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A theoretical mathematical assessment of the effectiveness of coartemether in the treatment of *Plasmodium falciparum* malaria infection

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ABSTRACT

This study analysed the dynamics of blood stage malaria with immune response and under administration of Coartem as a combination therapy. The techniques of mathematical modelling were used in coming up and analysing the deterministic model. Sensitivity analysis and statistical approaches were used to compare model simulated treatment results with the use of Coartem and other antimalarial drugs. We sought to theoretically assess if Coartem can bring improvement in the treatment of malaria as compared to the other drugs. Our analysis and numerical results suggest that Coartem compares well with other antimalarial drug that have been on the market. However, the shortfall of our model is that it could not give good comparative results between Coartem treatment and other combination treatment schemes with similar mode of action. Our study predicted effects of different drug treatment protocols in malaria using a theoretical mathematical model, which gives an insight into potential effective treatment schemes.

1. Introduction

Malaria is one of the most prevalent parasitic infections in the world and certainly the most detrimental [1,27–29]. While the disease affects the lives of most people across the African continent, children under the age of five and pregnant women are the most vulnerable due to their lower levels of malaria immunity. Malaria epidemics may be caused by many factors but in Africa are mostly a result of an unusual increase in vector abundance caused by climate change, e.g. increased temperature or abnormal rainfall. Although the extent of suffering caused by malaria epidemics is not adequately documented, it is generally believed that morbidity, mortality and overall economic impact of these epidemics are enormous [2,27]. In addition to the direct health impact, epidemic malaria also results in economic losses at the household, community, and country levels.

The infection of human erythrocytes is ultimately responsible for clinical pathologies associated with the disease [1,3]. Upon invading circulating erythrocytes, the parasite then causes the clinical malaria which is then fought by the human immune system before treatment is introduced. Immunity is associated with ability to regulate the production of pro-inflammatory cytokines to an intermediate level, which mediate parasite clearance while simultaneously avoiding severe pathology. The rapid increase in the parasite biomass then activates the innate immune mechanisms [6–8], this then triggers activation of monocytes and macrophages leading to the secretion of cytokines that stimulate the immune system [5].

The cluster of differentiation 8 ($CD8^+$) T cells response cannot be induced by the blood stage malaria and though it is induced by other infected tissues such as the liver, it is not cytotoxic to blood stage malaria parasite [35]. $CD4^+$ T cells respond to malaria antigens by proliferation and/or secretion of cytokines (INF-γ and IL-4, IL-10) [34–36]. On re-infection, the malaria primed T cells produce greatly increased amounts of INF-γ which synergize with malaria glycosyphosphatidylinositol (GPI) to upregulate the production of TNF-α [33]. Induction of INF-γ is a direct consequence of the $CD8^+$ and $CD4^+$ T cell activation. INF-γ production by T cells precede and initiate production of IL-12, and IL-12 in turn induces INF-γ production by NK cells (and perhaps by other cells) in a positive feedback loop that represents an important amplifying mechanism [6,14,7,8,33,35]. IL-12 also stimulates enhanced antibody production [8]. A clear role for TNF-α has been shown in killing parasites. At physiological concentrations, recombinant TNF-α is

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antiparasitic, synergizing with INF-γ to induce the production of NO and other toxic radicals. Thus the successful resolution of a malaria infection and evasion of symptoms appear to depend on achieving an optimal level of TNF-α and other inflammatory cytokines.

In the treatment of malaria WHO recommends use of combination therapy due to the rising threat of resistance to available drugs and to reduce the intolerable burden of malaria [9,27]. Coartem is the only drug which uses the theory of combination therapy as a fixed dose. The drug is a fixed dose combination tablet of Artemether (which is an artemisinin derivative) and Lumefantrine in a ratio 1:6. Both components of the drug are blood schizonticides, and they have complementary pharmacokinetics and dissimilar modes of action thus providing synergistic antimalarial activity. Artemisinin derivatives act as blood schizonticides and they kill the plasmodium parasites more quickly than any other antimalarial agent and are toxic to the parasite at very low concentrations [9,11]. An investigation of the mode of action of artemisinin using a yeast model, demonstrated that the drug acts on the electron transport chain, generates local reactive oxygen species, and causes the depolarisation of mitochondrial membrane [12]. The exact antimalarial activity of Lumefantrine is not well defined. However, available data suggests that Lumefantrine inhibits the formation of beta-haematin (β-haematin) by forming a complex with haemin. In the study [3], Coartem was shown to have corrected parasitological cure rate (PCR-corrected) greater than 95 per cent in both adults and paediatric patients in China, Thailand, sub-Saharan Africa, Europe and South America populations. Coartem is a safe and effective drug in the treatment of uncomplicated *Plasmodium falciparum* malaria. However, treatment failure may occur due to incomplete absorption of the drug [13].

