Editorial

Recent evidence on delamanid use for rifampicin-resistant tuberculosis

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Delamanid is one of the two most recently approved new anti-tuberculosis (TB) drugs.

Delamanid (Deltyba) has been developed by the Japanese Otsuka Pharmaceuticals. Delamanid, a nitroimidazole derivate, acts inhibiting the cell wall of mycobacteria, and more specifically the mycolic acids synthesis (1).

Based on *in vitro* and animal studies, its clinical development has addressed its use in the treatment of resistant forms of TB, in particular for multidrug-resistant (MDR)-TB (i.e., TB due to a strain resistant to at least isoniazid and rifampicin) and extensively drug-resistant (XDR)-TB [i.e., MDR-TB with additional resistance to fluoroquinolones and second-line injectables (SLIs)] (1).

Its use has been recommended in 2014 for the treatment of MDR-TB by WHO (World Health Organization) after having received conditional approval by the European Medicines Agency on the previous year (2,3). It has later been registered in other countries such as Japan and South Korea.

In the first clinical studies delamanid has shown promising results in terms of favourable treatment outcomes and of good surrogate markers of efficacy such as time to sputum-culture conversion (SCC) and early bactericidal activity (EBA) (4-6).

Delamanid is being increasingly used in several countries either after regular approval or through compassionate use programmes or through international non-governmental organizations (NGOs) programmes (7-9).

Unfortunately, only a few reports on its use in real-life settings have been published so far (7-11). Such papers report experiences from Africa, Asia and Europe including more than 200 patients (7-11).

Results from a phase III trial on delamanid (study #242-09-213) have been presented in Guadalajara (Mexico) during the 48th World Conference on Lung Health organised by the Union (12). Such results were actually disappointing, showing a limited impact of delamanid on treatment outcomes of the cohort studied. Although evaluation of the primary end-point (time to SCC—sputum smear conversion—after 6 months) showed that the patients treated with delamanid converted bacteriologically (SCC) 6–13 days earlier than the placebo ones within 24 weeks (significant P values), the long-term outcomes were disappointing (12). In fact, no statistically significant differences in treatment success were found between delamanid-treated and placebo patients.

After 30 months, cure was observed in 77.1% of delamanid-treated versus 77.6% of placebo-managed patients [risk ratio (RR) 0.993; 95% confidence interval (CI): 0.899–1.097] (13). Furthermore, no statistically significant differences were found both on mortality (all causes) and on SCC at 6 months (13).

While waiting for the final results to be fully published, such unexpected findings seem to be the consequence of an

improperly designed clinical trial rather than of the actual drug inefficacy. In this regard, information from clinical studies carried out in the field are desperately needed to confirm (or not) delamanid efficacy in the treatment of drug-resistant TB.

The paper recently published by the Mohr's group ("Delamanid for Rifampicin-Resistant Tuberculosis: A Retrospective Study from South Africa") reports about delamanid use in a real-life setting where drug-resistant TB treatment is challenging (14). Currently, in South Africa, clinicians treating Rifampicin-Resistant (RR)-TB treatment have access to bedaquiline (already registered in the country) and other repurposed drugs such as linezolid and clofazimine, in line with WHO recommendations (14-16). Conversely, delamanid is not registered in the country, and therefore it is available through pilot studies or through compassionate use or similar programmes (14).

Erika Mohr from Médecins Sans Frontières (MSF) and her colleagues report in this paper on the interim treatment outcomes and safety information from a South African cohort of patients receiving a delamanid-containing regimen from November 2015 to August 2017 for RR-TB in district of Khayelitsha.

The published cohort included 103 patients who initiated delamanid following diagnosis of RR-TB. Delamanid had been prescribed in most cases because of intolerance to second-line anti-TB drugs (58 cases, 56%); other reasons for prescription included previous failure of RR-TB treatment and/or the impossibility to ensure—without delamanid—a minimum of five effective medicines in the regimen.

Resistance profile was challenging with 78 (75.7%) patients with strains at least MDR. In particular, there were 41 cases (39.8%) with MDR-TB, 20 (19.4%) with pre-XDR (defined as MDR-TB cases whose strains have also resistance to either SLIs or fluoroquinolones) while 17 (16.5%) had XDR-TB.

The large majority of patients (79, 77%) was co-infected with HIV. In particular, they had advanced HIV infection, as the median interquartile range [IQR] CD4 count was 141 [61–252] cells/mm^3 with most patients (57%) with CD4 count <200 cells/mm^3.

Several patients (32, 31%) received a regimen where delamanid was co-administered with bedaquiline in the absence of other possibilities to design an adequate regimen (only 2 with "simple" RR-TB).

Another aspect showing why this cohort was challenging is the large proportion of patients (54, 52%) who was prescribed a prolonged course of delamanid, i.e., beyond the six months recommended by WHO.

