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Review Article

The Case for the Use of PPARγ Agonists as an Adjunctive Therapy for Cerebral Malaria

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Cerebral malaria is a severe complication of *Plasmodium falciparum* infection associated with high mortality even when highly effective antiparasitic therapy is used. Adjunctive therapies that modify the pathophysiological processes caused by malaria are a possible way to improve outcome. This review focuses on the utility of PPARγ agonists as an adjunctive therapy for the treatment of cerebral malaria. The current knowledge of PPARγ agonist use in malaria is summarized. Findings from experimental CNS injury and disease models that demonstrate the potential for PPARγ agonists as an adjunctive therapy for cerebral malaria are also discussed.

1. Introduction

Few diseases have the global health and economic impact of malaria [1]. In 2009, an estimated 225 million people were infected with malaria and close to a million people succumbed to their infection [2]. Malaria is caused by apicomplexan parasites belonging to the genus *Plasmodium*. Five species infect humans, *Plasmodium falciparum*, *P. vivax*, *P. ovale*, *P. malariae*, and most recently, *P. knowlesi* [3]. The majority of morbidity and mortality is caused by *P. falciparum* infection, with the highest burden born by children and pregnant women. In the absence of prompt and effective treatment, *P. falciparum* infection can progress quickly, rapidly becoming severe and fatal. The rise in drug-resistant parasites complicates the administration of effective treatment.

Severe malaria has multiple manifestations that can occur singly or in combination. They include hyperparasitemia, high fever, haemoglobinuria, acute renal failure, acute pulmonary edema, metabolic acidosis and respiratory distress, hypoglycemia, anemia, and cerebral malaria, which is characterized by coma and convulsions. Cerebral malaria has the highest mortality rate of all the severe complications and is associated with long-term cognitive and neurological deficits in surviving children [4–6].

Intravenous artesunate is now the standard of care for severe malaria in both adults and children following the landmark SEAQUAMAT and AQUAMAT trials that demonstrated the superiority of artesunate over quinine in adults and in children [7, 8]. However, even with the improved efficacy of artesunate, fatality rates remained high, 15% in adults and 10.9% in children. Adjunctive therapies, defined as therapies administered in combination with antiparasitic drugs that modify pathophysiological processes caused by malaria, have been pursued as a way to improve the outcome of severe malaria. Adjunctive therapies may also help extend the efficacy of antiparasitic drugs, an important consideration given the emergence of artemisinin resistance [9, 10]. Several adjunctive therapeutic strategies have been tested in *P. falciparum* cerebral and severe malaria so far, unfortunately with-out much success (see [11] for a recent review). A number of adjunctive therapies (including nitric oxide, arginine, erythropoietin, levamisole) have demonstrated encouraging results in experimental models of cerebral malaria or in clinical trials in uncomplicated malaria and are awaiting evaluation in severe malaria [11].

This review will focus on the utility of PPARγ agonists as an adjunctive therapy for the treatment of cerebral malaria. The current knowledge of PPARγ agonist use in malaria will be summarized. We will also summarize data on additional

mechanisms of action attributed to PPARγ agonists that may be of benefit in cerebral malaria.

2. The Pathogenesis of Cerebral Malaria

Cerebral malaria is a severe complication of *P. falciparum* infection. It occurs in nonimmune individuals, with the greatest burden born by children in sub-Saharan Africa. Although the parasite is a key player in the development of cerebral malaria, hyperparasitemia does not necessarily correlate with disease severity, and cerebral pathology can develop even with the use of effective antiparasitic therapy. It has long been recognized that the host immune response plays an important role in mediating pathology in malaria, and this has fueled the search for effective immunomodulatory adjunctive therapies.

Sequestration of parasitized erythrocytes (PEs) in the microvasculature of the brain (and other organs), resulting in vascular occlusion and local tissue hypoxia and ischemia, is the hallmark feature of cerebral malaria [12]. Sequestration of PEs occurs via receptor-ligand interactions, with parasite-derived ligands expressed on the surface of PEs (a major one being *P. falciparum* erythrocyte membrane protein-1 or Pfemp-1) binding to receptors expressed on microvascular endothelial cells. Postmortem, in vitro, and genetic studies support that ICAM-1 is the major sequestration receptor for PEs in the brain, while the scavenger receptor CD36 is the major receptor outside the brain [13–21].

Parasites produce a variety of bioactive molecules that can elicit innate immune responses in the host [22]. An excessive inflammatory response with elevated levels of pro-inflammatory cytokines, especially TNF, is a major contributor to cerebral malaria pathology [23]. TNF, produced by activated endothelium and recruited leukocytes, can upregulate cell adhesion molecules, including ICAM-1, and exacerbate PE sequestration. Higher levels of TNF have been observed in cerebral malaria and correlated with mortality [24–26], and genetic predisposition to overproduce TNF in response to infection has been associated with susceptibility to cerebral malaria [27, 28]. Elevated levels of TNF are also seen in the cerebral spinal fluid (CSF) of infected children and correlated with encephalopathy [29]. Interestingly, CSF TNF levels did not correlate with serum levels, implying independent cerebral generation of TNF. Elevated levels of additional inflammatory mediators including IFNγ, IL-6, IL-1β, IL-1ra, IL-10, MIP-1α and MIP-1β, MCP-1, and IP-10 have been observed in cerebral malaria patients [26, 30–34].

Parasite sequestration and inflammation can lead to endothelial activation and dysfunction. Activated endothelium can lead to monocyte and platelet recruitment further impeding vessel flow and contributing to tissue hypoxia and ischemia [35]. Widespread endothelial activation (including increased ICAM-1 expression and the disruption of cell-junction proteins) has been observed in postmortem studies of cerebral malaria patients [36], and markers of endothelial activation and dysfunction such as soluble ICAM-1, von Willebrand factor, and angiopoietin-2 are elevated in cerebral malaria [37–39]. Low nitric oxide (NO) bioavailability (potentially due to quenching by cell-free hemoglobin released during hemolysis) contributes to the development of endothelial dysfunction in malaria infection [40, 41].

Sequestration, inflammation, and endothelial dysfunction can lead to a breakdown of the blood-brain barrier (BBB). Hemorrhages are common autopsy findings in cerebral malaria [12, 42, 43], as are focal disruptions of the BBB [44]. The activation of perivascular macrophages and axonal damage observed in cerebral malaria may be the result of cytokines, parasite antigens, and plasma proteins crossing the BBB, in addition to local hypoxic and inflammatory conditions [36, 45, 46].

Metabolic perturbations are also common in children with cerebral malaria and may contribute to pathology. Vascular obstruction leading to hypoxia, or TNF-induced cytopathic hypoxia, have been proposed as possible causes [47–49].

Recent investigations using fluorescein angiography and fundoscopy have permitted a view of the brain microvasculature in living patients with cerebral malaria, by imaging the retina (the only part of the central nervous system (CNS) vasculature that is available for direct observation). Pediatric cerebral malaria patients had evidence of PE sequestration and thrombi (containing both fibrin and platelets) in their vasculature that were associated with perfusion abnormalities and areas of ischemia and tissue damage (retinal whitening). Focal disruptions of the BBB were observed most often, but not always, in association with hemorrhages [44, 50, 51]. Postmortem analysis revealed axonal damage not only in areas of hemorrhage but also in areas of vascular occlusion by sequestered parasites and/or fibrin-platelet thrombi [51].

Cerebral malaria is a complex disorder that is as yet not fully understood. Multiple processes likely contribute to its development including peripheral and CNS inflammation, PE sequestration, vascular endothelial activation, prothrombotic activation, blood flow obstruction, tissue hypoxia and ischemia, metabolic changes, and BBB dysfunction, leading to neurodegeneration. These processes can contribute to the seizures and coma seen in cerebral malaria patients and the neurologic and cognitive deficits which persist in a portion of cerebral malaria survivors [4, 29]. The activation of PPARγ appears to play an important role in recovery in several models of CNS injury and disease, by limiting inflammation and cytotoxicity and promoting reparative mechanisms. These mechanisms may also be protective in the context of cerebral malaria as well. Interestingly, PPARγ was one of only two genes in a malaria-resistance locus identified using a genome-wide analysis of inbred mouse lines [52], supporting a protective role for PPARγ in malaria.

3. PPARγ and Its Agonists

PPARγ is a member of the family of nuclear hormone receptors which function as ligand-activated transcription factors [53]. PPARγ endogenous ligands include oxidized fatty acids and prostanoids, and synthetic ligands include the thiazolidinedione (TZD) class of antidiabetic drugs (e.g., rosiglitazone and pioglitazone). Upon ligand activation, PPARγ

heterodimerizes with the retinoid X receptor (RXR), a nuclear receptor for 9-cis-retinoic acid. The ligand-bound PPARγ-RXR heterodimer regulates gene transcription by binding to conserved DNA sequences called PPRE (PPAR response elements) on target genes. PPARγ can also regulate other transcription factors, through nongenomic transrepression, where the inhibition of transcription occurs by preventing the dissociation of corepressors or by sequestering the coactivators necessary for the binding of the transcription factor to DNA [54].

Originally characterized in adipocytes as a regulator of lipid and glucose metabolism, current evidence indicates that PPARγ is present in most cell types (including immune cells, endothelial cells, and neurons) and mediates multiple functions in both physiological and pathological conditions [55, 56].

