Multidrug-resistant pulmonary tuberculosis and delamanid

No demonstrated clinical benefit

● **A double-blind randomised trial in 511 adult patients with multidrug-resistant pulmonary tuberculosis compared *delamanid* (an antibiotic) versus placebo, in combination with an optimised background multiple drug regimen. *Delamanid* did not reduce mortality, or improve the antibacterial efficacy of the antibiotic treatment.**

Pulmonary tuberculosis is a serious infectious disease caused by a mycobacterium, usually *Mycobacterium tuberculosis* (1). Tuberculosis is said to be multidrug-resistant when the mycobacteria show in vitro resistance to both *isoniazid* and *rifampicin*, two antimicrobial drugs used as standard treatment for tuberculosis. Treatment of multidrug-resistant tuberculosis involves a so-called optimised background regimen, i.e. a combination of antibiotics chosen primarily according to the results of in vitro tests of the antibiotic sensitivity of bacteria isolated from the patient's sputum (1).

Delamanid is an antibiotic which acts by inhibiting synthesis of the mycobacterial cell wall (1). Based on the data available in late 2016, use of *delamanid* as part of an optimised background antibiotic regimen seemed to increase the chances of achieving a negative sputum bacterial culture (sputum culture conversion), with perhaps also a reduction in mortality. However, these results represented a low level of evidence due to various methodological problems (1).

The results of a comparative trial of *delamanid* versus placebo now provide additional information (2).

No additional antibacterial efficacy and no reduction in mortality. This randomised double-blind trial included 511 adults with multidrug-resistant pulmonary tuberculosis (2). They were randomised to receive either *delamanid* (200 mg per day) or placebo, for 6 months. Patients in both groups also received an optimised background regimen of multiple antibiotics chosen by the investigators, which was continued beyond the first 6 months of treatment. The trial protocol allowed antibiotics to be changed as part of an optimised background regimen (2).

Thirty months after treatment initiation, there were no differences between the groups, either in terms of overall mortality (about 5%) or tuberculosis-related mortality (about 2%) (2). Sputum bacterial cultures became negative in a similar proportion of patients in the two groups: about 57% two months after starting treatment, and 87% six months after starting treatment. 77% of patients had a negative sputum culture at both 6 months and 30 months after initiating treatment (2).

According to the trial investigators, the lack of any difference between the groups could be explained in part by the greater efficacy of the optimised background regimen than that initially anticipated. This may have been due to a change in international recommendations during the course of the trial, resulting in the use of antibiotics judged to be more effective as part of the optimised background regimen (2).

QT interval prolongation, gastrointestinal and neuropsychiatric disorders. The trial described above confirmed the known adverse effect profile of *delamanid,* including headache (reported in 31% of patients in the *delamanid* group versus 23% of those in the placebo group), vomiting (27% versus 23%), gastritis (23% versus 16%), tremor (6.5% versus 3%) and electrocardiographic QT interval prolongation (5.3% versus 2.9%) (2). The other known adverse effects of *delamanid* are mainly hypokalaemia and psychiatric disorders (insomnia, anxiety, depression, psychotic disorders) (1,3,4).

In practice It is helpful to have an antibiotic available which is active against multidrug-resistant mycobacteria. However, as of early 2021, there is no demonstrated clinical benefit from addition of *delamanid* to an optimised multiple drug treatment regimen.

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Literature search up to 29 March 2021

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