Linezolid Manifests a Rapid and Dramatic Therapeutic Effect for Patients with Life-Threatening Tuberculous Meningitis

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We conducted a retrospective cohort study of patients with MRC grade II/III tuberculous meningitis (TBM) who accepted a background antitubercular regimen (BR) with or without linezolid (LZD). At the 4th week, the LZD-BR group achieved a faster and higher percentage of culture recovery and temperature recovery, a higher cerebrospinal fluid (CSF)/blood glucose ratio, and lower CSF white blood cell counts than did the BR group. Short-term linezolid supplementation may be a more effective treatment for life-threatening TBM.

Tuberculous meningitis (TBM) is one of the most common forms of central nervous system (CNS) infections, especially in developing countries, where tuberculosis (TB) is highly epidemic (1). The incidence of TBM is directly related to the prevalence of TB infection and comprises approximately 10% of all TB cases (2). Despite the advent of newer antitubercular agents and imaging techniques, TBM still causes high mortality rates and severe neurologic deficiencies (3, 4).

New TB drugs are required to manage patients with TBM who face an increasing threat of drug resistance. A recent study from southwestern China found a rate of 32.14% of multidrug-resistant tuberculosis (MDR-TB) in TBM patients, which is higher than the reported resistances for pulmonary tuberculosis (5). First approved in 2000 for treating drug-resistant Gram-positive bacterial infections (6), linezolid (LZD) has shown antituberculosis potential in recent years. A number of case reports and retrospective studies suggest that linezolid may be effective in treating MDR and extensively drug-resistant tuberculosis (XDR-TB) (7–15). Furthermore, a phase 2a randomized two-group study showed that linezolid was effective at achieving culture conversion among patients with treatment-refractory pulmonary XDR-TB, but patients must be monitored carefully for adverse events (16).

Diagnosis and management differ significantly between TBM and pulmonary TB (1, 17). Acid-fast bacilli (AFB) have been found in fewer than 20% of patients with TB (18), and the culture of cerebrospinal fluid (CSF), although considered the gold standard for diagnosis, is positive in only about 40% of cases (19). For most patients with TB, pathogenic evidence and drug susceptibility testing (DST) results are not available in the initial phase of treatment when patients present with serious manifestations, such as conscious disturbance, headache, and fever. Thus, CSF parameters (Glasgow coma scale [GCS] scores, and temperature, which are closely related to TBM severity), other than culture, are routinely used to evaluate the therapeutic effect of antitubercular regimens in the initial phase of treatment. Although primarily bacteriostatic, linezolid has been employed successfully for treating CNS infections caused by multiresistant organisms. A case report showed good results with linezolid for the treatment of CNS infections in 10 patients, among whom three were caused by mycobacteria (20). However, the efficacy and adverse effects of linezolid in treating TB have not been evaluated in sufficient detail. Here, we compared the treatment outcomes of linezolid use in the initiation phase of treatment and evaluated its adverse events in a cohort of patients with life-threatening TBM.

This retrospective cohort study was performed at Huashan Hospital, a tertiary hospital in eastern China. Ethics approval was obtained from the Institutional Review Board of Huashan Hospital, Fudan University. All patients who met the inclusion criteria from January 2010 to December 2012 were included (see Table S1 in the supplemental material). Cases of TBM were diagnosed as confirmed TBM, highly probable TBM, probable TBM, or possible TBM. Confirmed TBM was defined by results in the CSF culture that were positive for Mycobacterium tuberculosis. Highly probable TBM and probable TBM were diagnosed according to CSF criteria and supporting criteria. The CSF criteria included three parameters, (i) a CSF glucose level of <50%, (ii) >50% lymphocytes in the CSF, and (iii) a CSF protein level of >1.5 g/liter. Supporting criteria contained two items, (i) enhanced magnetic resonance imaging (MRI) brain scan features consistent with TB and (ii) evidence of extra-CNS tuberculosis or positive T-SPOT.TB assay results. Highly probable TB was diagnosed when at least 2 CSF criterion parameters and 2 CSF criterion items or 3 CSF criterion parameters and 1 CSF criterion item were fulfilled, and probable TB was diagnosed when 2 CSF criterion items and 1 CSF criterion item were fulfilled. A diagnosis of possible TB was made if patients did not fulfill the above criteria but a diagnosis of active TB could not be excluded. TBM severity was graded according to the modified MRC system: (i) grade I, a GCS score of 15, no focal neurology, (ii) grade II, a GCS score of 11 to 14 or a GCS score of 15 with focal neurology, and (iii) grade III, a GCS score of ≤10 (21).

