Long-term mortality assessment of multidrug-resistant tuberculosis patients treated with delamanid

To the Editor:

Multidrug-resistant tuberculosis (MDR-TB) is a serious obstacle to TB control [1]. The disproportionately negative outcomes among patients with drug resistance reflect a strong global need to develop new anti-TB drugs [2, 3]. Delamanid is a novel anti-TB agent that has recently been approved for the management of MDR-TB patients [4]. Treatment of MDR-TB patients with delamanid in combination with an optimised background regimen for 2 months significantly improved 2-month sputum culture conversion (SCC) by ~50%, in comparison to treatment with placebo plus an optimised background regimen [5]. Additionally, compared to ≤2 months of treatment, ≥6 months of treatment with delamanid plus an optimised background regimen was associated with higher favourable treatment outcomes (55.0% versus 74.5%) and significantly lower mortality (8.3% versus 1.0%, p<0.001) [6]. While early SCC is recognised as a biomarker in the development of anti-TB drugs [7–9], the impact of early SCC on long-term mortality in MDR-TB patients has only been assessed in retrospective cohort analyses [10–13]. Using updated prospective data from the delamanid development programme, we assessed the association between 2-month SCC and mortality in MDR-TB patients and expanded a previous analysis on the impact of long-term treatment with delamanid on mortality.

The clinical development programme for delamanid involved three consecutive trials: 1) a randomised placebo-controlled trial of 481 patients (Trial 204) for 3 months (2 months delamanid treatment plus 1 month blinded follow-up); 2) an open-label treatment trial of 213 patients (Trial 208) with delamanid for 6 months (for any patient participating in Trial 204); and 3) a follow-up study of treatment outcomes of 421 patients (Trial 116) 24 months post-randomisation in Trial 204 [14]. Patients also received an optimised background regimen under directly observed treatment (as per World Health Organization guidelines [15]) throughout Trial 204 and Trial 208 and for the duration of the treatment period, generally 18–24 months.

The definition used for 2-month SCC in Trial 204 was five or more consecutive weekly cultures that were negative for growth (measured on liquid broth medium using the mycobacterial growth indicator tube automated system (Becton Dickinson, Franklin Lakes, NJ, USA)) of Mycobacterium tuberculosis, and no subsequent positive cultures during the follow-up period. Mortality during MDR-TB treatment among patients was determined at 24 months post-randomisation in Trial 204 based on information available from Trial 116 [13].

The primary outcome of Trial 204, 2-month SCC, was assessed in all 481 patients. Vital status was assessed and updated at ≥24 months in 464 (96.5%) patients, including 43 patients who did not participate in previously reported results of Trial 116. Paralleling a previous analysis, long-term treatment with delamanid was indicated as ≥6 months, defined by assignment to delamanid or placebo in Trial 204 and participation in Trial 208, and short-term treatment with delamanid was indicated as ≤2 months, defined by assignment to delamanid or placebo in Trial 204 and no participation in Trial 208 [6]. Mortality was also assessed by fitting a logistic regression model with vital status as response variables, and 2-month SCC status and delamanid treatment duration as factors.

2-month SCC was significantly (p=0.002) associated with a lower likelihood of mortality (OR 0.25, 95% CI 0.10–0.61). Among patients with 2-month SCC, 3.1% (six out of 192) died compared to 11.4% (31 out of 272) who did not achieve 2-month SCC (table 1). Additionally, mortality was lower among patients within each of the original Trial 204 treatment groups for patients with 2-month SCC versus patients without 2-month SCC: 3.5% (five out of 142) versus 10.0% (17 out of 170) in the delamanid group and 2.0% (one out of 50) versus 13.7% (14 out of 102) in the placebo group.

