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Linezolid for XDR-TB: Final Study Outcomes

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TO THE EDITOR:

We previously reported 4-month culture conversion rates among chronic extensively drug-resistant (XDR) pulmonary tuberculosis (TB) patients who received linezolid.[1] By month 4, 15/19 (79%) in the immediate-start group and 7/20 (35%) in the delayed-start group converted their sputum culture to negative (P=0.001). By 6 months of linezolid treatment, 34/39 (87%) had negative sputum cultures. Here we report final study outcomes for these patients 1 year after the end-of-treatment (EOT), 36 months after they began the study.

Among 39 patients enrolled in this trial, 38 received linezolid: 27 experienced no relapse (remained sputum culture negative) 1 year after EOT, 3 were lost after EOT, and 8 withdrew before EOT including the 4 failures previously reported. Median duration of TB treatment was 789 days overall with 781 days of linezolid (final regimens included any remaining active second-line drugs, described in the original report). Most patients randomized to receive 600 mg ultimately reduced to 300 mg due to adverse events. Additional serious adverse events beyond our original report include 3 optic neuropathies and one anemia, which resolved with linezolid discontinuation. Acquired linezolid resistance was only observed in the 4 patients originally reported (11% of the 38 who received study drug). This low observed rate despite effective monotherapy may be related to the infrequent emergence of resistance to this drug observed *in vitro*.[2] Thus, 27/38 (71%) subjects with chronic, extensively drug-resistant tuberculosis achieved durable cure of their infection.

In the two years since our original report, one additional prospective clinical trial of linezolid for XDR-TB has been published, with results reported at EOT.[3] This report of our final study outcomes one year after EOT provides prospective evidence of the durable efficacy of linezolid to cure XDR-TB, albeit limited by small numbers. Because TB relapses

predominantly occur in the first year after EOT,[4] having no relapses in our cohort is extremely reassuring.

This report adds to the growing evidence of the efficacy of linezolid for drug-resistant TB, with use limited by side effects.[5] Notably these side effects were dose-related suggesting that future trials involving a lower dose of linezolid may be better tolerated. Newer oxazolidinones are also in development, some with potent *in vitro* activity against *Mycobacterium tuberculosis*, and are believed to have fewer side effects than linezolid with long-term use. If confirmed in future clinical trials, newer generation oxazolidinones may become an important part of combination regimens for TB treatment.

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