EDITORIAL

GUIDELINES FOR THE TREATMENT OF DRUG RESISTANT TUBERCULOSIS: THE 2018 REVISION

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Tuberculosis has been known to humans since time immemorial.[1] The earliest written records of tuberculosis originate from India and China, dating as far back as 3300 years and 2300 years respectively.[2,3] It is known by many names[4], and is still a deadly disease affecting significant number of people worldwide. According to most recent estimates[5], tuberculosis was diagnosed in 10 million people worldwide in 2017, and deaths attributable to tuberculosis in year 2017 among HIV-negative individuals were 1.3 million. Tuberculosis caused additional 0.3 million deaths among people living with HIV. Two-thirds of cases of tuberculosis in year 2017 were from eight countries and Pakistan contributed 5% of the global burden of tuberculosis in the year 2017.[5] According to the World Health Organization (WHO), Pakistan is among the top 20 countries which collectively contributed 84% and 87% to the world-wide burden of drug-susceptible and drug-resistant tuberculosis respectively in year 2017.[5] Infact, Pakistan contributes 61% of the cases of tuberculosis in the eastern Mediterranean region and has been estimated to have 4th highest burden of muti-drug resistant tuberculosis (MDR-TB) worldwide.[6]

As with most of infectious diseases, drug resistant tuberculosis has become a common clinical entity that is very difficult to treat. In the year 2017, 0.55 million new cases of rifampicin resistant tuberculosis were detected worldwide, of which more than 80% were categorized as MDR-TB.[5] Drug resistant tuberculosis (DRTB) stems from a number of causes[7-9], however, poor compliance with the treatment regimen is the most important and preventable cause of DRTB. In fact the incidence of DRTB in patients treated for tuberculosis is much higher than those not treated for tuberculosis as indicated by the incidence of DRTB in previously treated patients (18% vs 3.5%).[5] This situation warrants improved efforts in urgent / timely diagnosis and treatment of DRTB as the global incidence of DRTB each year is increasing.[5] With a treatment success rate of a little more than 50% for DRTB[5,10], efforts need to be aimed at prevention as well as treatment of DRTB to achieve a proposed 75% success rate for DRTB which was to be achieved by the end of 2015.[11]

The WHO has been leading the efforts aimed at diagnosis and treatment of tuberculosis worldwide. It has been issuing guidelines for the treatment of both drug-susceptible and drug-resistant tuberculosis. Recently, the WHO issued a rapid communication on the treatment of drug resistant tuberculosis. It heralded a new era in the management of drug resistant tuberculosis by taking the injectable drugs out of the equation.[12] According to the announcement, the medicines for use in the long-term regimen for the treatment of multi-drug resistant TB (MDR-TB) have been regrouped into three groups. The first group or Group A consists of fluoroquinolones, bedaquilline and linezolid. The second group or Group B consists of clofazimine and cycloserine or teriozodone (either of the two) and the last group or Group C consists of ethambutol, delamanid, pyrazinamide, meropenem or imipenem-cilastatin (either of the two), amikacin or streptomycin (either of the two), ethionamide or prothionamide (either of the two) and *p*-aminosalicylic acid.[12] This regrouping is significant because the injectable agents, such as amikacin, capreomycin, kanamycin and streptomycin, which were previously considered first line agents for the treatment of DRTB[13], are no longer recommended as the first line agents. Aminoglycosides had been an integral part of the DRTB treatment regimen till now. They were considered first line agents and their inclusion in a regimen was considered to be necessary for the efficacy of the regimen in terms of DRTB cure.[13–15]

Before the current announcement, injectables were usually recommended for at least 8 months in MDR TB and 12 months in XDR-TB.[13] Their use has been associated with considerable toxicity and their use for the treatment of MDR-TB has been questioned.[16] The injectables have to be administered via parenteral routes and this mode of administration is painful and causes distress to the patients in addition to causing a number of significant side effects including but not limited to permanent hearing loss.[17-19] While aminoglycoside-induced hearing loss may rarely develop even after a single dose[20], it is more common in the settings of anti-tuberculosis treatment because they are administered for prolonged period, i.e., months, and because cumulative dose of aminoglycosides has been found to be predictive of hearing loss.[21]

