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Drug-Resistant Tuberculosis and Group 5 Anti-Tuberculosis Drugs

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The first case of multi-drug resistant (MDR) tuberculosis (TB) was reported in 1993 in New York City and the next year the World Health Organization (WHO) declared a global TB emergency (1, 2). Two decades later, in 2010, WHO estimated that 650,000 cases of MDR TB have been reported worldwide (3). This was not the end of the explosive process, and estimation of WHO for 2015 was more than 1.3 million people in 27 countries (2). Unfortunately, the world confronted more complications during the 2000s. Reports of extensively drug-resistant TB (XDR) and totally drug-resistant TB (TDR) were published between 2003 and 2006 (2, 4). It seems that nearly 10% of previously diagnosed MDR-TB are indeed XDR-TB. Iran reported that the same proportion of MDR-TB cases is TDR-TB in 2009 (5). However, drug-resistant TB is increasing rapidly; reports on success rate of second-line anti-TB drugs are disappointing. The WHO reported in 2013, around 50% mortality rate and success rate for XDR-TB and MDR-TB (3). The aforementioned unsatisfactory statistics led to new research strategies for other treatment options including previously represented and novel drugs. The WHO has a classification for anti-TB drugs. Drugs that are not recommended for routine treatment due to unclear efficacy are classified as group 5, consisting of clofazimine, linezolid, amoxicillin-clavulanate, carbapenems, thiacetazone and clarithromycin (6). Group 5 is a heterogeneous group with different mechanisms, efficacy, adverse effects and resistance patterns. Nowadays, along-side working on novel drugs including bedaquiline or delamanid and new un-approved agents, the trend of research groups are also towards the usage old drugs that have been formerly presented for other microorganisms.

An exception is clofazimine. The drug had been introduced in 1954 for TB but primary results were not satisfactory (7). Recently, researches have brought hope and new insight for this drug. Van Deun and colleagues reported a 90% success rate for MDR-TB with a clofazimine-containing regimen (8). Gatifloxacin and high-dose isoniazid had been used in this study, thus the noticeable success rate was not solely attributable to clofazimine. Another research in New England journal of medicine (NEJM) in 2009 demonstrated more than 60% positive results for clofazimine in XDR-TB patients (9). Recently, according to the results of a systemic review of studies on the efficacy and safety of clofazimine with 3489 patients, treatment success was an overall pooled proportion of 61.96% (10). Although, optimal dose and duration of use is unclear, it seems that clofazimine could be considered as a salvage regimen for DR-TB. An interesting issue about clofazimine is that after 60 years, the main mechanism against Mycobacterium tuberculosis is unclear. Mechanisms for resistance have not been reported (7). Linezolid, an oxazolidinone antibiotic, is increasingly used for gram-positive bacterial infections. Also, several researches have been published on the efficacy of linezolid for DR-TB. All of them are case series. A recent systemic review, including 11 studies, representing 148 patients, revealed that 67.99% was the pooled proportion for treatment success without significant differences between daily linezolid dose and duration (< 600 and > 600 mg/daily; < 7 and > 7 months) (11). Although linezolid is a useful drug, the most important issue is cost and evident adverse events. At the end of 2012, a clinical trial was published in NEJM and demonstrated that linezolid is effective at achieving culture conversion among patients of the immediate start group with refractory XDR pulmonary TB (79%). The authors declared that the patients must be monitored carefully for adverse events (12). Novel oxazolidinone, including sutezolid, were examined in the phase 2 trial and had promising results for DR-TB. Whether hematologic and neurologic toxicity will be decreased with linezolid is unknown (6). Novel β-lactamase and β-lactam combinations were recently reconsidered as potential treatment options. The WHO recommended amoxicillin-clavulanate (dose of 500 and

125 mg to 1000 and 250 mg orally three times per day) and imipenem (dose of 500–1000 mg intravenously every six hours), yet these recommendations are not supported by clinical trials. Other limitations are that carbapenems are injectable drugs and require multiple doses, and clavulanate is not commercially available in combination with carbapenems (7). Mycobacterium tuberculosis might eventually develop resistance to β-lactam and β-lactamase inhibitor combinations, and even to carbapenems, however, a new study revealed that resistance to β-lactam-β-lactamase inhibitor combinations will likely not arise from structural alteration of BlaC, therefore establishing confidence that this therapeutic modality can be part of a successful treatment regimen against *M. tuberculosis* (13). Another confirmatory data declared that the combination of amoxicillin/clavulanate plus meropenem is active against MDR/XDR-TB in vitro, and this triple therapy could be a useful therapy for MDR/XDR-TB and possibly help to reduce the development of further resistance (14). Macrolides, particularly, clarithromycin have been used successfully to treat non-tuberculous mycobacterial infections, but *M. tuberculosis* has intrinsic and rapidly inducible resistance. Thus, the results regarding the success rate of clarithromycin are not promising and useful effects may be due to in vitro synergism with other first-line drugs and anti-inflammatory properties (7). The main mechanism of thiacetazone, an old anti-TB drug, remains unclear and it is use as a salvage regimen and mostly to prevent resistance to other drugs (7).

Novel drugs have completed several phases of the trial and two agents, delamanid and bedaquiline have received the food and drug administration (FDA) approval for use in XDR and MDR-TB patients. Furthermore, SQ109 and sutezolid seem to be effective drugs. The unresolved issue is drug-drug interactions of the combination of novel drugs with each other and first and second-line agents (2, 6, 7). An article in Lancet Infectious Disease Journal in 2013 estimated that if new drugs replace the current first-line treatment, then existing classifications of resistance might require new classifications and definitions. Consideration of these issues will hopefully now help foster an informed approach to the classification of drug-resistant tuberculosis in the era of new drugs (15). In conclusion, clinical evidence about group 5 anti-TB agents is limited to case series and a few small size trials. In spite of reports on the effectiveness of clofazimine, the main mechanisms of this effect are still unclear. Macrolides, particularly clarithromycin, are not favorable agents because *M. tuberculosis* is intrinsically resistant to clarithromycin. Thiacetazone has potentially serious effects with unresolved issues. Linezolid is an expensive drug and not available in low-income countries. Bone marrow suppression and neuropathy are not infrequent in long-term regimens, although we cannot overlook their efficacy. Beta-lactams, from amoxicillin-clavulanate to carbapenems, are a heterogeneous group. Amoxicillin-clavulanate is an oral agent, but carbapenems are injectable drugs requiring multiple infusions and inpatient settings; they are more expensive than oral agents and needs to be used in combination with clavulanate that is still not available as a single preparation. This means that amoxicillin-clavulanate must be added to carbapenems. Even though carbapenems are usually tolerated by most patients, gastrointestinal side effects of amoxicillin-clavulanate are frequent. To sum up, it seems that group 5 anti-TB agents, mainly clofazimine, beta-lactams and linezolid-probably will be substituted by new oxazolidinones, which are promising to superimpose drug-resistant tuberculosis accompanied by newer agents in these classes and also newer upcoming classes including riminophenazines.

Authors' Contributions

Dr Shokouhi and Dr Alavi Darazam contributed equally in article concept and design, drafting of the manuscript, critical revision of the manuscript.

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