine	Clofazimine	Unclear, but it appears that the bacterium's ineffective attempts to metabolize drug lead to cycle (redox cycle), which generates toxic reactive oxygen species within the bacteria; may target the bacterium's outer membrane by inhibiting the bacterial respiratory chain and ion transporters.

ed in TB regimens. Because newer generation fluoroquinolones may be effective against ofloxacin-resistant strains [19], these agents can also be selected for the treatment of XDR-TB if there is no previous history of treatment failure with this class of drug. Currently, the most potent drug in group 5 is linezolid, and it should thus always be included in XDR-TB regimens (clofazimine should be included when linezolid is not available). Surgical resection should also be considered to maximize the effects of drug treatment. Two Korean studies have reported treatment success rates for XDR-TB of 67% and 53.5%, respectively [33, 34].

New drugs for MDR-TB

In December 2012, the US FDA approved diarylquinoline as a new drug for MDR-TB [35]. Delamanid is already in phase II trials [36]. However, as anti-TB drugs are given in combination to overcome drug resistance, further studies of optimal companion drugs are needed. A 2013 pipeline report by the Treatment Action Group has highlighted drugs with anti-TB activity from various clinical studies, and these are listed in Table 2 [37].

Conclusion

Even though treatment success rates for MDR-TB are currently disappointing, the appropriate and considered use of current TB drugs can achieve 70–80% treatment success rates in MDR-TB. In selected patients with MDR-TB, rates can even be increased up to 80–90% by combining surgical resection with medications. In intractable cases of MDR-TB and in patients with XDR-TB, group 5 drugs such as linezolid and clofazimine may improve treatment success rates. It is hoped that new drugs with novel mechanisms of action, and that are effective even short durations of therapy, may significantly ameliorate the worldwide TB epidemic.

Conflicts of interest

No conflicts of interest.

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