PPARγ agonists have been extensively studied in many inflammatory settings, in vitro, in animal models, and in humans, and in most cases they have demonstrated anti-inflammatory properties [57]. These anti-inflammatory properties are early events (observed prior to any metabolic effects) and occur even with low-dose administration of the agonists [58]. PPARγ agonists can inhibit proinflammatory responses from a variety of cells including macrophages, dendritic cells, T cells, endothelial cells, vascular smooth muscle cells, microglia, and astrocytes [59–74]. The anti-inflammatory properties of the agonists are mediated by the transrepression effects of activated PPARγ on transcription factors including activator protein-1 (AP-1), signal transducers and activators of transcription 1 (STAT-1), nuclear factor kB (NF-κB), and nuclear factor of activated T cells (NFAT). PPARγ agonists can also suppress inflammation by PPARγ-independent mechanisms, for example, the suppression of JAK-STAT-dependent inflammatory responses in activated microglia and astrocytes via the induction of members of the suppressor of cytokine signaling (SOCS) family [75, 76].

Data have also been accruing on the neuroprotective properties of PPARγ agonists in models of CNS injury, ischemic stroke, and diseases of the CNS including multiple sclerosis, ALS, and Parkinson's disease [77–80]. These data suggest that PPARγ may be involved in coordinating cellular responses to CNS injury and disease. The potential benefit of the anti-inflammatory and neuroprotective properties of PPARγ agonists in cerebral malaria will be discussed below.

4. Generation of Endogenous PPARγ Ligands in Malaria Infection

Plasmodium falciparum may itself activate PPARγ, perhaps as part of a strategy aimed at enhancing symbiotic survival between the parasite and the host. Hemozoin, a pigment produced by *Plasmodium* to detoxify free heme generated by the degradation of haemoglobin [81], can produce large amounts of hydroxyl-fatty acids, including 15-hydroxyecosatetraenoic acid (15-HETE), 13-hydroxyoctadecadienoic acid (13-HODE), and 4-hydroxynonenal (4-HNE) by heme-catalyzed lipoperoxidation [82]. 15-HETE and 13-HODE are specific ligands of PPARγ, and 4-HNE is an inducer of PPARγ [83]. Hemozoin-mediated immunosuppressive effects on myeloid cell functions including phagocytosis, inflammatory responses, oxidative burst, and dendritic cell differentiation and maturation have been reported [84–89]. Hemozoin was able to induce the upregulation of PPARγ mRNA, while the inhibition of PPARγ reversed some of the hemozoin-mediated effects, suggesting that the immunomodulatory effects of hemozoin may be, at least partly, mediated by PPARγ activation [90].

5. The Use of PPARγ Agonists in Malaria: What We Know So Far

The use of PPARγ agonists to modulate immune responses to malaria was initially motivated by reports demonstrating that PPARγ regulates CD36 transcription and that PPARγ agonists have anti-inflammatory properties [61, 63].

At that time, the scavenger receptor CD36 was revealed to be a major, noninflammatory, phagocytic receptor for non-opsonised mature-stage PEs [91]. It was speculated that CD36-mediated phagocytosis of PEs represented an innate immune mechanism for controlling the parasite burden in nonimmune individuals (who are most at risk of developing severe disease) [91–94]. Later, CD36-mediated phagocytosis of ring-stage PEs and stage I and IIa gametocytes was also reported [95, 96]. The importance of CD36-mediated innate control of acute blood-stage malaria was demonstrated in vivo, in a murine model of hyperparasitemia (*P. chabaudi* AS infection) [97]. In this model, mice deficient in CD36 had higher parasitemia levels and higher mortality compared to CD36-sufficient mice [97].

Various PPARγ agonists including the natural ligands 15d-PGJ2 and 9-cis-retinoic acid (which binds RXR to activate the PPARγ-RXR heterodimer), and the synthetic TZDs, ciglitazone, troglitazone, and rosiglitazone, were shown to upregulate the CD36 expression on monocytes and enhance the CD36-mediated phagocytosis of PEs [92, 95, 96, 98]. And unlike Fc-mediated phagocytosis, CD36-mediated uptake of PEs occurred in a noninflammatory manner that was not associated with release of TNF or IL-6 [91, 99]. This process appeared similar to the CD36-mediated clearance of apoptotic cells, which is also non-inflammatory, but did not appear to involve cooperation with integrins [91, 100, 101]. PPARγ agonists also dramatically upregulated the uptake of ring-stage PEs and gametocytes [95, 96]. These findings where extended in vivo using the mouse model of hyperparasitemia. Mice receiving rosiglitazone had lower parasitemia compared to controls [102]. This reduction in parasitemia was CD36 dependent, as it was not observed in mice deficient in CD36.

These data are consistent with the reported ability of PPARγ activation to polarize macrophages towards an alternatively activated phenotype [57]. Alternatively activated macrophages have reduced expression of proinflammatory cytokines, enhanced expression of anti-inflammatory cytokines, in particular IL-10, and enhanced expression of pattern-recognition receptors, including CD36. They have been implicated in pathogen sequestration, wound healing,

and phagocytosis of apoptotic cells. In the context of malaria, alternatively activated macrophages could help control parasite burden while limiting associated inflammation, thus reducing host pathology [103].

Although reducing the parasite burden by enhancing phagocytic clearance of parasites (especially ring-stage PEs) will undoubtedly be beneficial to the outcome of infection and may be a contributing mechanism to the genetic resistance offered by hemoglobinopathies (sickle cell and both α-thalassemia and β-thalassemia) and glucose-6-phosphate dehydrogenase and pyruvate kinase deficiencies [104–106], in the context of cerebral malaria, parasitemia levels are not correlated with disease severity. Rather, inflammation, and especially TNF levels seem to correlate with disease severity, encephalopathy, and death [23, 29]. Thus, the anti-inflammatory properties of PPARγ agonists may be their most important quality when it comes to the treatment of cerebral malaria.

Human monocytes and murine macrophages treated with PPARγ agonists generate significantly less TNF in response to malaria-related inflammatory stimuli including parasite lysates and *P. falciparum* glycosylphosphatidyl inositol (GPI), a malaria toxin that interacts with TLR2 [98, 107, 108]. This was associated with the inhibition of NF-κB and MAPK signaling [102]. PPARγ is known to inhibit the NF-κB signaling [54], and a PPARγ-mediated inhibitory effect on MAPK signaling has recently been described [109]. However, whether the anti-inflammatory effects of the agonists were related to PPARγ activation was not directly examined.

The effects of PPARγ agonists in vivo have been tested in a mouse model of experimental cerebral malaria (*P. berghei* ANKA). Cerebral pathology in this model is the result of an uncontrolled proinflammatory response to infection [47, 110]. Infected mice treated with rosiglitazone had a more balanced inflammatory response, with reduced plasma levels of TNF, a reduced TNF to TGFβ ratio, and higher IL-10 levels ([102], and unpublished results by Serghides et al.). Mice receiving rosiglitazone were also protected from developing signs of cerebral pathology and had significantly improved survival rates. This was evident even when rosiglitazone was administered as late as 5 days postinfection, just prior to the initiation of cerebral pathology [102]. The effects of rosiglitazone treatment on endothelial dysfunction and cerebral pathology in this model are currently under investigation in our lab.

Given the encouraging data in the mouse models, a phase I/IIa randomized double-blind placebo-controlled trial was undertaken to test the safety, tolerability, and efficacy of rosiglitazone adjunctive therapy in 140 Thai adults with uncomplicated *falciparum* malaria [111]. Rosiglitazone (4mg twice daily for 4 days) was administered as an adjunctive therapy in combination with atovaquone-proguanil and was found to be safe and well tolerated. Patients receiving rosiglitazone had significantly reduced 50% and 90% parasite clearance times, with the mean 90% parasite clearance time being reduced by 25% in the rosiglitazone group (from 40.4 h in placebo to 30.9 h in the rosiglitazone group). It is tempting to speculate that improved parasite clearance was due to enhanced CD36-mediated clearance, but direct evidence is lacking. However, these findings do corroborate the effects of rosiglitazone on parasitemia observed in the mouse model, a process that was CD36 dependent [102]. A nonstatistically significant trend towards greater fever clearance at 4 hours posttreatment was observed in those receiving rosiglitazone (43% afebrile in the rosiglitazone group compared to 27% afebrile in the placebo group, $P = .073$). Patients receiving rosiglitazone also had significantly lower levels of IL-6 and MCP-1 and trended towards significantly lower levels of TNF at 24 and 48 hours posttreatment [111]. Both the fever reduction and the lower levels of proinflammatory biomarkers suggest that treatment with rosiglitazone was associated with anti-inflammatory effects that were obvious early during the course of therapy in these patients.

The findings in the rosiglitazone trial share some similarities to those of a randomized trial of vitamin A supplementation in children from Papua New Guinea [112]. 9-cis-retinoic acid is a metabolite of vitamin A and an agonist of PPARγ (via RXR ligation), and like rosiglitazone, has been shown to enhance CD36-mediated PE uptake and reduce malaria-induced TNF production in vitro [113]. Children supplemented with vitamin A had lower parasitemia levels and fewer febrile episodes than did children in the control group, although both groups had the same rate of infection [112], suggesting a common mechanism of enhanced innate clearance of PEs and reduced inflammation.

6. Lessons from the Use of PPARγ Agonists in Neuroinflammatory and Neurodegenerative Diseases

Data on the anti-inflammatory and neuroprotective properties of PPARγ agonists in models of neuroinflammatory and neurodegenerative disease states may give us an insight into how PPARγ agonist could function in cerebral malaria [77–80].

Relevant to cerebral malaria pathology, PPARγ is expressed not only in immune cells and in peripheral organs, but also in the CNS (microglia, astrocytes, perivascular macrophages, oligodendrocytes, and neurons) and in human brain microvascular endothelial cells [114–116]. Further, PPARγ agonists such as rosiglitazone and pioglitazone can cross the BBB [117], and thus, can exert their effects not only peripherally but also directly on the CNS.