Although this study presents the interim analysis of the cohort (the findings need to be considered with caution) encouraging results have been observed. For the 46 patients who were followed-up for 12 months a positive outcome (cure, treatment completed, or culture conversion) was observed in most of them (28, 61%). Among the 57 patients who had positive cultures before delamanid initiation SCC was observed in 16/31 (52%) and 25/31 (81%) within 2 and 6 months, respectively.

The results of this study, considering the severity of the patients managed, are really promising, with high SCC which are consistent with those observed recently in other studies with similar patients (SCC ranging from 67.6% to 94.4%) (7-9,12).

The results from this South African cohort are even more significant given the characteristics of this difficult-to-treat population (i.e., high frequency of advanced HIV infection, high levels of drug resistance, limited treatment option leading to combine delamanid to bedaquiline, prolonged prescription of delamanid).

As this was an interim analysis, we hope to see soon a final report with outcomes as good as these ones after adequate follow-up, ideally complemented by other studies/reports on the subject.

In addition, interesting results on the safety profile were also reported by the authors: they observed 67 serious adverse events (SAEs) in 29 cases (28%), only 22 of them (33%) having a causal relationship with delamanid. The commonest SAE was the prolongation of the QT interval (QTc, corrected for the frequency as per the Frederica formula)–seven cases (all attributed to delamanid), followed by vomiting (4, 75% attributed to delamanid). In addition, three hepatic SAEs were observed, two of them were attributed to delamanid.

In particular, the study team evaluated in depth the cardiac safety. They identified four instances of QTc prolongation >500 ms (significant risk factor for cardiac arrhythmias) in 2 cases (2%), obliging the treating physician to interrupt the drug in a case only.

Actually, several patients (48, 47%) were prescribed one or more medicines known to prolong the QT interval such as bedaquiline + clofazimine (24 cases, 23%), clofazimine (10 cases, 10%), bedaquiline (8 cases, 8%) and moxifloxacin (6 cases, 6%).

In addition, 14 episodes of QTc value >60 ms from baseline (another risk factor for cardiac arrhythmias)

were identified in 9 (9%) patients. In none of these cases arrhythmias were identified or interruption of delamanid was necessary, while QTc >500 ms was never observed. Important to comment that 8 of the latter cases were prescribed other agents with QT-prolonging potentialities: bedaquiline (1 case), clofazimine (2 cases), and bedaquiline + clofazimine (5 cases). Important, significantly more patients treated with both bedaquiline + clofazimine experienced increased QTc (>60 ms) from baseline (5 out of 24, 21%) when compared to the cases who were not prescribed the 3 drugs (4 patients out of 79, 5%) (RR 4.1, 95% CI: 1.2–14.1, P=0.030).

In summary, a real minority of cases (2%) reported QTc prolongation (>500 ms) when exposed to delamanid combined with other compounds with cardiotoxic features, and in <50% of them SAEs were observed. These results are comparable to the findings reported by the Phase III delamanid trial where only 5.3% of patients receiving delamanid experienced QTc prolongation (12). In other publications reporting programme experiences with delamanid in RR-TB cases, the proportion of episodes involving QTc prolongation (>500 ms) or increase (>60 ms) were low even when delamanid and other potentially QTc-prolonging agents were prescribed (range, 3.7–17.0%) (7-9,17-20).

The combined use of delamanid and bedaquiline is not recommended by WHO due to limited evidence of concomitant use and to the potential cardiotoxic risk (3). Nevertheless, in complex patients, where the identification of at least four active and well-tolerated drugs is not possible, the two drugs can be combined as a life-saving option as it was the case for this cohort (14,21,22).

A recent systematic review of combined use of delamanid and bedaquiline showed that prolonged use of delamanid with bedaquiline is frequent, and cardiac safety is probably better than expected (23). Actually, as of today there is no evidence that the two drugs have additive or synergistic QTc prolonging potentialities and just 2.3% of patients discontinued delamanid and/or bedaquiline because of SAEs (24).

In conclusion, this paper by Mohr and colleagues is among the largest programmatic studies available on cases managed with delamanid to treat RR-TB. This cohort largely composed of difficult-to-treat patients had, overall, excellent early outcomes and delamanid was well tolerated (14).

Although, generalisation of the reported findings is limited, the results obtained in this very challenging cohort of patients are promising.

Efficacy of delamanid is still questioned and further analyses of larger cohorts from programmatic settings with more follow-up time are urgently needed.

Furthermore, new large studies are required to better understand how to use delamanid in special population of patients, including pregnant women, children and individuals intolerant to other anti-TB drugs.

Data presented in this report and the growing experience in programmatic settings suggest that delamanid is a resource drug for MDR/XDR-TB cases when the minimum number of active (and tolerated) drugs is not available.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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