It is heartening to see that the dangers associated with the use of aminoglycosides have at last been realized and they have been taken off the drug regimen. But it is important to note that this decision has only been made possible in the light of success reported with newer agents such as linezolid, bedaquilline and delamanid as well as clofazimine[15,22–26], allowing for a choice of agents and re-structuring of DRTB treatment regimens. Additionally, newer anti TB agents such as

sutezolid and pretomanid are being studied as potential members of future DRTB treatment regimens with hopefully shorter treatment duration, in some cases as short as 6 months.[27–30]

While the detailed guidelines for management of drug resistant tuberculosis are yet to be published, the current recommendation looks good and a giant step towards simplifying the regimen.

This oral drug only regimen will most likely bolster treatment outcome by improving patient compliance and removing obstacles such as a need to access a health care giver for administration of injectables for prolonged periods of time. It is expected that the treatment duration of drug-resistant tuberculosis, particularly rifampicin resistant tuberculosis will be shortened by the approval and inclusion of newer agents. Although it is too early to say what the revised guidelines for the treatment of drug resistant tuberculosis by the WHO will suggest, it can now be said that the era of "better deaf than dead" is finally over.

REFERENCES

1. Barberis I, Bragazzi NL, Galluzzo L, Martini M. The history of tuberculosis: from the first historical records to the isolation of Koch's bacillus. J Prev Med Hyg 2017;58(1):E9–12.
2. Cave AJE, Demonstrator A. The evidence for the incidence of tuberculosis in ancient Egypt. Br J Tuberc 1939;33(3):142–52.
3. Brown L. The Story of Clinical Pulmonary Tuberculosis. 1st ed. Baltimore MD: Williams & Wilkins, 1941; p.411.
4. Frith J. History of Tuberculosis. Part 1-Phthisis, consumption and the White Plague. J Mil Veterans Health 2014;22(2):29–35.
5. WHO. Global tuberculosis report 2018. France: World Health Organization, 2018; p.277.
6. WHO. WHO EMRO | Tuberculosis | Programmes | Pakistan [Internet]. WHO EMRO. [cited 2018 Nov 27]. Available from: http://www.emro.who.int/pak/programmes/stop-tuberculosis.html
7. WHO. What is multidrug-resistant tuberculosis (MDR-TB) and how do we control it? [Internet]. WHO. 2018 [cited 2018 Nov 27]. Available from: http://www.who.int/features/qa/79/en/
8. Centers for Disease Control and prevention (CDC). Drug-Resistant TB [Internet]. CDC. 2017 [cited 2018 Nov 27]. Available from: https://www.cdc.gov/tb/topic/drtb/default.htm
9. Palomino JC, Martin A. Drug Resistance Mechanisms in Mycobacterium tuberculosis. Antibiotics (Basel) 2014;3(3):317–40.
10. Kanabus A. Multi Drug Resistant TB | What is MDR-TB, statistics, treatment [Internet]. TB Facts | TB, tests, drugs, statistics. 2018 [cited 2018 Nov 27]. Available from: https://www.tbfacts.org/multi-drug-resistant-tb/
11. WHO. Communicable Diseases Cluster, Stop TB Department. Towards universal access to diagnosis and treatment of multidrug-resistant and extensively drug-resistant tuberculosis by 2015: WHO progress report 2011. Geneva, Switzerland: World Health Organization; 2011.
12. WHO. Rapid Communication: Key changes to treatment of multidrug- and rifampicin-resistant tuberculosis (MDR/RR-TB). 2018;7.