As mentioned above cerebral malaria is an inflammatory disease [23, 49]. Proinflammatory cytokines, especially TNF, initiate an inflammatory cascade that leads to endothelial activation, cell adhesion molecule upregulation, enhanced PE, leukocyte- and platelet-endothelial adhesion, endothelial dysfunction, and BBB breakdown [47]. Perivascular macrophages, astrocytes, and microglia are also activated in cerebral malaria and can produce inflammatory mediators leading to neuronal damage [118]. Several anti-inflammatory properties of relevance to cerebral malaria pathology have been ascribed to PPARγ agonists. PPARγ agonists have been shown to inhibit the following: the expression of inflammatory mediators, such as TNF, IL-6, IL-1b, and COX-2, from activated monocytes and microglial

[74, 119]; the release of chemokines including MCP-1, MIP-1a, and MIP-1b; the expression of chemokine receptors on leukocytes; the inflammation-induced upregulation of cell adhesion molecules on vascular endothelium, including ICAM-1 [120, 121]; the recruitment of leukocytes to injured sites [74, 122]; the release of matrix metalloproteinases (which degrade the extracellular matrix and contribute to BBB dysfunction) from macrophages and glial cells [123, 124]. In the context of cerebral malaria, these activities could result in less proinflammatory cytokines peripherally and in the CNS, a reduction in PE adhesion and leukocyte recruitment in the brain, and protection of the BBB integrity.

Malaria is associated not only with inflammation, but also with oxidative stress, conditions that together can lead to increased cytotoxicity. Elevated levels of TNF in addition to oxidants such as superoxide and free heme can lead to neuronal damage [125, 126]. TNF, superoxide, and free heme (caused by hemolysis) are all elevated in cerebral malaria and may contribute to the neuronal damage detected in brains of cerebral malaria patients [43, 45, 46, 127]. In addition to their anti-inflammatory properties, PPARγ agonists also have antioxidant properties. PPARγ agonists enhance the endothelial and neuronal expression and activity of superoxide dismutase-1 (SOD-1) and catalase (both of them have functional PPREs in their promoter) [128–132]. SOD-1 and catalase detoxify superoxide by catalyzing its conversion into water and oxygen. PPARγ can also suppress superoxide generation by decreasing the expression of components of the NAD(P)H oxidase complex [129, 130, 133]. Rosiglitazone-induced reduction in NAD(P)H oxidase activity has been detected in models of hypertension and diabetes [128, 134]. Heme oxygenase-1 (HO-1) also contains a PPRE in its promoter and can be upregulated by PPARγ activation [135]. HO-1 is induced during conditions of oxidative stress and catalyses the breakdown of heme into biliverdin, iron, and CO. CO is anti-inflammatory and can inhibit TNF while inducing IL-10 release [136]. HO-1 induction protects astrocytes from heme-mediated oxidative injury, and astrocytes deficient in HO-1 are much more susceptible to cell death [137]. HO-1 and CO have been shown to be protective in experimental cerebral malaria and were associated with reduced inflammation, protection of the BBB, and enhanced survival [138].

Oxidative stress can also result in decreased NO bioavailability, via scavenging by cell-free hemoglobin and/or superoxide-mediated formation of the toxic peroxynitrite [139]. Low NO bioavailability has been associated with disease severity, while NO supplementation improves disease outcome in human and experimental cerebral malaria ([40, 41, 140–143], submitted by Serghides et al.). By enhancing cell-free hemoglobin detoxification (via HO-1 upregulation) and by reducing the levels of reactive oxygen species (via SOD-1 and catalase upregulation), PPARγ agonist activity may enhance NO bioavailability [144]. A trial in diabetic patients is currently underway examining whether pioglitazone will improve NO bioavailability (clinicaltrials.gov ID NCT00770367).

An additional neuroprotective property of PPARγ agonists is their ability to regulate the expression of the glutamate receptor GLT1/EAAT2 (GLT1/EAAT2 has six putative PPREs in its promoter region) [145]. Glutamate is the major excitatory neurotransmitter in the mammalian CNS, but high amounts of glutamate released in the intersynaptic spaces can cause neurodegeneration and excitotoxic neuronal death. Glutamate plays an important role in many CNS pathologic conditions including ischemia, trauma, and neurodegenerative disorders [146]. Glutamate levels have not been measured in humans but were shown to be elevated in the CSF and in the cerebral cortex of mice with experimental cerebral malaria, suggesting that glutamate toxicity may occur in cerebral malaria. In these mice, glutamate levels correlated with the development of cerebral symptoms [147, 148]. The mechanism for maintaining low extracellular glutamate levels is astrocytic uptake via glutamate transporters including GLT1/EAAT2, which is responsible for the removal of up to 90% of extracellular glutamate. PPARγ agonists increased astrocytic expression of GLT1/EAAT2 mRNA and protein in vitro [145] and protected astrocytes and neurons from glutamate-induced cell death [145, 149, 150]. In rats, rosiglitazone prevented the stress-induced decrease in synaptosomal glutamate uptake, by enhancing glial expression of GLT1/EAAT2 [151].

Collectively these data support a neuroprotective role for PPARγ agonists via the attenuation of inflammation, oxidative stress, and cytotoxicity [152]. Such protective effects have been observed with PPARγ agonist use in models of ischemic and hemorrhagic stroke [153–158], and in models of CNS disease including Alzheimer's disease, multiple sclerosis (MS), amyotrophic lateral sclerosis, and Parkinson's disease [152]. In the ischemic models, PPARγ agonist use was associated with reduced brain injury and with improved neurological outcomes [124, 154, 159–162]. In the CNS disease models, PPARγ agonists attenuated neuron loss, prevented motor dysfunction, improved motor performance, and reversed memory decline [163–166]. Supporting data from human trials also exist. In a pilot study in Alzheimer's patients, rosiglitazone administration improved cognitive function [167, 168]. In a small placebo-controlled trial of pioglitazone use in patients with relapsing MS, gray matter atrophy and lesion burden, as assessed by MRI, were reduced in the pioglitazone group [169]. Diabetic patients receiving pioglitazone or rosiglitazone had improved functional recovery after stroke compared to patients not taking TZDs [170]. Clinical trials are underway testing the efficacy of TZDs in Alzheimer's (phase III), ALS (phase I/II), and Friedreich's ataxia (pilot).

7. Are PPARγ Agonists Promising Candidates for Adjunctive Therapy in Cerebral Malaria?

PPARγ activation may enhance the tolerance of the host to malaria infection by immunoregulatory mechanisms (modulation of the inflammatory response to infection), and by mechanisms that render tissues more resistant to inflammatory damage. Such immunomodulatory effects are likely to be protective in the context of cerebral malaria. However,

whether PPARγ activation following the onset of cerebral malaria (once the inflammatory cascade has begun) will be protective is an open question. Other immunomodulatory therapies tested in cerebral malaria in the past (e.g., anti-TNF antibodies, dexamethasone) have failed [11]. That PPARγ activation impacts several pathways and may have not only neuroprotective but also neuroregenerative effects improves the likelihood of efficacy. However, it is unknown whether the regenerative effects seen with long-term PPARγ agonist use in chronic CNS disease will also be obvious with a short treatment course, as would be administered in cerebral malaria.

Rosiglitazone (4 mg twice daily for 4 days administered in combination with atovaquone-proguanil) was found to be safe and well tolerated in uncomplicated malaria. Mean serum glucose, alanine aminotransferase, and aspartate aminotransferase levels did not differ between patients receiving placebo and those receiving rosiglitazone [111]. In addition, there were no differences observed in the incidences of adverse events including headache, myalgia, weakness, nausea, vomiting, diarrhea, or palpitations between the two groups [111]. TZDs are antidiabetic drugs, and so a concern would be the possible exacerbation of the hypoglycemia commonly seen in severe malaria; however, rosiglitazone and other TZDs function as insulin sensitizers and are generally not known to cause hypoglycemia, and as mentioned above, rosiglitazone did not cause hypoglycemia in patients with uncomplicated malaria [111]. Rosiglitazone may also worsen edema by increasing fluid retention, but clinically significant fluid retention tends to occur only with long-term use [171]. Increased risk of myocardial infarction and hepatotoxicity are risk factors associated with rosiglitazone use, but again these are complications associated with long-term use [172]. Finally, it is worth considering whether PPARγ agonists could have an impact on the acquisition of adaptive immunity to malaria via modulatory effects on dendritic cells, T cells, and B cells [57].

The existing data on the use of PPARγ agonists in malaria are encouraging, with rosiglitazone being safe, well tolerated, and efficacious in uncomplicated malaria patients. Given the anti-inflammatory, neuroprotective, and neuroregenerative properties reported for PPARγ agonists in models of CNS injury, ischemic stroke, and diseases of the CNS, we can hypothesize that PPARγ activation in cerebral malaria may lead to improved outcome and possibly less long-term cognitive and neurological deficits. However, a randomized double-blind placebo-controlled trial in patients with cerebral malaria will be required to determine if these hypotheses are correct.

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References

[1] R. W. Snow, C. A. Guerra, A. M. Noor, H. Y. Myint, and S. I. Hay, "The global distribution of clinical episodes of *Plasmodium falciparum* malaria," *Nature*, vol. 434, no. 7030, pp. 214–217, 2005.

[2] WHO, *World Malaria Report*, 2010.

[3] B. Singh, L. K. Sung, A. Matusop et al., "A large focus of naturally acquired Plasmodium knowlesi infections in human beings," *The Lancet*, vol. 363, no. 9414, pp. 1017–1024, 2004.

