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**Use of peroxisome proliferator-activated receptor gamma agonists as adjunctive treatment for Plasmodium falciparum malaria: a randomized, double-blind, placebo-controlled trial.**

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**BACKGROUND:** Despite the use of potent antimalarial drugs, the fatality rate associated with severe malaria remains high. Adjunctive therapies that target the immunopathological responses to infection may decrease mortality associated with severe malaria. We hypothesized that peroxisome proliferator-activated receptor gamma agonists (eg, rosiglitazone) would modulate the host's innate immune response to malaria and improve outcome.

**METHODS:** In a randomized, double-blind, placebo-controlled, phase I/II trial of treatment for malaria acquired in Thailand, we investigated the safety, tolerability, and efficacy of rosiglitazone use for parasite clearance and for reducing malaria-induced inflammation. Sequential patients with uncomplicated Plasmodium falciparum malaria were randomly assigned to 1 of 2 groups: 70 patients received rosiglitazone 4 mg twice daily for 4 days, and 70 patients received a placebo twice daily for 4 days. Both groups also received standard antimalarial therapy (ie, a fixed combination of 1000 mg of atovaquone per day for 3 days and 400 mg of proguanil per day for 3 days). Primary efficacy outcomes were 50% and 90% parasite clearance times (PCTs). Secondary outcomes were fever clearance time, levels of inflammatory mediators, blood glucose measurements, aminotransferase levels, admission to intensive care, and subjective tolerability of study drug.

**RESULTS:** For the 70 patients who received rosiglitazone, parasite clearance from peripheral blood was significantly enhanced, compared with the 70 patients who received a placebo (mean 50% PCT, 19.0 h vs. 24.6 h [p = .029]; mean 90% PCT, 30.9 h vs. 40.4 h [p = .004]). Also, the patients who received rosiglitazone had reduced inflammatory responses to infection, compared with the patients who received a placebo (ie, interleukin-6 levels at 24 h [p < .005] and at 48 h [p = .013] and monocyte chemoattractant protein-1 level at 48 h [p = .05]). There were no significant differences between the 2 groups with regard to safety and tolerability of treatment, and there were no admissions the intensive care unit or deaths.

**CONCLUSIONS:** The use of rosiglitazone is a well-tolerated adjunct to standard therapy for nonsevere *P. falciparum* malaria. Treatment with rosiglitazone increased parasite clearance and decreased inflammatory biomarkers associated with adverse malaria outcomes.

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