## Correspondence

# Linezolid for multidrug-resistant tuberculosis

In their Comment in *The Lancet Infectious Diseases*, Kwok-Chiu Chang and colleagues[1] concluded that expansion of access to linezolid for complicated cases of drug-resistant tuberculosis risks the loss of a potentially useful drug and could promote the emergence and spread of drug-resistant tuberculosis in the community. The rationale behind this idea seems to be the scarcity of controlled clinical trials and, in particular, data for optimum linezolid dose. Although we agree that the evidence base is small, our recent systematic review[2] suggests that good outcomes can be achieved with linezolid among patients who would otherwise have very poor outcomes and high mortality. Among 148 patients treated with linezolid, the rate of treatment success (68%) was at least as good as that expected for multidrug-resistant tuberculosis treatment overall (62%).[2,3] None of the authors of the studies included in that review advocates large-scale and indiscriminate use of linezolid for drug-resistant tuberculosis. Conversely, in view of the poor side-effect profile and treatment complexity, linezolid is recommended for patients with few remaining treatment options, treated in well functioning programmes.

The risk of emerging drug resistance is relevant, but no more so than for other second-line drugs presently used for drug-resistant tuberculosis. Existing treatment regimens are lengthy, are associated with substantial side-effects, and result in overall poor outcomes. Unfortunately, controlled trials to define better regimens are scarce. However, failure to scale up treatment access will lead to continued community transmission and worsening of the epidemic.[4]

Newer derivatives of linezolid with improved side-effect profiles are under development.[5] Meanwhile, linezolid should be available for patients with few treatment options, owing to either extensive drug resistance or previous treatment failure. We have started five patients on strengthened linezolid and clofazimine-containing regimens in Khayelitsha, South Africa, all of whom produced negative sputum cultures within 3 months. Subsequent linezolid withdrawal was necessary in one patient because of severe peripheral neuropathy. Although side-effects need to be monitored and managed carefully, the restricting factor in the use of linezolid in our setting, where Pfizer holds a patent, is cost, rather than scarcity of evidence. In South Africa, linezolid is available in the public sector at a cost of US$1000 per patient per month.

Although improved access to linezolid alone will not solve the worldwide drug-resistant tuberculosis crisis, facilitation of access to new and repurposed drugs for drug-resistant tuberculosis will contribute to the overall goal of a shorter, more tolerable, and more effective treatment regimen than is available at present, and will offer the hope of cure to patients who would otherwise die.

We declare that we have no conflicts of interest.

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## Authors' reply

In our recent Comment,[1] we concluded that a "non-expensive and non-proprietary source of linezolid is insufficient to tackle the evolving global crisis of drug-resistant tuberculosis". This conclusion was not simply based on "scarcity of controlled clinical trials and, in particular, data for optimum linezolid dose", as suggested by Helen Cox and colleagues. Rather, the rationale was the difficult lessons that mankind has learned since anti-tuberculosis chemotherapy became available, especially in view of the wide social divide between rich and poor people, both within and between countries. We added a note of caution against the "introduction of linezolid on a large scale without careful planning or a well-functioning health infrastructure",[1] which was reiterated by Cox and colleagues when they also suggested that "in view of the poor side-effect profile and treatment complexity, linezolid is recommended for patients with few remaining treatment options, treated in well functioning programmes".

For people who are unaware of the problems in translation of anecdotal treatment efficacy into an actual public health effect, and the crucial need to promote treatment adherence by direct observation,[2] the description of successful outcomes after unsupervised use of inexpensive linezolid in a case series of 29 patients with multidrug-resistant tuberculosis could inadvertently encourage indiscriminate use of the drug.[3] Although the high cost of linezolid might have hindered its proper use, this factor has probably also reduced its indiscriminate use outside the programme setting. Whereas a pooled proportion of treatment success of 68% among patients with multidrug-resistant tuberculosis treated with linezolid

is at least as good as the expected success rate of 62%,[4] this figure still falls substantially short of treatment success rates reported for drug-susceptible tuberculosis. This fact emphasises the need for other essential elements to achieve fully effective disease control.

To tackle drug-resistant tuberculosis, we need large-scale implementation of an effective tuberculosis control programme built on the directly observed treatment short-course strategy, supported by proper regulation of high-quality drug supply and a well funded health infrastructure, including fundamental laboratory diagnostic services. Although linezolid might be the most promising repurposed agent in the treatment of complicated multi-drug-resistant tuberculosis, its indiscriminate or unsupervised use still creates a major risk of treatment failure and further amplification of drug resistance. Since several new drugs are now at an advanced stage of development, assessment of their clinical roles alongside linezolid in controlled clinical trials in a well functioning programme could be valuable.

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# Daclatasvir: a promising triple therapy for children with chronic hepatitis C

We read with great interest the Article by Stanislas Pol and colleagues[1] on the use of daclatasvir in previously untreated adult patients with chronic hepatitis C genotype 1 infection.

Daclatasvir belongs to a class of new directly acting antivirals that inhibit non-structural protein NS5A, inhibiting hepatitis C virus RNA replication. Daclatasvir has inhibitory activity against hepatitis C virus, with broad genotypic coverage and a pharmacokinetic profile that supports once-daily dosing.[2,3]

Emerging drug-resistant hepatitis C virus variants have been reported previously in patients given daclatasvir in phase 1 monotherapy studies.[3] However, as Pol and colleagues showed,[1] an appropriate dose of daclatasvir, combined with peginterferon alfa-2a and ribavirin, suppresses resistant virus variants, and results in a more rapid and earlier decrease in plasma hepatitis C virus RNA than does dual peginterferon alfa-2a and ribavirin treatment. This randomised, multicentre, double-blind, placebo-controlled phase 2a trial showed that patients given daclatasvir, mainly at a 10 mg or 60 mg dose, had a better extended rapid virological response at both 4 and 12 weeks of treatment, and a better sustained virological response at 24 months, than did those in the group given peginterferon alfa-2a plus ribavirin. Moreover, the investigators reported no differences in side-effects between the two treatment groups.

Although the treatment of children with chronic hepatitis C is controversial, daclatasvir's good tolerability and the favourable effects of its combination with peginterferon alfa-2a plus ribavirin (triple therapy) encourage clinical trials in children, as suggested by the North American Society for Pediatric Gastroenter-ology, Hepatology, and Nutrition (NASPGHAN).[4] Because no data exist for the toxicology of daclatasvir in children, a phase 1 clinical trial should be a prerequisite for a phase 2 trial; however, Pol and colleagues' results support the possibility of a randomised, multicentre, blinded, placebo-controlled, dose-escalation phase 1–2 clinical trial being started. 48 children (age range 6–17 years) with chronic hepatitis C genotype 1 infection and with the eligibility criteria recommended by NASPGHAN[4] could be included in the trial. The patients should then be randomly assigned (1:1:1:1) into four groups, including 3 mg, 10 mg, and 30 mg doses of oral daclatasvir once daily, and a placebo. The recommended length of therapy is at least 48 months, and all 48 patients should receive once-weekly injections of 60 µg/m$^2$ peginterferon alfa-2a and 15 mg/kg per day of oral ribavirin.[5] As primary endpoints, this phase 1 or 2 clinical trial should include both the identification of side-effects associated with increasing doses and the effectiveness of daclatasvir that was measured by assessment of virological response during follow-up.

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