[4] C. C. John, P. Bangirana, J. Byarugaba et al., "Cerebral malaria in children is associated with long-term cognitive impairment," *Pediatrics*, vol. 122, no. 1, pp. e92–e99, 2008.

[5] M. J. Boivin, "Effects of early cerebral malaria on cognitive ability in Senegalese children," *Journal of Developmental and Behavioral Pediatrics*, vol. 23, no. 5, pp. 353–364, 2002.

[6] M. J. Boivin, P. Bangirana, J. Byarugaba et al., "Cognitive impairment after cerebral malaria in children: a prospective study," *Pediatrics*, vol. 119, no. 2, pp. e360–e366, 2007.

[7] A. Dondorp, F. Nosten, K. Stepniewska, N. Day, and N. White, "Artesunate versus quinine for treatment of severe falciparum malaria: a randomised trial," *The Lancet*, vol. 366, no. 9487, pp. 717–725, 2005.

[8] A. M. Dondorp, C. I. Fanello, I. C. Hendriksen et al., "Artesunate versus quinine in the treatment of severe falciparum malaria in African children (AQUAMAT): an open-label, randomised trial," *The Lancet*, vol. 376, no. 9753, pp. 1647–1657, 2010.

[9] A. M. Dondorp, F. Nosten, P. Yi et al., "Artemisinin resistance in *Plasmodium falciparum* malaria," *The New England Journal of Medicine*, vol. 361, no. 5, pp. 455–467, 2009.

[10] N. J. White, "Artemisinin resistance—the clock is ticking," *The Lancet*, vol. 376, no. 9758, pp. 2051–2052, 2010.

[11] C. C. John, E. Kutamba, K. Mugarura, and R. O. Opoka, "Adjunctive therapy for cerebral malaria and other severe forms of *Plasmodium falciparum* malaria," *Expert Review of Anti-Infective Therapy*, vol. 8, no. 9, pp. 997–1008, 2010.

[12] T. E. Taylor, W. J. Fu, R. A. Carr et al., "Differentiating the pathologies of cerebral malaria by postmortem parasite counts," *Nature Medicine*, vol. 10, no. 2, pp. 143–145, 2004.

[13] A. R. Berendt, D. L. Simmons, J. Tansey, C. I. Newbold, and K. Marsh, "Intercellular adhesion molecule-1 is an endothelial cell adhesion receptor for *Plasmodium falciparum*," *Nature*, vol. 341, no. 6237, pp. 57–59, 1989.

[14] K. Silamut, N. H. Phu, C. Whitty et al., "A quantitative analysis of the microvascular sequestration of malaria parasites in the human brain," *American Journal of Pathology*, vol. 155, no. 2, pp. 395–410, 1999.

[15] G. D. H. Turner, H. Morrison, M. Jones et al., "An immunohistochemical study of the pathology of fatal malaria: evidence for widespread endothelial activation and a potential role for intercellular adhesion molecule-1 in cerebral sequestration," *American Journal of Pathology*, vol. 145, no. 5, pp. 1057–1069, 1994.

[16] A. Craig, D. Fernandez-Reyes, M. Mesri et al., "A functional analysis of a natural variant of intercellular adhesion molecule-1 (ICAM-1(Kilifi))," *Human Molecular Genetics*, vol. 9, no. 4, pp. 525–530, 2000.

[17] D. Fernandez-Reyes, A. G. Craig, S. A. Kyes et al., "A high frequency African coding polymorphism in the N-terminal domain of ICAM-1 predisposing to cerebral malaria in Kenya," *Human Molecular Genetics*, vol. 6, no. 8, pp. 1357–1360, 1997.

[18] J. W. Barnwell, A. S. Asch, R. L. Nachman, M. Yamaya, M. Aikawa, and P. Ingravallo, "A human 88-kD membrane glycoprotein (CD36) functions in vitro as a receptor for a cytoadherence ligand on *Plasmodium falciparum*-infected erythrocytes," *Journal of Clinical Investigation*, vol. 84, no. 3, pp. 765–772, 1989.

[19] C. F. Ockenhouse, N. N. Tandon, C. Magowan, G. A. Jamieson, and J. D. Chulay, "Identification of a platelet membrane glycoprotein as a falciparum malaria sequestration receptor," *Science*, vol. 243, no. 4897, pp. 1469–1471, 1989.

[20] P. Oquendo, E. Hundt, J. Lawler, and B. Seed, "CD36 directly mediates cytoadherence of *Plasmodium falciparum* parasitized erythrocytes," *Cell*, vol. 58, no. 1, pp. 95–101, 1989.

[21] C. Newbold, A. Craig, S. Kyes, A. Rowe, D. Fernandez-Reyes, and T. Fagan, "Cytoadherence, pathogenesis and the infected red cell surface in *Plasmodium falciparum*," *International Journal for Parasitology*, vol. 29, no. 6, pp. 927–937, 1999.

[22] L. Schofield and G. E. Grau, "Immunological processes in malaria pathogenesis," *Nature Reviews Immunology*, vol. 5, no. 9, pp. 722–735, 2005.

[23] G. E. Grau, T. E. Taylor, M. E. Molyneux et al., "Tumor necrosis factor and disease severity in children with falciparum malaria," *The New England Journal of Medicine*, vol. 320, no. 24, pp. 1586–1591, 1989.

[24] D. Kwiatkowski, A. V. S. Hill, I. Sambou et al., "TNF concentration in fatal cerebral, non-fatal cerebral, and uncomplicated *Plasmodium falciparum* malaria," *The Lancet*, vol. 336, no. 8725, pp. 1201–1204, 1990.

[25] B. D. Akanmori, J. A. L. Kurtzhals, B. Q. Goka et al., "Distinct patterns of cytokine regulation in discrete clinical forms of *Plasmodium falciparum* malaria," *European Cytokine Network*, vol. 11, no. 1, pp. 113–118, 2000.

[26] H. Brown, G. Turner, S. Rogerson et al., "Cytokine expression in the brain in human cerebral malaria," *Journal of Infectious Diseases*, vol. 180, no. 5, pp. 1742–1746, 1999.

[27] W. McGuire, A. V. S. Hill, C. E. M. Allsopp, B. M. Greenwood, and D. Kwjatkowski, "Variation in the TNF-α promoter region associated with susceptibility to cerebral malaria," *Nature*, vol. 371, no. 6497, pp. 508–511, 1994.

[28] J. C. Knight, I. Udalova, A. V. S. Hill et al., "A polymorphism that affects OCT-1 binding to the TNF promoter region is associated with severe malaria," *Nature Genetics*, vol. 22, no. 2, pp. 145–150, 1999.

[29] C. C. John, A. Panoskaltsis-Mortari, R. O. Opoka et al., "Cerebrospinal fluid cytokine levels and cognitive impairment in cerebral malaria," *American Journal of Tropical Medicine and Hygiene*, vol. 78, no. 2, pp. 198–205, 2008.

[30] C. C. John, R. Opika-Opoka, J. Byarugaba, R. Idro, and M. J. Boivin, "Low levels of RANTES are associated with mortality in children with cerebral malaria," *Journal of Infectious Diseases*, vol. 194, no. 6, pp. 837–845, 2006.

[31] C. C. John, G. S. Park, N. Sam-Agudu, R. O. Opoka, and M. J. Boivin, "Elevated serum levels of IL-1ra in children with *Plasmodium falciparum* malaria are associated with increased severity of disease," *Cytokine*, vol. 41, no. 3, pp. 204–208, 2008.

[32] V. Jain, H. B. Armah, J. E. Tongren et al., "Plasma IP-10, apoptotic and angiogenic factors associated with fatal cerebral malaria in India," *Malaria Journal*, vol. 7, article 83, 2008.

[33] K. E. Lyke, R. Burges, Y. Cissoko et al., "Serum levels of the proinflammatory cytokines interleukin-1 beta (IL-1β), IL-6, IL-8, IL-10, tumor necrosis factor alpha, and IL-12(p70) in Malian children with severe *Plasmodium falciparum* malaria and matched uncomplicated malaria or healthy controls," *Infection and Immunity*, vol. 72, no. 10, pp. 5630–5637, 2004.

[34] G. A. Awandare, B. Goka, P. Boeuf et al., "Increased levels of inflammatory mediators in children with severe *Plasmodium falciparum* malaria with respiratory distress," *Journal of Infectious Diseases*, vol. 194, no. 10, pp. 1438–1446, 2006.

[35] D. Faille, F. El-Assaad, M. C. Alessi, T. Fusai, V. Combes, and G. E. R. Grau, "Platelet-endothelial cell interactions in cerebral malaria: the end of a cordial understanding," *Thrombosis and Haemostasis*, vol. 102, no. 6, pp. 1093–1102, 2009.

[36] H. Brown, T. T. Hien, N. Day et al., "Evidence of blood-brain barrier dysfunction in human cerebral malaria," *Neuropathology and Applied Neurobiology*, vol. 25, no. 4, pp. 331–340, 1999.

[37] A. L. Conroy, H. Phiri, M. Hawkes et al., "Endothelium-based biomarkers are associated with cerebral malaria in Malawian children: a retrospective case-control study," *PLoS ONE*, vol. 5, no. 12, Article ID e15291, 2010.

[38] T. W. Yeo, D. A. Lampah, R. Gitawat et al., "Angiopoietin-2 is associated with decreased endothelial nitric oxide and poor clinical outcome in severe falciparum malaria," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 105, no. 44, pp. 17097–17102, 2008.

