Use of Peroxisome Proliferator-Activated Receptor γ Agonists as Adjunctive Treatment for *Plasmodium falciparum* Malaria: A Randomized, Double-Blind, Placebo-Controlled Trial

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(See the editorial commentary by Shanks, on pages 850–1.)

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 γ 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.

Trial registration. ClinicalTrials.gov identifier NCT00149383.

Plasmodium falciparum malaria remains a major cause of global morbidity and mortality, resulting each year in an estimated 300 million clinical cases and 1 million deaths, predominantly among young children and other nonimmune individuals [1, 2]. Potent artemisinin-based therapies have improved the clinical outcome of the disease; however, the case-fatality rates for severe malarial syndromes remain high [3–5]. This may reflect the observation that adverse outcomes of se-

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vere malaria are mediated, at least partly, by immunopathological responses to infection rather than by the pathogen directly [3, 6].

Key events in the pathogenesis of malaria include: (1) sequestration of parasitized erythrocytes within the microvasculature of vital organs; (2) dysregulated inflammatory responses to infection, contributing to immune-mediated tissue injury and upregulation of sequestration receptors; and (3) high parasite burdens that further enhance sequestration and host-mediated inflammatory injury [2, 7]. The ability of the host's innate immune response to contain blood-stage parasite replication during the acute phase of infection, when adaptive responses are largely absent, appears to be critically linked to survival [2, 6]. In addition to artemisinin-based therapies, adjunctive treatments that target innate immunity and modify deleterious host response to infection may further improve the clinical outcome of malaria.

Pattern recognition receptors, including Toll-like receptors (TLRs) and scavenger receptors, are important components of the innate immune system to malaria. Pattern recognition receptors sense a wide range of microbial molecules and activate proinflammatory responses. Parasites and parasite products, such as *P. falciparum* glycosylphosphatidylinositol (*pf*GPI) and hemozoin complexed with parasite DNA, induce the release of proinflammatory cytokines (eg, tumor necrosis factor [TNF]) via interaction with pattern recognition receptors, including TLR2, TLR9, and CD36 [8–10]. CD36 has been shown to mediate macrophage clearance of *P. falciparum*–parasitized erythrocytes in vitro and to contribute to survival in experimental models of malaria [10–15]. On the basis of these observations, we hypothesized that pharmacological modulation of innate immunity, through pattern recognition receptors and related pathways, might increase parasite clearance, modify deleterious host inflammatory responses to infection, and improve clinical outcome of *P. falciparum* malaria.

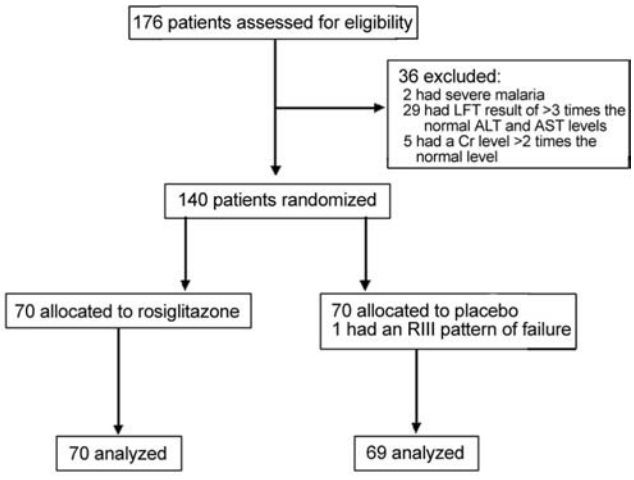

Figure 1. Profile of 176 patients screened for enrollment in a randomized, double-blind, placebo-controlled, phase I/II trial of treatment for malaria acquired in Thailand; 140 patients fulfilled the inclusion criteria and were randomly assigned to receive rosiglitazone or placebo. ALT, alanine aminotransferase; AST, aspartate aminotransferase; Cr, creatinine; LFT, liver function test; RIII, treatment was unable to reduce the parasite density to <25% of the baseline value within 48 h.

