

Recent Advances in Effective Management of Patients with Multidrug-Resistant Tuberculosis (MDR-TB)

Suhail Ahmad

Department of Microbiology, Faculty of Medicine, Health Sciences Center, Kuwait University, Kuwait

EDITORIAL

Tuberculosis (TB) is a major infectious disease worldwide. Most active TB disease cases in humans are caused by *Mycobacterium tuberculosis* [1]. Some cases in Africa are caused by *Mycobacterium africanum* while *Mycobacterium bovis* (bovine bacillus) can also cause TB in individuals who consume unpasteurized milk [1,2]. The global burden of TB is still enormous. According to the World Health Organization (WHO), an estimated 10 million new active TB diseases cases and 1.451 million deaths occurred in 2018, making TB as one of the top 10 killers and the leading cause of death from a single infectious agent [3]. Near 87% of TB cases occurred in 30 high TB burden countries and two-third of all cases in only eight (India, China, Indonesia, Philippines, Pakistan, Nigeria, Bangladesh and South Africa) countries [3]. Most active TB disease cases in high TB burden countries occur as a result of recent infection/reinfection while in low TB incidence countries, they usually arise as a result of reactivation of latent infection, acquired few to several years earlier [2,4,5].

Most TB deaths recorded in recent years have been attributed to emergence of drug-resistant TB, particularly multidrug-resistant (MDR)-TB (defined as infection with *M. tuberculosis* strain resistant at least to rifampicin and isoniazid, the two most effective first-line drugs) [6]. Worldwide, 484000 people developed TB in 2018 that was resistant to rifampicin, and of these, nearly 378000 (78%) were MDR-TB cases [3]. Compared to drug-susceptible TB, treatment of MDR-TB in resource-limited settings is difficult due to lengthy, more expensive and more toxic regimens and leads to higher rates of clinical failure or disease relapse [6,7]. MDR-TB is also a risk factor for the development of extensively drug-resistant TB (XDR-TB), infection with MDR-TB strains additionally resistant to a fluoroquinolone and an injectable anti-TB drug, which is even more difficult to treat than MDR-TB [6,7]. Treatment success rates for susceptible TB, MDR-TB and XDR-TB are estimated as nearly 85%, 56% and 39%, respectively [3]. Rapid accurate diagnosis and effective treatment are crucial for proper management, which will also limit further transmission of MDR-TB and evolution of XDR-TB [6-10].

Recent availability of two anti-TB drugs, bedaquiline and delamanid, has resulted in re-classification of available drugs which are now categorized into four groups (Group A to Group D) specifically for the treatment of MDR-TB and to prevent development of XDR-TB [11]. Other first-line drugs (pyrazinamide, ethambutol and possibly high-dose isoniazid and rifampin and/or rifabutin) have a minor role as a subclass of Group D agents mainly due to problems associated with accurate phenotypic drug susceptibility testing (DST) for these drugs [11].

Group A includes fluoroquinolones with bactericidal and sterilizing activity (moxifloxacin, gatifloxacin or high-dose levofloxacin). They are preferred over injectable agents since their use is associated with a favorable outcome [11]. Group B includes amikacin, kanamycin and capreomycin (injectable drugs) which are bactericidal but lack sterilizing activity. In future, Group B may include three oral drugs; linezolid (or their derivatives sutezolid or tedizolid), bedaquiline and delamanid, if their use is more effective and less toxic than injectables [11,12]. Group C currently includes second-line oral drugs; linezolid, clofazimine, ethionamide, prothionamide, cycloserine and terizidone [11]. Linezolid is bactericidal with sterilizing action and its toxicity can be mitigated by dose reduction [12]. Clofazimine has sterilizing activity while ethionamide/prothionamide exhibit some bactericidal activity but are also toxic [11].

Group D drugs are divided into three sub-groups; D1, D2 and D3. Group D1 includes pyrazinamide and ethambutol provided they are likely to be effective [13,14]. High-dose isoniazid may be used for *M. tuberculosis* isolates with mutations that confer low-level resistance to isoniazid [6,15]. Similarly, rifabutin may be used if *M. tuberculosis* isolates are susceptible to rifabutin [11,16]. Group D2 includes bedaquiline and delamanid that are bactericidal with sterilizing activity and have also been used simultaneously [8,17]. Group D3 includes p-aminosalicylic acid, thiacetazone, amoxicillin-clavulanate, imipenem-clavulanate and meropenem-clavulanate some of which are toxic [11]. The meropenem/clavulanate is bactericidal and may be used as a core drug for pre-XDR/XDR-TB cases with resistance to injectable drugs [11,18].