[39] F. E. Lovegrove, N. Tangpukdee, R. O. Opoka et al., "Serum angiopoietin-1 and -2 levels discriminate cerebral malaria from uncomplicated malaria and predict clinical outcome in African children," *PLoS ONE*, vol. 4, no. 3, Article ID e4912, 2009.

[40] T. W. Yeo, D. A. Lampah, E. Tjitra et al., "Relationship of cell-free hemoglobin to impaired endothelial nitric oxide bioavailability and perfusion in severe falciparum malaria," *Journal of Infectious Diseases*, vol. 200, no. 10, pp. 1522–1529, 2009.

[41] T. W. Yeo, D. A. Lampah, R. Gitawati et al., "Impaired nitric oxide bioavailability and L-arginine-reversible endothelial dysfunction in adults with falciparum malaria," *Journal of Experimental Medicine*, vol. 204, no. 11, pp. 2693–2704, 2007.

[42] G. Turner, "Cerebral malaria," *Brain Pathology*, vol. 7, no. 1, pp. 569–582, 1997.

[43] V. A. White, S. Lewallen, N. Beare, K. Kayira, R. A. Carr, and T. E. Taylor, "Correlation of retinal haemorrhages with brain haemorrhages in children dying of cerebral malaria in Malawi," *Transactions of the Royal Society of Tropical Medicine and Hygiene*, vol. 95, no. 6, pp. 618–621, 2001.

[44] H. Brown, S. Rogerson, T. Taylor et al., "Blood-brain barrier function in cerebral malaria in Malawian children," *American Journal of Tropical Medicine and Hygiene*, vol. 64, no. 3-4, pp. 207–213, 2001.

[45] I. M. Medana, N. P. Day, T. T. Hien et al., "Axonal injury in cerebral malaria," *American Journal of Pathology*, vol. 160, no. 2, pp. 655–666, 2002.

[46] I. M. Medana and M. M. Esiri, "Axonal damage: a key predictor of outcome in human CNS diseases," *Brain*, vol. 126, no. 3, pp. 515–530, 2003.

[47] R. Idro, N. E. Jenkins, and C. R. J. Newton, "Pathogenesis, clinical features, and neurological outcome of cerebral malaria," *The Lancet Neurology*, vol. 4, no. 12, pp. 827–840, 2005.

[48] N. H. Hunt, J. Golenser, T. Chan-Ling et al., "Immunopathogenesis of cerebral malaria," *International Journal for Parasitology*, vol. 36, no. 5, pp. 569–582, 2006.

[49] I. A. Clark, L. M. Alleva, and B. Vissel, "The roles of TNF in brain dysfunction and disease," *Pharmacology & Therapeutics*, vol. 128, no. 3, pp. 519–548, 2010.

[50] N. A. V. Beare, S. P. Harding, T. E. Taylor, S. Lewallen, and M. E. Molyneux, "Perfusion abnormalities in children with cerebral malaria and malarial retinopathy," *Journal of Infectious Diseases*, vol. 199, no. 2, pp. 263–271, 2009.

[51] V. A. White, S. Lewallen, N. A. V. Beare, M. E. Molyneux, and T. E. Taylor, "Retinal pathology of pediatric cerebral malaria in Malawi," *PLoS ONE*, vol. 4, no. 1, Article ID e4317, 2009.

[52] S. E.R. Bopp, V. Ramachandran, K. Henson et al., "Genome wide analysis of inbred mouse lines identifies a locus containing ppar-γ as contributing to enhanced malaria survival," *PLoS ONE*, vol. 5, no. 5, Article ID e10903, 2010.

[53] J. Berger and D. E. Moller, "The mechanisms of action of PPARs," *Annual Review of Medicine*, vol. 53, pp. 409–435, 2002.

[54] G. Pascual, A. L. Fong, S. Ogawa et al., "A SUMOylation-dependent pathway mediates transrepression of inflammatory response genes by PPAR-γ," *Nature*, vol. 437, no. 7059, pp. 759–763, 2005.

[55] S. Giannini, M. Serio, and A. Galli, "Pleiotropic effects of thiazolidinediones: taking a look beyond antidiabetic activity," *Journal of Endocrinological Investigation*, vol. 27, no. 10, pp. 982–991, 2004.

[56] M. Lehrke and M. A. Lazar, "The many faces of PPARγ," *Cell*, vol. 123, no. 6, pp. 993–999, 2005.

[57] A. Szanto and L. Nagy, "The many faces of PPARγ: anti-inflammatory by any means?" *Immunobiology*, vol. 213, no. 9-10, pp. 789–803, 2008.

[58] H. Ghanim, S. Dhindsa, A. Aljada, A. Chaudhuri, P. Viswanathan, and P. Dandona, "Low-dose rosiglitazone exerts an antiinflammatory effect with an increase in adiponectin independently of free fatty acid fall and insulin sensitization in obese type 2 diabetics," *Journal of Clinical Endocrinology and Metabolism*, vol. 91, no. 9, pp. 3553–3558, 2006.

[59] D. G. Alleva, E. B. Johnson, F. M. Lio, S. A. Boehme, P. J. Conlon, and P. D. Crowe, "Regulation of murine macrophage proinflammatory and anti-inflammatory cytokines by ligands for peroxisome proliferator-activated receptor-γ: counter-regulatory activity by IFN-γ," *Journal of Leukocyte Biology*, vol. 71, no. 4, pp. 677–685, 2002.

[60] S. W. Chung, B. Y. Kang, S. H. Kim et al., "Oxidized low density lipoprotein inhibits interleukin-12 production in lipopolysaccharide-activated mouse macrophages via direct interactions between peroxisome proliferator-activated receptor-γ and nuclear factor-κB," *The Journal of Biological Chemistry*, vol. 275, no. 42, pp. 32681–32687, 2000.

[61] C. Jiang, A. T. Ting, and B. Seed, "PPAR-γ agonists inhibit production of monocyte inflammatory cytokines," *Nature*, vol. 391, no. 6662, pp. 82–86, 1998.

[62] M. Li, G. Pascual, and C. K. Glass, "Peroxisome proliferator-activated receptor γ-dependent repression of the inducible nitric oxide synthase gene," *Molecular and Cellular Biology*, vol. 20, no. 13, pp. 4699–4707, 2000.

[63] M. Ricote, A. C. Li, T. M. Willson, C. J. Kelly, and C. K. Glass, "The peroxisome proliferator-activated receptor-γ is a negative regulator of macrophage activation," *Nature*, vol. 391, no. 6662, pp. 79–82, 1998.

[64] M. Ricote, J. T. Huang, J. S. Welch, and C. K. Glass, "The peroxisome proliferator-activated receptorγ (PPARγ) as a regulator of monocyte/macrophage function," *Journal of Leukocyte Biology*, vol. 66, no. 5, pp. 733–739, 1999.

[65] D. S. Straus, G. Pascual, M. Li et al., "15-Deoxy-Δ-prostaglandin J2 inhibits multiple steps in the NF-κB signaling pathway," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 97, no. 9, pp. 4844–4849, 2000.

[66] J. S. Welch, M. Ricote, T. E. Akiyama, F. J. Gonzalez, and C. K. Glass, "PPARγ and PPARδ negatively regulate specific subsets of lipopolysaccharide and IFN-γ target genes in macrophages," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 100, no. 11, pp. 6712–6717, 2003.

[67] C. Faveeuw, S. Fougeray, V. Angeli et al., "Peroxisome proliferator-activated receptor γ activators inhibit interleukin-12 production in murine dendritic cells," *FEBS Letters*, vol. 486, no. 3, pp. 261–266, 2000.

[68] P. Gosset, A. S. Charbonnier, P. Delerive et al., "Peroxisome proliferator-activated receptor γ activators affect the maturation of human monocyte-derived dendritic cells," *European Journal of Immunology*, vol. 31, no. 10, pp. 2857–2865, 2001.

[69] P. Wang, P. O. Anderson, S. Chen, K. M. Paulsson, H. O. Sjögren, and S. Li, "Inhibition of the transcription factors AP-1 and NF-κB in CD4 T cells by peroxisome proliferator-activated receptor γ ligands," *International Immunopharmacology*, vol. 1, no. 4, pp. 803–812, 2001.

[70] R. B. Clark, D. Bishop-Bailey, T. Estrada-Hernandez, T. Hla, L. Puddington, and S. J. Padula, "The nuclear receptor PPARγ and immunoregulation: PPARγ mediates inhibition of helper T cell responses," *Journal of Immunology*, vol. 164, no. 3, pp. 1364–1371, 2000.

[71] R. Cunard, M. Ricote, D. DiCampli et al., "Regulation of cytokine expression by ligands of peroxisome proliferator activated receptors," *Journal of Immunology*, vol. 168, no. 6, pp. 2795–2802, 2002.

[72] N. Marx, F. Mach, A. Sauty et al., "Peroxisome proliferator-activated receptor-γ activators inhibit IFN-γ- induced expression of the T cell-active CXC chemokines IP-10, Mig, and I-TAC in human endothelial cells," *Journal of Immunology*, vol. 164, no. 12, pp. 6503–6508, 2000.

[73] V. Pasceri, H. D. Wu, J. T. Willerson, and E. T. H. Yeh, "Modulation of vascular inflammation in vitro and in vivo by peroxisome proliferator-activated receptor-γ activators," *Circulation*, vol. 101, no. 3, pp. 235–238, 2000.

[74] P. D. Storer, J. Xu, J. Chavis, and P. D. Drew, "Peroxisome proliferator-activated receptor-gamma agonists inhibit the activation of microglia and astrocytes: implications for multiple sclerosis," *Journal of Neuroimmunology*, vol. 161, no. 1-2, pp. 113–122, 2005.