Major economic obstacles impede the development and evaluation of therapeutics for diseases that occur predominately in the developing world. One strategy to expedite the discovery of new drugs and to overcome potential financial barriers is to screen drugs approved by the US Food and Drug Administration for new indications. CD36 transcription is regulated by the nuclear receptor heterodimer peroxisome proliferator-activated receptor γ (PPARγ)–retinoic X receptor, activated when either partner is ligand bound [16]. We postulated that currently licensed PPARγ agonists (eg, rosiglitazone [17]) might represent novel immunomodulatory agents for the treatment of malaria by virtue of their potential to modify CD36, TLR, and related innate pathways. To test this hypothesis, we initially examined the activity of rosiglitazone in vitro and in murine models in vivo [15]. In these studies, the use of rosiglitazone modified inflammatory and phagocytic responses to *P. falciparum* infection in vitro, reduced parasitemia in vivo in a CD36-dependent manner in the *Plasmodium chaubaudi* model, and improved survival in the *Plasmodium berghei* ANKA model of experimental cerebral malaria.

Prior to a study of severe malaria among humans, we wanted to examine the safety and potential efficacy of using PPARγ agonists as adjunctive therapy for uncomplicated *P. falciparum* malaria and demonstrated that the use of rosiglitazone was well tolerated, enhanced parasite clearance, and modulated inflammatory responses to infection in a phase I/II randomized controlled trial.

METHODS

Participants and recruitment. Our study was conducted at the Hospital for Tropical Diseases, Mahidol University, Bangkok, Thailand, during the period from December 2004 through December 2005 and was approved by the Ethics Committee of Mahidol University. The trial is registered with ClinicalTrials.gov (identifier NCT00149383). Sequential symptomatic patients presenting to hospital clinics with *P. falciparum* malaria were asked to participate in the trial and were screened for eligibility criteria after providing written informed consent. Patients presented as part of routine care; no financial incentives were provided. Patients were included if they had a microscopically confirmed *P. falciparum* infection, were older than 14 years of age, and were able to tolerate oral therapy. Patients were excluded if they fulfilled any of the World Health Organization criteria for severe malaria [2], had been treated in the past with thiazolidinediones, had an allergy to atovaquone-proguanil or thiazolidinediones,

Table 1. Comparison of the Clinical and Laboratory Characteristics of the 2 Study Groups before Treatment

Characteristic	Rosiglitazone group ($n = 70$)	Placebo group ($n = 70$)	P
Sex			
Male	61 (87)	61 (87)	
Female	9 (13)	9 (13)	
Age, years			
Mean (±SD)	26.5 ± 10.3	26.1 ± 9.5	.833
Range	14–56	14–54	
Weight, kg	49.6 (7.2)	51.0 (7.7)	.241
Fever			
Duration before hospital admission, days	4.4 (3.9)	5.0 (3.8)	.332
Temperature before treatment, °C	37.8 (0.9)	37.7 (0.8)	.818
Splenomegaly	2 (3)	4 (6)	.681
Hepatomegaly	11 (16)	11 (16)	
Urine positive for drugs[a]	0 (0)	0 (0)	
First malaria attack	35 (50)	33 (47)	.866
Geometric mean parasite load (range), parasites/μL	491.17 (15–192,000)	443.02 (19–127,600)	.957
Packed cell volume, %	36.2 (5.6)	36.0 (6.0)	.859
WBC count, cells/μL	5260 (1390)	5514 (1838)	.359
Glucose level, mg/dL	118.4 (23.4)	123.7 (34.4)	.291
Blood urea level, mg/dL	14.4 (5.1)	15.8 (6.3)	.161
Serum creatinine, mg/dL	0.84 (0.16)	0.89 (0.23)	.189
Total bilirubin level, mg/dL	1.06 (0.68)	1.22 (0.85)	.219
Serum AST level, U/L	29.7 (20.6)	26.5 (15.1)	.318
Serum ALT level, U/L	26.6 (22.0)	23.1 (13.9)	.270
Albumin level, mg/dL	3.8 (0.4)	3.7 (0.4)	.342
ALP level, U/L	98.9 (52.2)	87.5 (43.5)	.165
Cholesterol, mg/dL	100.0 (27.0)	95.0 (28.1)	.459
G6PD deficiency	6 (9)	7 (10)	.729

NOTE. Data are no. (%) of patients or mean (± standard deviation [SD]). ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; G6PD, glucose-6-phosphate dehydrogenase; WBC, white blood cell.

[a] Sulfonamides and 4-aminoquinolones.

had a history of diabetes mellitus or decompensated liver disease, were pregnant or breast-feeding, had a history of congestive heart failure, had an elevated level of alanine aminotransferase (ALT; ie, >3 times the normal level) or creatinine (ie, ⩾2 times the normal level), and/or were engaged in active treatment for any systemic disease. After providing informed consent and enrolling, patients were hospitalized in Bangkok, a nontransmission area, and observed for a total of 28 days. This is a common trial design, to prevent reinfection and to reliably monitor for tolerability and treatment failure [18, 19].

