

Anti-malarial Activity of CEM-101, A Fluoroketolide Antimicrobial, in Both Bloodstage and Presumptive Causal Prophylactic Mouse Models

Abstract 265

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Background

CEM-101 is a new broad spectrum macrolide that has completed Phase 1 trials that inhibits protein synthesis through binding to bacterial ribosomal RNA. A comparator drug, azithromycin, causes a delayed death effect *in vitro* *P. falciparum* blood stage assays and demonstrates antimalarial activity against liver stage parasites. CEM-101 was recently shown to be active *in vitro* against *P. falciparum* in extended incubation assays which measure the potency of inhibitors that demonstrate delayed death effects. CEM-101 is also active against blood stages in *P. berghei*-infected mice.

Method

Dose-response for CEM-101 was characterized in both blood stage treatment and causal prophylactic *P. berghei*-infected mice models using 3 day PO or SC dosing. Efficacy was measured by number of mice with delayed parasitemia and mice that were malaria free at day 31. Antimalarial liver stage activity was assessed in mice infected with luciferase expressing *P. berghei* parasites using an *in vivo* imaging system.

Results

For blood stage infections, the minimum curative SC dose was 40 mg/kg/d X 3 days, while 80 mg/kg/d X 3 was the minimum active dose for PO route. In the *P. berghei* causal prophylactic mouse model, CEM-101 was curative at 40 mg/kg/d X 3 days with SC or PO dosing. No systemic toxicity was observed with SC or PO dosing as high as 160 mg/kg/d X 3 days. No demonstrable antimalarial activity against liver stage parasites was observed by *in vivo* imaging analysis of luciferase-expressing *P. berghei* with PO dosing at 40 mg/kg/d X 3 days. While drug activity against liver stage parasites could not be measured by *in vivo* imaging, no blood stage infection was detected in mice dosed as low as 40 mg/kg/d X 3 days and the minimum active dose was 20 mg/kg/d X 3 days.

Conclusion

CEM-101 shows 100% prophylactic activity in causal mouse malaria models with PO dosing at 40 mg/kg/d X 3 days and 3/5 mice remain parasite free at 20 mg/kg/d X 3 days. The *in vivo* imaging analysis of liver stage parasites suggests that CEM-101 does not affect parasite growth at 40 mg/kg/d X 3 days. Based on *in vitro* blood stage drug assays and the mechanism of inhibition of this class of compounds, the lack of demonstrable liver stage activity suggest that CEM-101, like azithromycin, demonstrate a delayed death effect; that is, developing liver stage merozoites are effectively non-viable blood stage parasites.