13. National Tuberculosis Control Program. Handbook of DR-TB practice. National Tuberculosis Control Program Pakistan; 2017.
14. WHO. Global Tuberculosis Programme. WHO treatment guidelines for drug-resistant tuberculosis: 2016 update. Geneva, Switzerland: World Health Organization, 2016; p.58.
15. WHO. World Health Organization. Companion handbook to the WHO guidelines for the programmatic management of drug-resistant tuberculosis. Geneva, Switzerland: World Health Organization; 2014.
16. Reuter A, Tisile P, von Delft D, Cox H, Cox V, Ditiu L, *et al*. The devil we know: is the use of injectable agents for the treatment of MDR-TB justified? Int J Tuberc Lung Dis 2017;21(11):1114–26.
17. Keal JL, Khachi H, Hanzaree E, White VLC. P56 Treatment of multidrug resistant tuberculosis: where are the guidelines for monitoring? Thorax 2011;66(Suppl 4):A91.
18. Shringarpure KS, Isaakidis P, Sagili KD, Baxi RK, Das M, Daftary A. "When Treatment Is More Challenging than the Disease": A Qualitative Study of MDR-TB Patient Retention. PLoS One 2016;11(3):e0150849.
19. Shin SS, Pasechnikov AD, Gelmanova IY, Peremitin GG, Strelis AK, Mishustin S, *et al*. Adverse reactions among patients being treated for MDR-TB in Tomsk, Russia. Int J Tuberc Lung Dis 2007;11(12):1314–20.
20. Guthrie OW. Aminoglycoside induced ototoxicity. Toxicology 2008;249(2-3):91–6.
21. Modongo C, Pasipanodya JG, Zetola NM, Williams SM, Sirugo G, Gumbo T. Amikacin Concentrations Predictive of Ototoxicity in Multidrug-Resistant Tuberculosis Patients. Antimicrob Agents Chemother 2015;59(10):6337–43.
22. Furin J, Brigden G, Lessem E, Rich M, Vaughan L, Lynch S. Global Progress and Challenges in Implementing New Medications for Treating Multidrug-Resistant Tuberculosis. Emerg Infect Dis 2016;22(3):e151430.
23. WHO. The use of delamanid in the treatment of multidrug-resistant tuberculosis: interim policy guidance. World Health Organization; 2014.
24. WHO. A 2016 review of available evidence on the use of bedaquiline in the treatment of multidrug-resistant tuberculosis. Geneva, Switzerland: World Health Organization, 2017; p.52.
25. Lee M, Lee J, Carroll MW, Choi H, Min S, Song T, *et al*. Linezolid for Treatment of Chronic Extensively Drug-Resistant Tuberculosis. N Engl J Med 2012;367(16):1508–18.
26. Tang S, Yao L, Hao X, Zhang X, Liu G, Liu X, *et al*. Efficacy, safety and tolerability of linezolid for the treatment of XDR-TB: a study in China. Eur Respir J 2015;45(1):161–70.
27. Mitnick CD, Rusen ID, Bain LJ, Horsburgh CR. Issues in design and interpretation of MDR-TB clinical trials: report of the first Global MDR-TB Clinical Trials Landscape Meeting. BMC Proc 2015;9(Suppl 8):S1.
28. The TB Alliance. Pretomanid [Internet]. 2018 [cited 2018 Nov 27]. Available from: https://www.tballiance.org/portfolio/compound/pretomanid
29. Silva DR, Dalcolmo M, Tiberi S, Arbex MA, Munoz-Torrico M, Duarte R, *et al*. New and repurposed drugs to treat multidrug- and extensively drug-resistant tuberculosis. J Bras Pneumol 2018;44(2):153–60.
30. Safety and Efficacy of Various Doses and Treatment Durations of Linezolid Plus Bedaquiline and Pretomanid in Participants With Pulmonary TB, XDR-TB, Pre- XDR-TB or Non-responsive/Intolerant MDR-TB (ZeNix) - Full Text View - ClinicalTrials.gov [Internet]. Clinicaltrials.gov. 2017 [cited 2018 Nov 27]. Available from: https://clinicaltrials.gov/ct2/show/NCT03086486

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