Procedures for study entry and randomization. Employing a table of random numbers generated by Epi Info, version 6.04d (Centers for Disease Control and Prevention), by use of a blocked randomization design with permuted blocks of 10, we randomized participants (at a 1:1 ratio) to receive either rosiglitazone or placebo. Allocation of the study drug was double blinded and concealed until eligibility had been ascertained.

Intervention. Participants were treated with a fixed combination of atovaquone-proguanil (ie, 1000 mg of atovaquone per day for 3 days and 400 mg of proguanil per day for 3 days). Patients were randomized to receive 4 mg of rosiglitazone twice a day or a placebo twice a day, starting with their first dose of atovaquone-proguanil, for a duration of 96 h. The study drug (either rosiglitazone or placebo) was packaged in its own bottle and was labeled with the protocol number and dosing instructions to ensure blinding of both treating medical personnel and hospital staff. We felt that unblinding was unlikely to occur as a result of adverse events of drug use, because of the rarity of these events and the short duration of therapy.

Laboratory tests and data collection. Demographic data (including age, sex, past medical history, allergies, and previous history of malaria) were collected at enrollment and documented on individual case record forms. Oral temperature was documented at enrollment and every 4 h thereafter until the patient remained afebrile for ⩾24 h. Fever was defined as a temperature of ⩾38°C. Parasite load was quantified at baseline

Table 2. Comparison of Therapeutic Responses of the 2 Groups in Randomized, Double-Blind, Placebo-Controlled Trial

Parameter	Rosiglitazone group (n = 70)	Placebo group (n = 70)	P
Patients who dropped out	2 (3)	2 (3)	
Patients with 28-day follow-up	68 (97)	68 (97)	
Patients cured at 28 days	66 (94)	67 (96)	.843
Fever clearance time, h			
Mean (±SD)	35.6 ± 39.9	40.7 ± 34.3	.486
Range	4–158	4–148	
90% parasite clearance time, h			
Mean (±SD)	30.9 ± 18.2	40.4 ± 21.9	.004
Range	5–78	5–84	
50% parasite clearance time, h			
Mean (±SD)	19.0 ± 15.4	24.6 ± 19.1	.029
Range	3–72	3–75	

NOTE. Data are no. (%) of patients, unless otherwise indicated. SD, standard deviation.

by microscopy of Giemsa-stained smears and every 6 h thereafter until clearance of asexual parasite stages. After clearance, thick and thin blood films were repeated at 7, 14, 21, and 28 days of follow-up and/or if any recurrence of symptoms occurred. Expert microscopists were blinded to allocation status. Capillary blood glucose measurements were taken every 6 h for a total of 96 h (duration of study drug) and once on each of days 7, 14, 21, and 28 of follow-up. Serum samples (for monitoring aspartate aminotransferase [AST] and ALT levels) were drawn at baseline, at 24 h, at 96 h, and once on each of days 7 and 28 of follow-up. Hematological parameters, including hemoglobin level and white blood cell count, were monitored daily during administration of the study drug and at 7 days and 28 days of follow-up. Blood samples (for platelet counts) were obtained at baseline, at 24 h, and at 96 h and again on days 7 and 28 of follow-up. Renal function was documented at baseline and monitored at 24 h, at 96 h, and on days 7 and 28 of follow-up. Plasma levels of inflammatory mediators, including TNF, interleukin (IL)–6, and monocyte chemoattractant protein (MCP)–1, were assessed using multiplex bead assays (Luminex).

Patients kept a log of symptoms subjectively graded as "absent," "mild," "moderate," or "severe," on each of days 1, 4, and 7 after initiation of treatment. An independent data and safety monitoring committee reviewed the data periodically, and a provision was in place for discontinuation of the study medication if grade 3 or grade 4 toxicity [20] was experienced by any participant. Admissions to the intensive care unit (ICU) were to be reported to the committee chairman, and the study was to be terminated if there were more ICU admissions in the rosiglitazone arm.