[75] J. D. Ji, H. J. Kim, Y. H. Rho et al., "Inhibition of IL-10-induced STAT3 activation by 15-deoxy-Δ12,14-prostaglandin J," *Rheumatology*, vol. 44, no. 8, pp. 983–988, 2005.

[76] E. J. Park, S. Y. Park, E. H. Joe, and I. Jou, "15d-PGJ and rosiglitazone suppress Janus kinase-STAT inflammatory signaling through induction of suppressor of cytokine signaling 1 (SOCS1) and SOCS3 in glia," *The Journal of Biological Chemistry*, vol. 278, no. 17, pp. 14747–14752, 2003.

[77] P. D. Drew, J. Xu, and M. K. Racke, "PPAR-γ: therapeutic potential for multiple sclerosis," *PPAR Research*, vol. 2008, Article ID 627463, 2008.

[78] R. Vemuganti, "Therapeutic potential of PPARγ activation in stroke," *PPAR Research*, vol. 2008, Article ID 461981, 2008.

[79] J. J. Bright, S. Kanakasabai, W. Chearwae, and S. Chakraborty, "PPAR regulation of inflammatory signaling in CNS diseases," *PPAR Research*, vol. 2008, Article ID 658520, 2008.

[80] R. Kapadia, J. H. Yi, and R. Vemuganti, "Mechanisms of anti-inflammatory and neuroprotective actions of PPAR-gamma agonists," *Frontiers in Bioscience*, vol. 13, no. 5, pp. 1813–1826, 2008.

[81] C. A. Homewood, G. A. Moore, D. C. Warhurst, and E. M. Atkinson, "Purification and some properties of malarial pigment," *Annals of Tropical Medicine and Parasitology*, vol. 69, no. 3, pp. 283–287, 1975.

[82] E. Schwarzer, H. Kühn, E. Valente, and P. Arese, "Malaria-parasitized erythrocytes and hemozoin nonenzymatically generate large amounts of hydroxy fatty acids that inhibit monocyte functions," *Blood*, vol. 101, no. 2, pp. 722–728, 2003.

[83] S. Pizzimenti, S. Laurora, F. Briatore, C. Ferretti, M. U. Dianzani, and G. Barrera, "Synergistic effect of 4-hydroxynonenal and PPAR ligands in controlling human leukemic cell growth and differentiation," *Free Radical Biology and Medicine*, vol. 32, no. 3, pp. 233–245, 2002.

[84] E. Schwarzer, M. Alessio, D. Ulliers, and P. Arese, "Phagocytosis of the malarial pigment, hemozoin, impairs expression of major histocompatibility complex class II antigen, CD54, and CD11c in human monocytes," *Infection and Immunity*, vol. 66, no. 4, pp. 1601–1606, 1998.

[85] D. Taramelli, "The heme moiety of malaria pigment (β-Hematin) mediates the inhibition of nitric oxide and tumor necrosis factor-α production by lipopolysaccharide-stimulated macrophages," *Experimental Parasitology*, vol. 81, no. 4, pp. 501–511, 1995.

[86] P. Deshpande and P. Shastry, "Modulation of cytokine profiles by malaria pigment—Hemozoin: role of IL-10 in suppression of proliferative responses of mitogen stimulated human PBMC," *Cytokine*, vol. 28, no. 6, pp. 205–213, 2004.

[87] O. Skorokhod, E. Schwarzer, T. Grune, and P. Arese, "Role of 4-hydroxynonenal in the hemozoin-mediated inhibition of differentiation of human monocytes to dendritic cells induced by GM-CSF/IL-4," *BioFactors*, vol. 24, no. 1–4, pp. 283–289, 2005.

[88] O. R. Millington, C. Di Lorenzo, R. S. Phillips, P. Garside, and J. M. Brewer, "Suppression of adaptive immunity to heterologous antigens during Plasmodium infection through hemozoin-induced failure of dendritic cell function," *Journal of Biology*, vol. 5, article 5, 2006.

[89] T. Scorza, S. Magez, L. Brys, and P. De Baetselier, "Hemozoin is a key factor in the induction of malaria-associated immunosuppression," *Parasite Immunology*, vol. 21, no. 11, pp. 545–554, 1999.

[90] O. A. Skorokhod, M. Alessio, B. Mordmüller, P. Arese, and E. Schwarzer, "Hemozoin (malarial pigment) inhibits differentiation and maturation of human monocyte-derived dendritic cells: a peroxisome proliferator-activated receptor-γ-mediated effect," *Journal of Immunology*, vol. 173, no. 6, pp. 4066–4074, 2004.

[91] I. D. McGilvray, L. Serghides, A. Kapus, O. D. Rotstein, and K. C. Kain, "Nonopsonic monocyte/macrophage phagocytosis of *Plasmodium falciparum*-parasitized erythrocytes: a role for CD36 in malarial clearance," *Blood*, vol. 96, no. 9, pp. 3231–3240, 2000.

[92] S. N. Patel, L. Serghides, T. G. Smith et al., "CD36 Mediates the Phagocytosis of *Plasmodium falciparum*-Infected Erythrocytes by Rodent Macrophages," *Journal of Infectious Diseases*, vol. 189, no. 2, pp. 204–213, 2004.

[93] Z. Su, A. Fortin, P. Gros, and M. M. Stevenson, "Opsonin-independent phagocytosis: an effector mechanism against acute blood-stage Plasmodium chabaudi AS infection," *Journal of Infectious Diseases*, vol. 186, no. 9, pp. 1321–1329, 2002.

[94] L. Serghides, T. G. Smith, S. N. Patel, and K. C. Kain, "CD36 and malaria: friends or foes?" *Trends in Parasitology*, vol. 19, no. 10, pp. 461–469, 2003.

[95] K. Ayi, S. N. Patel, L. Serghides, T. G. Smith, and K. C. Kain, "Nonopsonic phagocytosis of erythrocytes infected with ring-stage *Plasmodium falciparum*," *Infection and Immunity*, vol. 73, no. 4, pp. 2559–2563, 2005.

[96] T. G. Smith, L. Serghides, S. N. Patel, M. Febbraio, R. L. Silverstein, and K. C. Kain, "CD36-mediated nonopsonic phagocytosis of erythrocytes infected with stage I and IIA gametocytes of *Plasmodium falciparum*," *Infection and Immunity*, vol. 71, no. 1, pp. 393–400, 2003.

[97] S. N. Patel, Z. Lu, K. Ayi, L. Serghides, D. C. Gowda, and K. C. Kain, "Disruption of CD36 impairs cytokine response to *Plasmodium falciparum* glycosylphosphatidylinositol and confers susceptibility to severe and fatal malaria in vivo," *Journal of Immunology*, vol. 178, no. 6, pp. 3954–3961, 2007.

[98] L. Serghides and K. C. Kain, "Peroxisome proliferator-activated receptor γ-retinoid X receptor agonists increase CD36-dependent phagocytosis of *Plasmodium falciparum*-parasitized erythrocytes and decrease malaria-induced TNF-α secretion by monocytes/macrophages," *Journal of Immunology*, vol. 166, no. 11, pp. 6742–6748, 2001.

[99] L. K. Erdman, G. Cosio, A. J. Helmers, D. C. Gowda, S. Grinstein, and K. C. Kain, "CD36 and TLR interactions in inflammation and phagocytosis: implications for malaria," *Journal of Immunology*, vol. 183, no. 10, pp. 6452–6459, 2009.

[100] V. A. Fadok, M. L. Warner, D. L. Bratton, and P. M. Henson, "CD36 is required for phagocytosis of apoptotic cells by human macrophages that use either a phosphatidylserine receptor or the vitronectin receptor (α(V)β3)," *Journal of Immunology*, vol. 161, no. 11, pp. 6250–6257, 1998.

[101] N. Platt, R. P. da Silva, and S. Gordon, "Recognizing death: the phagocytosis of apoptotic cells," *Trends in Cell Biology*, vol. 8, no. 9, pp. 365–372, 1998.

[102] L. Serghides, S. N. Patel, K. Ayi et al., "Rosiglitazone modulates the innate immune response to *Plasmodium falciparum* infection and improves outcome in experimental cerebral malaria," *Journal of Infectious Diseases*, vol. 199, no. 10, pp. 1536–1545, 2009.

[103] S. Gordon and F. O. Martinez, "Alternative activation of macrophages: mechanism and functions," *Immunity*, vol. 32, no. 5, pp. 593–604, 2010.

[104] K. Ayi, F. Turrini, A. Piga, and P. Arese, "Enhanced phagocytosis of ring-parasitized mutant erythrocytes: a common mechanism that may explain protection against falciparum malaria in sickle trait and beta-thalassemia trait," *Blood*, vol. 104, no. 10, pp. 3364–3371, 2004.

[105] T. N. Williams, "Human red blood cell polymorphisms and malaria," *Current Opinion in Microbiology*, vol. 9, no. 4, pp. 388–394, 2006.

[106] K. Ayi, G. Min-Oo, L. Serghides et al., "Pyruvate kinase deficiency and malaria," *The New England Journal of Medicine*, vol. 358, no. 17, pp. 1805–1810, 2008.

[107] L. Schofield and F. Hackett, "Signal transduction in host cells by a glycosylphosphatidylinositol toxin of malaria parasites," *Journal of Experimental Medicine*, vol. 177, no. 1, pp. 145–153, 1993.

[108] G. Krishnegowda, A. M. Hajjar, J. Zhu et al., "Induction of proinflammatory responses in macrophages by the glycosylphosphatidylinositols of *Plasmodium falciparum*:

cell signaling receptors, glycosylphosphatidylinositol (GPI) structural requirement, and regulation of GPI activity," *The Journal of Biological Chemistry*, vol. 280, no. 9, pp. 8606–8616, 2005.