The patients included in our study were divided into one of two groups based on whether their antitubercular regimen contained...
linezolid. We compared the following results associated with recovery in the first 4 weeks between these two groups, (i) CSF changes, including higher blood glucose ratio, lower white blood cell counts, and lower protein concentrations, (ii) consciousness recovery, indicated by a GCS score that increased to 15 and did not decrease later, and (iii) temperature recovery, indicated by a patient’s oral temperature decreasing to no higher than 37.2°C and not increasing thereafter.

The regular protocol for the management of tuberculous meningitis and the data collection process are described in File S1 in the supplemental material. Statistical analysis was performed using GraphPad Prism version 5 and SPSS version 17.0. Categorical variables were compared using the Fisher exact test. Continuous variables were compared between the groups using the Wilcoxon rank sum test. Survival curves were compared between the groups using the log-rank test. Significance testing was done using 2-sided \( P \) values, with a \( P \) value of \(<0.05\) considered statistically significant.

The final diagnoses and reasons for the inclusion and exclusion of the cases are shown in Fig. 1. Among 77 patients with TBM, 29 were excluded, as they did not meet the criteria; they died, lacked one of three lumbar punctures, or had an uncertain diagnosis. Among the remaining 48 patients with TBM, 15 were excluded due to mild grade I disease. Thirty-three patients with grade II/III TBM were assigned to the background regimen group (17 patients) or the linezolid-plus-background-regimen group (16 patients). Three lumbar punctures were performed, one at tuberculous meningitis diagnosis, one 2 weeks after treatment, and one 4 weeks after treatment. TB, tuberculosis; TBM, tuberculous meningitis.

FIG 1 Patient enrollment and treatment group assignment. Among 77 patients with TBM, 29 were excluded, as they did not meet the criteria; they died, lacked one of three lumbar punctures, or had an uncertain diagnosis. Among the remaining 48 patients with TBM, 15 were excluded due to mild grade I disease. Thirty-three patients with grade II/III TBM were assigned to the background regimen group (17 patients) or the linezolid-plus-background-regimen group (16 patients). Three lumbar punctures were performed, one at tuberculous meningitis diagnosis, one 2 weeks after treatment, and one 4 weeks after treatment. TB, tuberculosis; TBM, tuberculous meningitis.
Previous studies suggested that linezolid might be useful in most complicated cases of pulmonary MDR/XDR-TB when other treatment alternatives are not available (7, 12, 13, 16). In our retrospective cohort study involving 33 patients with severe TBM, we found that the short-term addition of linezolid at a dosage of 1,200 mg per day to the background regimen showed significant beneficial effects on CSF improvement, consciousness recovery, and temperature recovery compared to the background regimen without linezolid. In particular, we noticed that the LZD-BR group showed a higher percentage of patients with consciousness recovery just after 1 or 2 weeks of treatment than did the BR group, which did not show significant improvement in CSF parameters. It seems that consciousness recovery occurred faster than did CSF parameter improvement. Considering that consciousness is a very important manifestation related to TBM severity, our finding that linezolid has a remarkable therapeutic effect on improving consciousness may prove to be critical for saving the lives of patients with life-threatening TBM. To our knowledge, this is the first report that demonstrates the dramatic therapeutic effects of linezolid on improving life-threatening TBM, which saves valuable time that is critical for the survival of such patients and should have implications for clinical care.

Several factors may explain this remarkable recovery from life-threatening TBM conferred by linezolid. First, a previous early bactericidal activity (EBA) study showed that linezolid has early bactericidal activity against rapidly dividing tubercle bacilli in patients during the first 2 days of administration (22). In addition, linezolid is active against drug-sensitive and drug-resistant TB strains (23, 24). Second, due to its amphiphilic properties, 80% to 100% of the linezolid administered penetrates the CSF (25), with an area under the concentration-time curve for CSF (AUCCSF)/AUC for serum (AUCS) ratio close to 1 (26). The linezolid dosage in our study, 600 mg twice a day, is the highest daily dosage at present, which ensures an effective therapeutic concentration in the CSF.

Most previous studies evaluated the efficacy of linezolid against pulmonary tuberculosis, with few reports on TBM. A meta-analysis showed that times for smear and culture conversions were...
perature recovery, and CSF improvement in the first 4 weeks of life-threatening TBM, as shown by rapid consciousness recovery, temperature recovery, and CSF improvement in the first 4 weeks of treatment. Although a small number of patients (12.5%) developed linezolid-attributed adverse events, these effects were generally mild and reversible upon drug discontinuation or dose reduction. We conclude that short-term linezolid supplementation is likely a more effective treatment for patients with life-threatening TBM than the current regimen without linezolid and warrants further clinical evaluation with more patients in future studies.

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