Outcome measures. Primary efficacy outcomes were the 50% and 90% parasite clearance times (PCTs), which correspond to the time (in hours) at which a 50% and 90% respective reduction in baseline parasite load is observed. Secondary efficacy outcomes included the fever clearance time—defined as the time (in hours) to resolution of fever for ⩾24 h—and levels of inflammatory mediators on days 1–4. Secondary safety outcomes included capillary blood glucose measurements, aminotransferase levels, need for ICU admission, and tolerability of the study drug as assessed by patient log.

Sample size. The sample size was calculated for the primary efficacy outcomes. The mean PCT (± standard deviation) was estimated to be 40 ± 18 h in the group that received standard treatment plus placebo, on the basis of previously reported treatment studies of nonsevere *P. falciparum* malaria [19, 21]. Patients were expected to achieve clearance of parasitemia while on the study regimen. To detect a 25% difference in PCT with a power of 80% and $\alpha = .05$, a minimum of 63 patients were required per group (ie, a total of 126 patients) [22]. We assumed a loss to follow-up rate of 10% and targeted our enrollment at 140 patients.

Statistical analysis. Data were analyzed on an intention-to-treat basis. Patients with RIII patterns of failure (ie, treatment was unable to reduce the parasite density to <25% of the baseline value within 48 h) [23] were censored from the analyses of efficacy. Differences in normally distributed baseline data were compared by using analysis of variance. Proportions of categorical variables were compared using Yates-corrected χ^2 analysis. Differences in cure rates between treatment groups were compared using χ^2 analysis with Yates continuity correction. Differences in outcome measures were compared using an unpaired, 1-tailed t test (primary outcomes) or a 2-tailed $t$test (secondary outcomes). In the case of nonnormally distributed data, comparisons between ordinally transformed continuous variables were made using the Mann-Whitney

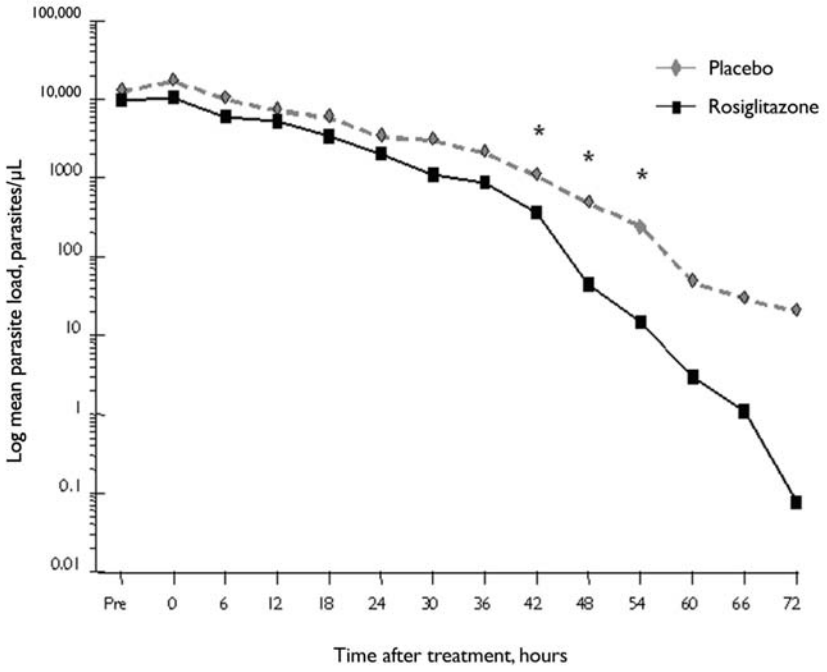

Figure 2. Log mean parasite load over time; the trial included patients who were aparasitemic. *Statistically significant differences in parasite load were observed between the rosiglitazone and placebo groups at 42 h ($P = .026$), 48 h ($P = .014$), and 54 h ($P = .016$). Pre, pretreatment.

rank sum test. Kaplan-Meier curves were generated for time to fever clearance, and differences in proportions were compared using Yates-corrected χ^2 analysis.

RESULTS

Of 176 individuals screened, 140 fulfilled the inclusion criteria and were randomly assigned to receive rosiglitazone or placebo (figure 1). The treatment groups were comparable at baseline (table 1). There were 2 participants from each arm that dropped out of the study, leaving a total of 136 participants who completed the 28-day follow-up period (table 2). The geometric mean parasite load was 491.2 parasites/μL in the rosiglitazone group, compared with 443.0 parasites/μL in the placebo group ($P = .957$).

