

Predictors of Treatment Success for Multidrug Resistant Tuberculosis

Sang Won Park

Department of Internal Medicine, Seoul Metropolitan Government Seoul National University Boramae Medical Center, Seoul National University College of Medicine, Seoul, Korea

After decades of relatively little attention, the field of tuberculosis (TB) research has drawn much attention in recent years. New anti-TB drugs, those already commercially available and others still in the development pipeline, are among the primary drivers of active research, along with commitments from governmental and non-governmental entities for the global eradication of TB. However, many issues remain to be solved, requiring additional attention, resources, and cooperation.

One of the urgent issues regarding TB is multidrug-resistant TB (MDR-TB). MDR-TB is defined as *Mycobacterium tuberculosis* that is resistant to at least isoniazid and rifampin. In 2015, there were estimated 480,000 new cases of MDR-TB, and additional 100,000 cases of RFP-resistant TB. Of the estimated 580,000 patients that are newly eligible for MDR-TB treatment, only 125,000 (20%) were enrolled in treatment programs. Globally, the MDR-TB treatment success rate was 52% in 2013 [1]. In South Korea, 2.7% of new patients with TB and 14% of patients undergoing retreatment of TB were infected with MDR-TB [2], which continues the decrease in incidence since 2012 [3].

For drug-susceptible TB, the standard therapeutic approach includes a combination of four drugs administered for 6-9 months [4]. In patients with MDR-TB, at least five effective anti-TB drugs during intensive phase are recommended, comprising pyrazinamide and four core second-line anti-TB drugs [5]. The suggested timeline of treatment includes the intensive phase for eight months, based on the use of a parenteral agent, a minimum of an additional four months after culture conversion, and a minimum total length of treatment of 18 months after culture conversion. The duration of treatment may be modified according to the patient's response to therapy [6]. Overall, treatment of MDR-TB is more expensive, longer, and more toxic as compared to the relatively short-course treatment for drug-susceptible TB.

In pulmonary TB, conversion of serial sputum culture results from positive to negative is an important indicator of treatment response and infectious state. Culture or smear conversion after 2 months of treatment is widely used as an indicator of treatment effectiveness in drug-susceptible TB.

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Corresponding Author : Sang-Won Park, MD

Department of Internal Medicine, Seoul Metropolitan Government Seoul National University Boramae Medical Center, Seoul National University College of Medicine, 20 Boramae-ro 5-gil, Dongjak-gu, Seoul 07061, Korea

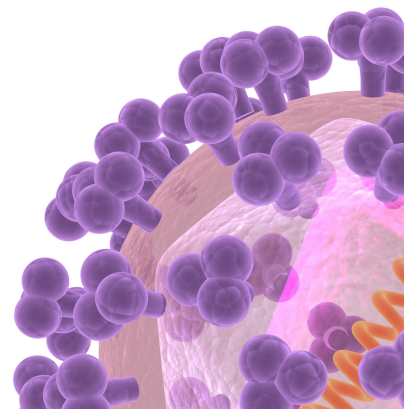
Tel: +82-2-870-2224, Fax: +82-2-870-3863

E-mail: hswon1@snu.ac.kr

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For MDR-TB, clinicians often use culture conversion to determine the duration of treatment with an injectable agent and the overall duration of MDR-TB treatment. The use of sputum smear and culture rather than smear alone is recommended for treatment monitoring of drug-susceptible TB. However, evidence to guide treatment monitoring for MDR-TB is limited. Based on a consensus of expert opinions, the World Health Organization (WHO) guidelines recommend evaluating sputum smear and culture status 6 months after initiation of MDR-TB treatment. Although culture conversion after 6 months of treatment has a high negative predictive value for treatment failure, persistent positive sputum cultures after 6 months of treatment had only a modest positive predictive value. The combined predictive value improved as the number of negative cultures increased at all time points and the combined predictive value of persistent positive cultures was maximized with five cultures after 9 months of treatment [7].

In a report published in this *Infection & Chemotherapy*, Park et al. demonstrated the negative association of body mass index (BMI) on sputum culture conversion after 3 months of treatment in Korean patients with MDR-TB. However, the final outcome was not mentioned: treatment failure or death [8]. TB is a consumptive disease and, as a result, the wasting could result from TB. There is uncertainty about the overall importance of BMI in the treatment of MDR-TB in South Korea owing to its relatively good national health insurance coverage and social welfare system. Further investigation is warranted to elucidate its role.

