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Evaluation of high-dose rifapentine plus clofazimine in the first-line regimen for tuberculosis in the mouse model of chemotherapy

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Background: In mouse models of tuberculosis (TB) chemotherapy, increasing the rifamycin exposure, especially by replacing rifampicin with high-dose rifapentine, or adding clofazimine to the first-line regimen have both been separately associated with decreasing the duration of treatment necessary to achieve relapse-free cure from 6 months to 3 months. We thus hypothesize that replacing rifampicin with high-dose rifapentine and adding clofazimine in the first-line regimen will further decrease the duration of treatment necessary for the cure of drug-susceptible TB in mice.

Material/methods: *Mycobacterium tuberculosis*-infected BALB/c mice were treated for 12 weeks with one of the following regimens: (i) no drug control; (ii) RHZE (standard first-line regimen, rifampicin [R] 10 mg/kg, isoniazid [H] 10 mg/kg, pyrazinamide [Z] 150 mg/kg, and ethambutol [E] 100 mg/kg); (iii) RHZEC (addition of clofazimine [C] 12.5 mg/kg to the first-line regimen); (iv) PHZE (replacing rifampicin with high-dose rifapentine [P] 20 mg/kg in the first-line regimen); and (v) PHZEC (replacing rifampicin with high-dose rifapentine as well as adding clofazimine to the first-line regimen). The bacterial load in the mouse lungs (colony forming units or CFUs) was determined before and during treatment at 4, 6, 8, 10 and 12 weeks after treatment initiation, and 6 months after stopping treatment (administered for 6, 8, 10 or 12 weeks) to assess relapse.

Results: Treatment was initiated when the bacterial burden in the mouse lungs was high (mean 7.1 $\log_{10}$ CFU). All untreated control mice were moribund by 3-4 weeks after infection and were euthanized. After 4 weeks of treatment, it was clearly evident that PHZEC was the most bactericidal

regimen, followed by PHZE, then RHZEC; the control regimen RHZE was the least bactericidal. After 6 weeks of treatment, the decline in lung $\log_{10}$ CFU counts (compared to the start of treatment) was 6.4, 5.7, 3.9, and 3.2 in mice receiving PHZEC, PHZE, RHZEC, and RHZE, respectively. Furthermore, lung culture conversion (*i.e.*, the lungs were culture-negative) occurred after 8, 10, and 12 weeks of treatment for the mice receiving PHZEC, PHZE, and RHZEC, respectively. As expected, mice that received the RHZE regimen remained culture-positive after 12 weeks (when treatment ended). Relapse will be assessed 6 months after stopping treatment.

Conclusions: In the mouse model, replacing rifampicin with high-dose rifapentine and adding clofazimine in the first-line TB regimen (PHZEC) results in much earlier lung culture-conversion and has the potential to shorten the treatment duration for drug-susceptible TB to less than 3 months.