Efficacy. Rosiglitazone-treated patients had significantly faster 50% and 90% PCTs. The mean 50% PCT was 19.0 h in

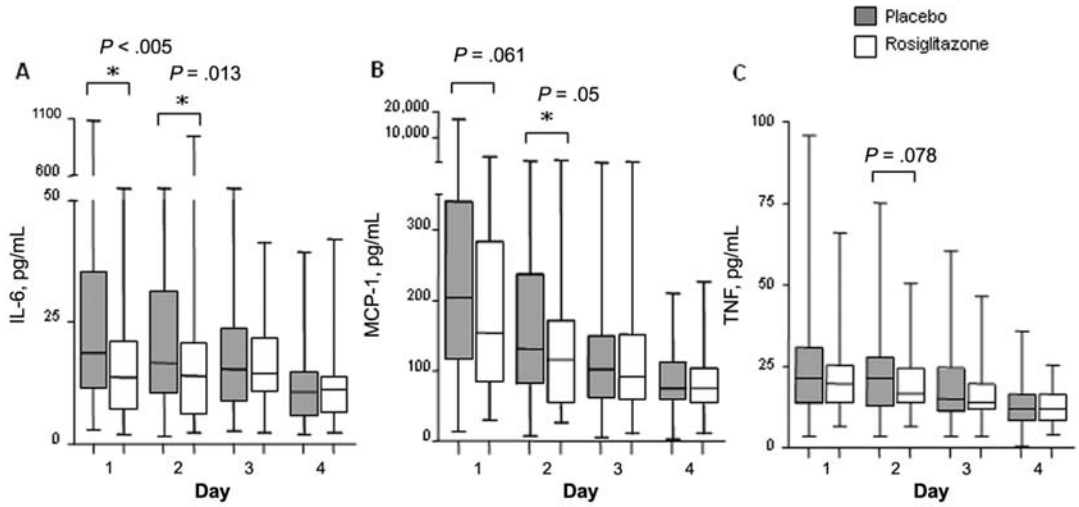

Figure 3. Serum levels of interleukin (IL)–6 *(A),* monocyte chemoattractant protein (MCP)–1 *(B),* and tumor necrosis factor (TNF) *(C).* Median values and ranges are indicated. Statistical significance was determined by use of the Mann-Whitney rank sum test.

Table 3. Secondary Biochemical Outcome Measures during Treatment and Follow-Up of the 2 Groups of Patients in the Randomized, Double-Blind, Placebo-Controlled Trial

	Rosiglitazone group		Placebo group		
Parameter	Mean (±SD)	Range	Mean (±SD)	Range	*P*
Serum glucose level, mg/dL					
At 24 h	105.3 (23.9)	58–195	105.5 (19.3)	58–195	.943
At 48 h	102.3 (15.9)	78–153	105.6 (20.3)	58–200	.260
At 72 h	100.2 (16.9)	71–163	103.1 (21.8)	75–196	.680
At 96 h	97.5 (11.8)	66–136	106.1 (31.8)	66–322	.067
At 7 days	85.0 (7.7)	66–103	87.0 (10.4)	53–116	.254
Serum AST level, U/L					
At day 1	29.8 (20.7)	10–107	26.9 (15.7)	11–91	.602
At day 4	26.0 (18.2)	9–99	22.0 (10.4)	10–65	.500
At day 7	27.1 (20.7)	10–147	28.5 (21.9)	9–133	.595
At day 28	25.1 (18.4)	10–138	23.3 (11.7)	11–81	.676
Serum ALT level, U/L					
At day 1	26.6 (22.3)	6–137	23.5 (14.3)	6–77	.607
At day 4	26.5 (20.8)	6–110	22.7 (13.0)	7–72	.636
At day 7	31.4 (26.8)	5–169	36.6 (33.5)	8–247	.179
At day 28	24.2 (23.9)	6–176	25.1 (24.3)	3–185	.605

NOTE. ALT, alanine aminotransferase; AST, aspartate aminotransferase; SD, standard deviation.