[109] G. Cantini, A. Lombardi, E. Borgogni et al., "Peroxisome-proliferator-activated receptor gamma (PPARγ) is required for modulating endothelial inflammatory response through a nongenomic mechanism," *European Journal of Cell Biology*, vol. 89, no. 9, pp. 645–653, 2010.

[110] M. M. Stevenson and E. M. Riley, "Innate immunity to malaria," *Nature Reviews Immunology*, vol. 4, no. 3, pp. 169–180, 2004.

[111] A. K. Boggild, S. Krudsood, S. N. Patel et al., "Use of peroxisome proliferator-activated receptor γ agonists as adjunctive treatment for *Plasmodium falciparum* malaria: a randomized, double-blind, placebo-controlled trial," *Clinical Infectious Diseases*, vol. 49, no. 6, pp. 841–849, 2009.

[112] A. H. Shankar, B. Genton, R. D. Semba et al., "Effect of vitamin A supplementation on morbidity due to *Plasmodium falciparum* in young children in Papua New Guinea: a randomised trial," *The Lancet*, vol. 354, no. 9174, pp. 203–209, 1999.

[113] L. Serghides and K. C. Kain, "Mechanism of protection induced by vitamin A in falciparum malaria," *The Lancet*, vol. 359, no. 9315, pp. 1404–1406, 2002.

[114] N. C. Inestrosa, J. A. Godoy, R. A. Quintanilla, C. S. Koenig, and M. Bronfman, "Peroxisome proliferator-activated receptor γ is expressed in hippocampal neurons and its activation prevents β-amyloid neurodegeneration: role of Wnt signaling," *Experimental Cell Research*, vol. 304, no. 1, pp. 91–104, 2005.

[115] S. H. Ramirez, D. Heilman, B. Morsey, R. Potula, J. Haorah, and Y. Persidsky, "Activation of peroxisome proliferator-activated receptor γ (PPARγ) suppresses rho GTPases in human brain microvascular endothelial cells and inhibits adhesion and transendothelial migration of HIV-1 infected monocytes," *Journal of Immunology*, vol. 180, no. 3, pp. 1854–1865, 2008.

[116] S. Moreno, S. Farioli-vecchioli, and M. P. Cerù, "Immunolocalization of peroxisome proliferator-activated receptors and retinoid X receptors in the adult rat CNS," *Neuroscience*, vol. 123, no. 1, pp. 131–145, 2004.

[117] W. H.-H. Sheu, H. C. Chuang, S. M. Cheng, M. R. Lee, C. C. Chou, and F. C. Cheng, "Microdialysis combined blood sampling technique for the determination of rosiglitazone and glucose in brain and blood of gerbils subjected to cerebral ischemia," *Journal of Pharmaceutical and Biomedical Analysis*, vol. 54, no. 4, pp. 759–764, 2011.

[118] A. Szklarczyk, M. Stins, E. A. Milward et al., "Glial activation and matrix metalloproteinase release in cerebral malaria," *Journal of Neurovirology*, vol. 13, no. 1, pp. 2–10, 2007.

[119] C. K. Combs, D. E. Johnson, J. C. Karlo, S. B. Cannady, and G. E. Landreth, "Inflammatory mechanisms in Alzheimer's disease: inhibition of β- amyloid-stimulated proinflammatory responses and neurotoxicity by PPARγ agonists," *Journal of Neuroscience*, vol. 20, no. 2, pp. 558–567, 2000.

[120] A. Lombardi, G. Cantini, E. Piscitelli et al., "A new mechanism involving ERK contributes to rosiglitazone inhibition of tumor necrosis factor-α and interferon-γ inflammatory effects in human endothelial cells," *Arteriosclerosis, Thrombosis, and Vascular Biology*, vol. 28, no. 4, pp. 718–724, 2008.

[121] S. Z. Duan, M. G. Usher, and R. M. Mortensen, "Peroxisome proliferator-activated receptor-γ-mediated effects in the vasculature," *Circulation Research*, vol. 102, no. 3, pp. 283–294, 2008.

[122] M. Joner, A. Farb, QI. Cheng et al., "Pioglitazone inhibits in-stent restenosis in atherosclerotic rabbits by targeting transforming growth factor-β and MCP-1," *Arteriosclerosis, Thrombosis, and Vascular Biology*, vol. 27, no. 1, pp. 182–189, 2007.

[123] N. Marx, G. Sukhova, C. Murphy, P. Libby, and J. Plutzky, "Macrophages in human atheroma contain PPARγ: differentiation-dependent peroxisomal proliferator-activated receptor γ (PPARγ) expression and reduction of MMP-9 activity through PPARγ activation in mononuclear phagocytes in vitro," *American Journal of Pathology*, vol. 153, no. 1, pp. 17–23, 1998.

[124] C. X. Wang, X. Ding, R. Noor, C. Pegg, C. He, and A. Shuaib, "Rosiglitazone alone or in combination with tissue plasminogen activator improves ischemic brain injury in an embolic model in rats," *Journal of Cerebral Blood Flow and Metabolism*, vol. 29, no. 10, pp. 1683–1694, 2009.

[125] A. Ferreira, J. Balla, V. Jeney, G. Balla, and M. P. Soares, "A central role for free heme in the pathogenesis of severe malaria: the missing link?" *Journal of Molecular Medicine*, vol. 86, no. 10, pp. 1097–1111, 2008.

[126] R. Medzhitov, "Damage control in host-pathogen interactions," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 106, no. 37, pp. 15525–15526, 2009.

[127] M. C. Delmas-Beauvieux, E. Peuchant, M. F. Dumon, M. C. Receveur, M. Le Bras, and M. Clerc, "Relationship between red blood cell antioxidant enzymatic system status and lipoperoxidation during the acute phase of malaria," *Clinical Biochemistry*, vol. 28, no. 2, pp. 163–169, 1995.

[128] Z. Bagi, A. Koller, and G. Kaley, "PPARγ activation, by reducing oxidative stress, increases NO bioavailability in coronary arterioles of mice with Type 2 diabetes," *American Journal of Physiology*, vol. 286, no. 2, pp. H742–H748, 2004.

[129] I. Inoue, S. -I. Goto, T. Matsunaga et al., "The ligands/activators for peroxisome proliferator-activated receptor α (PPARα) and PPARγ increase Cu^{2+},Zn^{2+}-superoxide dismutase and decrease p22phox message expressions in primary endothelial cells," *Metabolism*, vol. 50, no. 1, pp. 3–11, 2001.

[130] J. Hwang, D. J. Kleinhenz, B. Lassègue, K. K. Griendling, S. Dikalov, and C. M. Hart, "Peroxisome proliferator-activated receptor-γ ligands regulate endothelial membrane superoxide production," *American Journal of Physiology*, vol. 288, no. 4, pp. C899–C905, 2005.

[131] X. Zhao, R. Strong, J. Zhang et al., "Neuronal PPARγ deficiency increases susceptibility to brain damage after cerebral ischemia," *Journal of Neuroscience*, vol. 29, no. 19, pp. 6186–6195, 2009.

[132] X. Zhao, G. Sun, J. Zhang et al., "Hematoma resolution as a target for intracerebral hemorrhage treatment: role for peroxisome proliferator-activated receptor γ in microglia/macrophages," *Annals of Neurology*, vol. 61, no. 4, pp. 352–362, 2007.

[133] J. Hwang, D. J. Kleinhenz, H. L. Rupnow et al., "The PPARγ ligand, rosiglitazone, reduces vascular oxidative stress and NADPH oxidase expression in diabetic mice," *Vascular Pharmacology*, vol. 46, no. 6, pp. 456–462, 2007.

[134] C. De Ciuceis, F. Amiri, M. Iglarz, J. S. Cohn, R. M. Touyz, and E. L. Schiffrin, "Synergistic vascular protective effects

of combined low doses of PPARα and PPARγ activators in angiotensin II-induced hypertension in rats," *British Journal of Pharmacology*, vol. 151, no. 1, pp. 45–53, 2007.

[135] G. Krönke, A. Kadl, E. Ikonomu et al., "Expression of heme oxygenase-1 in human vascular cells is regulated by peroxisome proliferator-activated receptors," *Arteriosclerosis, Thrombosis, and Vascular Biology*, vol. 27, no. 6, pp. 1276–1282, 2007.

[136] L. E. Otterbein, F. H. Bach, J. Alam et al., "Carbon monoxide has anti-inflammatory effects involving the mitogen- activated protein kinase pathway," *Nature Medicine*, vol. 6, no. 4, pp. 422–428, 2000.

[137] J. Chen-Roetling, L. Benvenisti-Zarom, and R. F. Regan, "Cultured astrocytes from heme oxygenase-1 knockout mice are more vulnerable to heme-mediated oxidative injury," *Journal of Neuroscience Research*, vol. 82, no. 6, pp. 802–810, 2005.

[138] A. Pamplona, A. Ferreira, J. Balla et al., "Heme oxygenase-1 and carbon monoxide suppress the pathogenesis of experimental cerebral malaria," *Nature Medicine*, vol. 13, no. 6, pp. 703–710, 2007.

[139] J. S. Beckman and W. H. Koppenol, "Nitric oxide, superoxide, and peroxynitrite: the good, the bad, and the ugly," *American Journal of Physiology*, vol. 271, no. 5, pp. C1424–C1437, 1996.