Correspondence to: Suhail Ahmad, Department of Microbiology, Faculty of Medicine, Health Sciences Center, Kuwait University, Kuwait, Tel: 00965-24636503; E-mail: suhail_ah@hsc.edu.kw

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Patients with MDR-TB should be treated with at least five effective drugs during the intensive phase and the regimens should include pyrazinamide and four core drugs including one each from Group A and B and at least 2 drugs from Group C [11]. Other first-line drugs (ethambutol, high-dose isoniazid and/or rifabutin) may be used based on drug resistance profile. An agent from Group D2 or other agents from Group D3 may be added if sufficient numbers of effective drugs are not available. If genotypic testing indicates resistance to pyrazinamide or if it cannot be used due to toxicity concerns, drug regimens may be reinforced with a drug from Group C or D2 or from Group D3 [11]. The drugs should be carefully chosen for maximum benefits and minimum risk of adverse reactions and non-adherence. Recognizing and promptly managing adverse drug reactions in the treatment of MDR-TB should be a priority [3,11]. Culture conversion within 6 months of treatment is achieved in 80% of MDR-TB patients receiving delamanid as part of a multidrug regimen [19].

A shorter and cheaper 'Bangladesh regimen' of 9-months duration was recommended for male and female (if not pregnant) MDR-TB patients who do not have extrapulmonary TB, previous exposure to second-line drugs or resistance to pyrazinamide, ethambutol, kanamycin, moxifloxacin, ethionamide, or clofazimine [11,20]. This regimen originally included 4-months intensive phase with high-dose gatifloxacin, pyrazinamide, ethambutol, clofazimine, kanamycin, prothionamide and isoniazid and 5-months continuation phase with high-dose gatifloxacin, pyrazinamide, ethambutol, clofazimine with treatment success rate of nearly 90% [11,20]. However, gatifloxacin which played a central role in its success was recently withdrawn from the market due to toxicity concerns (dysglycaemia). The regimen has now been revised (and recommended by WHO) with moxifloxacin replacing gatifloxacin. It includes an initial phase of 4-6 months of treatment with pyrazinamide, kanamycin, moxifloxacin, prothionamide, clofazimine, high-dose isoniazid and ethambutol followed by 5 months of continuation phase with pyrazinamide, kanamycin, moxifloxacin and ethambutol [11,21]. However, in the USA, only 59 (10%) of 586 MDR-TB cases were eligible for the shorter regimen as MDR-TB isolates from most patients for whom full DST profiles were available were resistant to ethambutol and pyrazinamide [22]. It is pertinent to mention here that gatifloxacin was recently shown to be superior to levofloxacin- or moxifloxacin-based shorter regimens renewing the call for reintroduction of this efficacious, effective and inexpensive drug [23].

Individualized MDR-TB treatment with carefully chosen (such as bedaquiline, linezolid, clofazimine or meropenem) drugs and guided by genotypic and phenotypic DST can improve treatment outcomes [7,8]. Treatment success rate for MDR-TB depends heavily on resistance to additional drugs and is lower for MDR-TB strains with additional resistance to fluoroquinolones alone than for those with resistance to second-line injectable drugs only [7,8]. In fact, an injection-free MDR-TB treatment regimen is now recommended in which kanamycin and capreomycin are not recommended at all. These regimens are also based on safety and mortality benefits of bedaquiline, the observations that the 9-11 month injectable-based 'Bangladesh' regimen was non-

inferior to longer regimens, and promising interim results of a novel 6 month 3-drug regimen comprising bedaquiline, pretomanid, and linezolid [8,24].

Clinical trials are evaluating 6-month oral regimens to simplify management and improve outcome of patients with MDR-TB [7,8,11]. Three oral medicines (levofloxacin or moxifloxacin, bedaquiline and linezolid) are strongly recommended to be used in a longer individualized regimen together with other medicines ranked by a relative balance of benefits to harms to complete the regimen [7,11]. Most individualized MDR-TB regimens would include at least four agents likely to be effective in the first 6 months and three thereafter for a total duration of 18-20 months, modified depending upon patient response. The standardised, shorter MDR-TB regimen lasting for 9-12 months may also be offered to eligible patients though it may be less effective than an individualized longer regimen and will require a daily injectable agent (amikacin or meropenem/clavulanate) for at least four months [7,11,24]. Also, monitoring MDR-TB regimens with monthly culture and sputum microscopy rather than smear microscopy alone offers the best option to detect a failing regimen in time for corrective action [7].

The selection and optimal number of drugs and their route of administration, duration of the regimen and other desirable standards of patient care including recognition and management of adverse drug reactions will improve treatment outcome for MDR-TB. Until the results of all-oral long and modified all-oral short regimens are available, the WHO has recommended that short MDR-TB regimens remain a better treatment option for management of eligible MDR-TB patients in low-income and middle-income countries with monitoring for ototoxicity. Furthermore, National Tuberculosis Programs of high MDR-TB incidence countries are required to strengthen their capacity for detection and management of fluoroquinolone-resistant MDR-TB (pre-XDR-TB) to prevent development of XDR-TB [25].

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