the rosiglitazone arm, compared with 24.6 h in the placebo arm ($P = .029$) (table 2). The mean 90% PCT was 30.9 h in the rosiglitazone arm, compared with 40.4 h in the placebo arm ($P = .004$) (table 2). At 42 h, 48 h, and 54 h after initiation of treatment, there was a greater reduction in parasite load, compared with baseline, in the rosiglitazone arm than in the placebo arm (figure 2). These findings were unaffected by inclusion of the censored patient with an RIII pattern of failure. The overall mean fever clearance time did not differ between the rosiglitazone and placebo groups (35.6 h vs. 40.7 h; $P = .486$). However, there was a trend toward a statistically significant increase in fever clearance after 4 h of treatment in the rosiglitazone arm, compared with the placebo arm (43% vs. 27% afebrile at 4 h; $P = .073$). Treatment with rosiglitazone also resulted in significantly lower levels of inflammatory biomarkers IL-6 at 24 h and 48 h after treatment and MCP-1 at 48 h after treatment (figure 3*A* and 3*B*). Rosiglitazone-treated patients also had lower levels of TNF, although this did not reach statistical significance ($P = .078$) (figure 3*C*). There were no significant differences in levels of macrophage inflammatory protein–1α, interferon-γ, IL-8, IL-10, IL-1β, or vascular endothelial growth factor between the rosiglitazone and placebo arms at any time point tested.

Safety. There were no ICU admissions or deaths among participants. Mean serum glucose levels were similar between the groups, although there was a trend toward a difference in mean glucose levels at 96 h (97.5 mg/dL in the rosiglitazone arm vs. 106.1 mg/dL in the placebo arm; $P = .067$) (table 3). There were no significant differences in serum AST or ALT levels between the groups at 1 day, 4 day, 7 day, and 28 days after initiation of treatment (table 3).

Tolerability. Symptom profiles were similar between groups on days 1 and 4 of treatment (table 4). A trend toward increased complaints of mild diarrhea in the rosiglitazone arm was observed on day 1, but these had resolved by day 4. Symptoms were graded as "mild" by all but 2 individuals: 1 participant from the placebo group complained of a "moderate" headache on day 1, and 1 participant from the rosiglitazone group complained of "moderate" myalgia on day 1. There were no subjective symptoms graded as "severe" and no discontinuations of medications as a result of adverse events.

DISCUSSION

Host response is an important determinant of the severity and outcome of malaria infections; however, few therapeutics have been developed that target deleterious host responses to infection [2, 4, 5, 24–26]. In a randomized, double-blind, placebo-controlled treatment trial of *P. falciparum* malaria, we report that rosiglitazone is a well-tolerated adjunctive therapy to standard antimalarial treatment and improves parasite clearance times (table 2), reduces parasite burden as assessed by peripheral parasitemia (figure 2), and decreases inflammatory biomarkers (figure 3), high levels of which are associated with adverse clinical outcomes.

Our study extends to human malaria infections recent results

Table 4. Secondary Tolerability Outcomes Assessed by Subjective Patient Log

Symptom	Rosiglitazone group (n = 70)	Placebo group (n = 70)	P
Headache			
Day 1	64 (91)	67 (96)	.284
Day 4	8 (11)	10 (14)	.776
Myalgia			
Day 1	60 (86)	62 (89)	.627
Day 4	4 (6)	8 (11)	.351
Weakness			
Day 1	59 (84)	62 (87)	.468
Day 4	3 (4)	7 (10)	.313
Dizziness			
Day 1	44 (63)	49 (70)	.400
Day 4	6 (9)	5 (7)	.975
Nausea			
Day 1	36 (51)	44 (63)	.194
Day 4	1 (1)	5 (7)	.204
Vomiting			
Day 1	26 (37)	34 (49)	.203
Day 4	0 (0)	3 (4)	.238
Diarrhea			
Day 1	9 (13)	2 (3)	.063
Day 4	0 (0)	1 (1)	…
Palpitations			
Day 1	5 (7)	5 (7)	.783
Day 4	1 (1)	0 (0)	…
Insomnia			
Day 1	6 (9)	5 (7)	.975
Day 4	0 (0)	1 (1)	…
Pruritus			
Day 1	0 (0)	1 (1)	…
Day 4	0 (0)	0 (0)	…
Cough			
Day 1	3 (4)	4 (6)	.99
Day 4	1 (1)	1 (1)	…

NOTE. Data are no. (%) of patients.

from experimental in vivo models showing that use of rosiglitazone improves outcome in acute malaria infection. Previous studies have demonstrated that use of rosiglitazone increases macrophage clearance of malaria-parasitized erythrocytes, modifies inflammatory responses to infection, and improves survival in models of experimental severe and cerebral malaria [11–15]. Extending observations from murine models to human trials represents an important step, particularly in light of recent systematic reviews highlighting discordance between treatment outcomes in animal models and those in human clinical trials [27].