[140] N. M. Anstey, J. B. Weinberg, M. Y. Hassanali et al., "Nitric oxide in Tanzanian children with malaria: inverse relationship between malaria severity and nitric oxide production/nitric oxide synthase type 2 expression," *Journal of Experimental Medicine*, vol. 184, no. 2, pp. 557–567, 1996.

[141] I. Gramaglia, P. Sobolewski, D. Meays et al., "Low nitric oxide bioavailability contributes to the genesis of experimental cerebral malaria," *Nature Medicine*, vol. 12, no. 12, pp. 1417–1422, 2006.

[142] T. W. Yeo, D. A. Lampah, R. Gitawati et al., "Recovery of endothelial function in severe falciparum malaria: relationship with improvement in plasma L-arginine and blood lactate concentrations," *Journal of Infectious Diseases*, vol. 198, no. 4, pp. 602–608, 2008.

[143] D. Garcia-Santos and J. A. B. Chies, "HO-1 polymorphism as a genetic determinant behind the malaria resistance afforded by haemolytic disorders," *Medical Hypotheses*, vol. 74, no. 5, pp. 807–813, 2010.

[144] T. Matsumoto, E. Noguchi, T. Kobayashi, and K. Kamata, "Mechanisms underlying the chronic pioglitazone treatment-induced improvement in the impaired endothelium-dependent relaxation seen in aortas from diabetic rats," *Free Radical Biology and Medicine*, vol. 42, no. 7, pp. 993–1007, 2007.

[145] C. Romera, O. Hurtado, J. Mallolas et al., "Ischemic preconditioning reveals that GLT1/EAAT2 glutamate transporter is a novel PPARγ target gene involved in neuroprotection," *Journal of Cerebral Blood Flow and Metabolism*, vol. 27, no. 7, pp. 1327–1338, 2007.

[146] Y. Wang and Z. H. Qin, "Molecular and cellular mechanisms of excitoxic neuronal death," *Apoptosis*, vol. 15, no. 11, pp. 1382–1402, 010.

[147] A. S. Miranda, L. B. Vieira, N. Lacerda-Queiroz et al., "Increased levels of glutamate in the central nervous system are associated with behavioral symptoms in experimental malaria," *Brazilian Journal of Medical and Biological Research*, vol. 43, no. 12, pp. 1173–1177, 2010.

[148] L. A. Sanni, C. Rae, A. Maitland, R. Stocker, and N. H. Hunt, "Is ischemia involved in the pathogenesis of murine cerebral malaria?" *American Journal of Pathology*, vol. 159, no. 3, pp. 1105–1112, 2001.

[149] X. Zhao, Z. Ou, J. C. Grotta, N. Waxham, and J. Aronowski, "Peroxisome-proliferator-activated receptor-gamma (PPARγ) activation protects neurons from NMDA excitotoxicity," *Brain Research*, vol. 1073-1074, no. 1, pp. 460–469, 2006.

[150] S. Uryu, J. Harada, M. Hisamoto, and T. Oda, "Troglitazone inhibits both post-glutamate neurotoxicity and low-potassium-induced apoptosis in cerebellar granule neurons," *Brain Research*, vol. 924, no. 2, pp. 229–236, 2002.

[151] B. García-Bueno, J. R. Caso, B. G. Pérez-Nievas, P. Lorenzo, and J. C. Leza, "Effects of peroxisome proliferator-activated receptor gamma agonists on brain glucose and glutamate transporters after stress in rats," *Neuropsychopharmacology*, vol. 32, no. 6, pp. 1251–1260, 2007.

[152] R. K. Kaundal and S. S. Sharma, "Peroxisome proliferator-activated receptor gamma agonists as neuroprotective agents," *Drug News Perspect*, vol. 23, no. 4, pp. 241–256, 2010.

[153] S. Sundararajan and G. E. Landreth, "Antiinflammatory properties of PPARγ agonists following ischemia," *Drug News and Perspectives*, vol. 17, no. 4, pp. 229–236, 2004.

[154] S. Sundararajan, J. L. Gamboa, N. A. Victor, E. W. Wanderi, W. D. Lust, and G. E. Landreth, "Peroxisome proliferator-activated receptor-γ ligands reduce inflammation and infarction size in transient focal ischemia," *Neuroscience*, vol. 130, no. 3, pp. 685–696, 2005.

[155] Y. Zhao, A. Patzer, P. Gohlke, T. Herdegen, and J. Culman, "The intracerebral application of the PPARγ-ligand pioglitazone confers neuroprotection against focal ischaemia in the rat brain," *European Journal of Neuroscience*, vol. 22, no. 1, pp. 278–282, 2005.

[156] Y. Zhao, A. Patzer, T. Herdegen, P. Gohlke, and J. Culman, "Activation of cerebral peroxisome proliferator-activated receptors gamma promotes neuroprotection by attenuation of neuronal cyclooxygenase-2 overexpression after focal cerebral ischemia in rats," *FASEB Journal*, vol. 20, no. 8, pp. 1162–1175, 2006.

[157] Y. Luo, W. Yin, A. P. Signore et al., "Neuroprotection against focal ischemic brain injury by the peroxisome proliferator-activated receptor-γ agonist rosiglitazone," *Journal of Neurochemistry*, vol. 97, no. 2, pp. 435–448, 2006.

[158] K. Tureyen, R. Kapadia, K. K. Bowen et al., "Peroxisome proliferator-activated receptor-γ agonists induce neuroprotection following transient focal ischemia in normotensive, normoglycemic as well as hypertensive and type-2 diabetic rodents," *Journal of Neurochemistry*, vol. 101, no. 1, pp. 41–56, 2007.

[159] Y. Kasahara, A. Taguchi, H. Uno et al., "Telmisartan suppresses cerebral injury in a murine model of transient focal ischemia," *Brain Research*, vol. 1340, pp. 70–80, 2010.

[160] T. Haraguchi, K. Iwasaki, K. Takasaki et al., "Telmisartan, a partial agonist of peroxisome proliferator-activated receptor γ, improves impairment of spatial memory and hippocampal apoptosis in rats treated with repeated cerebral ischemia," *Brain Research*, vol. 1353, pp. 125–132, 2010.

[161] A. Hyong, V. Jadhav, S. Lee et al., "Rosiglitazone, a PPAR gamma agonist, attenuates inflammation after surgical brain injury in rodents," *Brain Research*, vol. 1215, pp. 218–224, 2008.

[162] M. Allahtavakoli, A. Shabanzadeh, A. Roohbakhsh, and A. Pourshanazari, "Combination therapy of rosiglitazone, a peroxisome proliferator-activated receptor-γ ligand, and NMDA receptor antagonist (MK-801) on experimental

embolic stroke in rats," *Basic and Clinical Pharmacology and Toxicology*, vol. 101, no. 5, pp. 309–314, 2007.

[163] N. Schintu, L. Frau, M. Ibba et al., "PPAR-gamma-mediated neuroprotection in a chronic mouse model of Parkinson's disease," *European Journal of Neuroscience*, vol. 29, no. 5, pp. 954–963, 2009.

[164] L. P. Quinn, B. Crook, M. E. Hows et al., "The PPARγ agonist pioglitazone is effective in the MPTP mouse model of Parkinson's disease through inhibition of monoamine oxidase B," *British Journal of Pharmacology*, vol. 154, no. 1, pp. 226–233, 2008.

[165] M. Kiaei, K. Kipiani, J. Chen, N. Y. Calingasan, and M. F. Beal, "Peroxisome proliferator-activated receptor-gamma agonist extends survival in transgenic mouse model of amyotrophic lateral sclerosis," *Experimental Neurology*, vol. 191, no. 2, pp. 331–336, 2005.

[166] L. Escribano, A. M. Simón, A. Pérez-Mediavilla, P. Salazar-Colocho, J. D. Río, and D. Frechilla, "Rosiglitazone reverses memory decline and hippocampal glucocorticoid receptor down-regulation in an Alzheimer's disease mouse model," *Biochemical and Biophysical Research Communications*, vol. 379, no. 2, pp. 406–410, 2009.

[167] G. S. Watson, B. A. Cholerton, M. A. Reger et al., "Preserved cognition in patients with early Alzheimer disease and amnestic mild cognitive impairment during treatment with rosiglitazone: a preliminary study," *American Journal of Geriatric Psychiatry*, vol. 13, no. 11, pp. 950–958, 2005.

[168] M. E. Risner, A. M. Saunders, J. F. B. Altman et al., "Efficacy of rosiglitazone in a genetically defined population with mild-to-moderate Alzheimer's disease," *Pharmacogenomics Journal*, vol. 6, no. 4, pp. 246–254, 2006.

[169] C. C. Kaiser, D. K. Shukla, G. T. Stebbins et al., "A pilot test of pioglitazone as an add-on in patients with relapsing remitting multiple sclerosis," *Journal of Neuroimmunology*, vol. 211, no. 1-2, pp. 124–130, 2009.

[170] J. A. Dormandy, B. Charbonnel, D. J. Eckland et al., "Secondary prevention of macrovascular events in patients with type 2 diabetes in the PROactive Study (PROspective pioglitAzone Clinical Trial in macroVascular Events): a randomised controlled trial," *The Lancet*, vol. 366, no. 9493, pp. 1279–1289, 2005.

[171] W. H. W. Tang, "Do thiazolidinediones cause heart failure? A critical review," *Cleveland Clinic Journal of Medicine*, vol. 73, no. 4, pp. 390–397, 2006.

[172] G. A. Diamond, L. Bax, and S. Kaul, "Uncertain effects of rosiglitazone on the risk for myocardial infarction and cardiovascular death," *Annals of Internal Medicine*, vol. 147, no. 8, pp. 578–581, 2007.