Patients with long-term treatment with delamanid also had a significantly (p=0.001) lower likelihood of mortality (OR 0.22, 95% CI 0.09–0.54). 2.9% (six out of 205) of patients receiving delamanid for ≥6 months died in comparison to 12.0% (31 out of 259) of patients who received delamanid for ≤2 months (table 1). In the original Trial 204 randomised population, mortality was lower at 7.1% (22 out of 312) in patients assigned to delamanid compared to 9.9% (15 out of 152) for patients assigned to...
placebo. Of note, mortality among patients receiving delamanid for $\geq 6$ months was 2.9% (six out of 205) compared to 14.5% (12 out of 83) in those patients not receiving any treatment with delamanid.

The potential association between delamanid treatment duration, 2-month SCC and reduced mortality was also assessed. Among the 192 patients with 2-month SCC in Trial 204, mortality was 0% among the 95 patients who then participated in Trial 208 versus 6.2% among the 97 who did not participate in Trial 208. Likewise, among the 272 patients without 2-month SCC in Trial 204, mortality was lower at 5.5% among the 110 patients who participated in Trial 208 versus 15.4% among the 162 patients who did not participate in Trial 208. Mortality was also consistently lower within each of the original Trial 204 treatment groups for patients with 2-month SCC who then participated in Trial 208 versus those who did not participate in Trial 208: 0% (none out of 70) versus 6.9% (five out of 72) in the delamanid group and 0% (none out of 25) versus 4.0% (one out of 25) in the placebo group. Finally, taken together and independent of Trial 204 treatment assignment, patients participating in Trial 208 had a lower mortality of 2.9% (six out of 205) compared to 12.0% (31 out of 59) in patients not participating in Trial 208.

To assess variation among patients who enrolled in Trial 208 versus those who did not, baseline characteristics (cavitation, degree of drug resistance and previous treatment history) generally associated with negative treatment outcomes in MDR-TB patients were assessed for the 44.3% (213 out of 481) of Trial 204 patients who participated in Trial 208 versus the 55.7% (268 out of 481) of Trial 204 patients not entering Trial 208. Bilateral cavitation was present in 29.6% (63 out of 213) of Trial 208 patients compared to 19.4% (52 out of 268) not entering Trial 208. Extensively drug-resistant patients and pre-extensively drug-resistant patients were in greater proportion among Trial 208 participants (81 (38.0%) out of 213) compared to nonparticipants (54 (20.1%) out of 268). Additionally, more patients in Trial 208 were previously treated with second- and third-line anti-TB drugs compared to patients not entering Trial 208 (109 (51.2%) out of 213 versus 77 (28.7%) out of 268).

This analysis is limited by at least three key issues: 1) the variable time-period between Trial 204 and Trial 208 allowing for continued treatment with an optimised background regimen in the absence of delamanid; 2) the open-label design of Trial 208; and 3) the lack of autopsy data to distinguish all-cause mortality from TB-related mortality. However, lower mortality trends with long-term treatment with delamanid were still observed despite more severely diseased patients participating in Trial 208 compared to nonparticipants.

These results support important conclusions regarding 2-month SCC and the treatment of MDR-TB patients with delamanid. First, 2-month SCC can be considered an important surrogate end-point in the treatment of MDR-TB patients, given the 3.7-fold lower mortality proportions among patients achieving 2-month SCC. Secondly, the expanded vital status results confirmed previously reported results [6] that the greatest reduction in mortality (a four-fold reduction) occurred among patients treated with delamanid for $\geq 6$ months versus those treated for $\leq 2$ months. Finally, delamanid may represent an important therapeutic option in the treatment of MDR-TB patients, as supported by the five-fold reduction in mortality among patients receiving delamanid for $\geq 6$ months compared to patients not receiving any treatment with delamanid.

Rapid evaluation of anti-TB drugs will require novel methods including the use of surrogate end-points. Such evaluations should ultimately include parameters to assess long-term outcomes, including mortality.

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MDR-TB patients treated with 6 months or more of delamanid had significantly lower likelihood of mortality http://ow.ly/HOv1d

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