Dysregulated inflammatory responses to malaria infection have been consistently implicated in malaria-associated pathology [6, 28–31]. In our study, the use of rosiglitazone reduced levels of inflammatory biomarkers, including IL-6 and MCP-1, the elevated levels of which have been correlated with poor outcomes in malaria [30, 31]. PPARγ agonists are known to modulate expression of proinflammatory cytokines and mediators via both PPARγ-dependent and PPARγ-independent mechanisms [32] and to inhibit TLR2- and CD36-dependent *pf*GPI-induced mitogen-activated protein kinase and nuclear factor κB-mediated inflammatory responses [13, 15]. Although there was no difference in the overall fever clearance time, there was a reduction in the proportion of rosiglitazone-treated participants who remained febrile early during therapy. This difference is difficult to explain by invoking a cytokine-mediated mechanism, because of the rapidity of the effect observed. It is possible that other inflammatory mediators, such as arachidonic acid metabolites and prostaglandins, may be affected by rosiglitazone, because of its action as a cyclyoxygenase-2 inhibitor [32].

In our trial, the individuals who received rosiglitazone were no more likely than those who received placebo to have elevated serum levels of hepatic aminotransferase. Although approximately one-third of all participants had an elevated AST or ALT level by day 7 after treatment, these elevated levels were anticipated for these patients with acute *P. falciparum* malaria [2] and are unlikely to be the result of the study drug. Overall, rosiglitazone has had an excellent safety profile. Documented adverse reactions such as hepatotoxicity and fluid overload are rare [33]. Although not a cause of congestive heart failure, rosiglitazone does cause marginal and clinically insignificant fluid retention in individuals with a normal left-ventricular ejection fraction [33, 34]. Clinically significant fluid retention tends to occur over a period of months in individuals with compromised left-ventricular function [33, 34]. A recent meta-analysis also reported the association of long-term (⩾24 weeks) rosiglitazone use with an increased risk of myocardial infarction [35]. However, these findings remain controversial, and it is unlikely that any potential adverse cardiac events associated with long-term use of rosiglitazone would be precipitated by the 4-day treatment period used in our study [36].

Although glycemic control is another potential issue with drugs indicated for the management of type 2 diabetes mellitus, the thiazolidinediones function as insulin sensitizers and are not known to cause hypoglycemia. We found no difference in the proportion of patients with hypoglycemia between the 2 treatment groups. This observation has important implications for the management of severe malaria in which hypoglycemia is common, in part, because of the use of intravenous antimalarial drugs, particularly quinine.

The mortality rate associated with cerebral malaria remains on the order of 10%–40% [2, 5, 24]. In attempts to improve outcome, a number of adjunctive therapies have been investigated, including the use of steroids [2, 25], TNF inhibitors

[2, 26, 37], heparin [2], and desferroxamine [38], although none has proven efficacious in large clinical trials [2–4]. In experimental models of cerebral malaria, the use of rosiglitazone significantly enhanced survival, even when initiated as late as 5 days after infection [15]. The present trial examined the safety, tolerability, and efficacy of rosiglitazone use in the management of uncomplicated disease and was conducted as a prelude to a trial of the treatment for severe malaria. Thus, although improvement in parasite clearance and inflammatory mediators associated with adverse outcomes was observed, it remains to be determined whether these findings will be generalizable to patients with severe or cerebral disease. Additional limitations include the possibility that observed differences in secondary outcomes were due to chance alone, because multiple comparisons were made between groups. However, because the secondary outcomes being analyzed were safety and tolerability, *P* values were set conservatively, thereby increasing the risk of a type I error. Finally, levamisole, a down-regulator of endothelial CD36 function, has been shown to reduce parasitized erythrocyte sequestration in humans with uncomplicated *P. falciparum* malaria in a study in which clinical outcomes were not assessed [39]. This raises a theoretical concern that the use of rosiglitazone, a CD36 upregulator, may lead to a functional increase in endothelial CD36 levels and to cytoadhesion. However, we have previously demonstrated that PPARγ agonists appear to have a maximal effect on monocyte and macrophage CD36 expression but only a minimal effect on endothelial surface levels of CD36, and that they do not significantly modify parasitized erythrocyte–endothelial cell interactions in vitro [40]. In summary, PPARγ agonists represent a novel class of immunomodulatory drugs that may have utility in the management of inflammatory states such as severe *P. falciparum* malaria.

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