Previous reports found that a baseline positive sputum smear; baseline resistance to key drugs like pyrazinamide and fluoroquinolones; previous treatment failure or default; and alcoholism were all independent predictors of delayed culture conversion [7, 9]. Previous reports also demonstrated that HIV infection, low BMI, extensive disease, previous treatment with specific drugs, baseline positive smear, resistance to specific drugs, and persistently positive cultures after 3 months of treatment were all independent predictors of death and treatment failure [10].

As the name implies, the core hurdle in adequately treating MDR-TB is drug-resistance. Owing to the limited availability of effective drugs, patients who are identified as having risk factors associated with increased likelihood of death or treatment failure (like low BMI) should receive targeted medical attention. Future studies will be needed to determine whether such treatment improves the time to culture conversion and treatment outcomes.

There are promising new anti-TB drugs on the market, and

more still in the development pipeline. These agents may lead to a paradigm shift in the treatment of MDR-TB and possibly drug-sensitive TB as well. Clinical trials seek to translate the promising results of preclinical trials. However, until then, a multifaceted approach to MDR-TB treatment is essential, and further region-specific research is needed to optimize treatment outcomes.

Conflicts of Interest

No conflicts of interest.

ORCID

Sang Won Park

<http://orcid.org/0000-0002-0550-1897>

References

1. World Health Organization (WHO). Global tuberculosis report 2016. Available at: http://www.who.int/tb/publications/global_report/en/. Accessed 1 December 2016.
2. Bai GH, Park YK, Choi YW, Bai JI, Kim HJ, Chang CL, Lee JK, Kim SJ. Trend of anti-tuberculosis drug resistance in Korea, 1994-2004. *Int J Tuberc Lung Dis* 2007;11:571-6.
3. Park WS, Kang HY, Kim SJ, Cha JO, Son HJ, Park O. Notified tuberculosis status in Korea, 2015. *Public Health Weekly Report* 2016;9:342-5.
4. Nahid P, Dorman SE, Alipanah N, Barry PM, Brozek JL, Catamanchi A, Chaisson LH, Chaisson RE, Daley CL, Grzemska M, Higashi JM, Ho CS, Hopewell PC, Keshavjee SA, Lienhardt C, Menzies R, Merrifield C, Narita M, O'Brien R, Peloquin CA, Raftery A, Saukkonen J, Schaaf HS, Sotgiu G, Starke JR, Migliori GB, Vernon A. Official ATS/CDC/IDSA practice guidelines: treatment of drug-susceptible tuberculosis. *Clin Infect Dis* 2016;63:e147-95.
5. World Health Organization (WHO). WHO treatment guidelines for drug-resistant tuberculosis, 2016 Update. Available at: <http://www.who.int/tb/MDRtBguidelines2016.pdf>. Accessed 1 December 2016.
6. World Health Organization (WHO). Guidelines for the programmatic management of drug-resistant tuberculosis. Available at: http://apps.who.int/iris/bitstream/10665/44597/1/9789241501583_eng.pdf. Accessed 1 December 2016.
7. Kurbatova EV, Gammmino VM, Bayona J, Becerra MC, Danilovitz M, Falzon D, Gelmanova I, Keshavjee S, Leimane V, Mitnick CD, Quelapio MI, Riekstina V, Taylor A, Viiklepp

- P, Zignol M, Cegielski JP. Predictors of sputum culture conversion among patients treated for multidrug-resistant tuberculosis. *Int J Tuberc Lung Dis* 2012;16:1335-43.
8. Park HO, Kim SH, Moon SH, Byun JH, Kim JW, Lee CE, Kim JD, Jang IS, Yang JH. Association between body mass index and sputum culture conversion among South Korean patients with multidrug resistant tuberculosis in a tuberculosis referral hospital. *Infect Chemother* 2016;48:317-23.
9. Velayutham B, Nair D, Kannan T, Padmapriyadarsini C, Sachdeva KS, Bency J, Klinton JS, Haldar S, Khanna A, Jayasankar S, Swaminathan S. Factors associated with sputum culture conversion in multidrug-resistant pulmonary tuberculosis. *Int J Tuberc Lung Dis* 2016;20:1671-6.
10. Kurbatova EV, Taylor A, Gammino VM, Bayona J, Becerra M, Danilovitz M, Falzon D, Gelmanova I, Keshavjee S, Leimane V, Mitnick CD, Quelapio MI, Riekstina V, Viiklepp P, Zignol M, Cegielski JP. Predictors of poor outcomes among patients treated for multidrug-resistant tuberculosis at DOTS-plus projects. *Tuberculosis* 2012;92:397-403.