We developed a model that represents the dynamics of immune cells (Antibodies, T Cells and Other Immune cells (macrophages, dendritic cells, monocytes and NK cells)), merozoites, cytokines (INF-γ, TNF-α and IL-12), infected red blood cells (IRBCs) and red blood cells (RBCs). Considerable work has been done on mathematical modelling of *P. falciparum* infection [19,4,20,22,23,9,24–26,30]. However, this study is different from all these studies in that, we consider the combination therapy of Coartem, that prevents recrudescence and transmission or emergence of resistance. There are many antimalarial drugs that are listed in the WHO recommended drugs list but this study focuses on Coartem. Sulfadoxine and pyrimethamine (SP) and atovaquone and proguanil hydrochloride (AP) are used as generic controls for comparison with Coartem.

2. Model development

In constructing the model we assumed the following: (i) The model assumes the interaction of ten cell populations at any given time, which are: RBCs (R_B), IRBCs (I_{RB}), $CD8^+$ T cells (T), extracellular merozoites (M), intracellular merozoites (M_I), antibodies (A), gamma interferon-IFN-γ (I_γ), tumour necrosis factor-alpha-TNF-α (N_F), interleukin-12: IL-12 (I_{12}), other immune cells (M_o) (Table 1), (ii) the RBCs are supplied from the bone marrow at a constant rate λ_B. They are reduced through infection by merozoites at a constant rate β and through natural death at a constant rate μ_B. The RBCs are destroyed through phagocytosis of erythrocytes bound to merozoites (term four of the first equation), (iii) IRBCs die at a constant rate μ_{iB} and are also killed by immune effectors (term two of second equation). IRBCs produce free merozoites by bursting, (iv) extracellular merozoites suffer a natural death at a constant rate of μ_m, are eliminated from circulation by immune cells (terms two and three of third equation) and are reduced by infecting RBCs (term four of third equation), (v) intracellular merozoites asexually reproduce inside IRBCs at a constant rate η. Parasite multiplication is inhibited by immune cells. Merozoites are also lost from the intracellular environment as a result of bursting, (vi) the production of $CD8^+$ T cells is stimulated by the presence of INF-γ, TNF-α and extracellular merozoites. They are reduced (deactivated) at a constant rate μ_T, (vii) extracellular merozoites and $CD8^+$ T cells induce the secretion of INF-γ and TNF-α. The secretion of INF-γ is also induced by IL-12. In turn INF-γ induces the secretion of TNF-α [6,7,33]. TNF-α and INF-γ decay at constant rates μ_f and μ_γ respectively, (viii) macrophages, monocytes, dendritic cells and NK cells as well as the density of the parasite in the blood induce the secretion of IL-12. IL-12 decay at a constant rate $\mu_{I_{12}}$, (ix) antibodies proliferate in the presence of infection specific $CD4^+$ T cells and decay at a constant rate μ_A.

Table 1
Table summarising the variables used in model system (1).

Variable	Description
R_B	Uninfected red blood cells
I_{RB}	Infected red blood cells
M	Extracellular merozoites
A	Antibodies
T	T cells
M_o	Other immune cells (e.g. macrophages, dendritic cells, monocytes, NK cells)
M_I	Intracellular merozoites
I_γ	Gamma interferon (INF-γ)
N_F	Tumour necrosis factor-alpha (TNF-α)
I_{12}	Interleukin-12 (IL-12)

The above assumptions led to the development of the system of differential Eqs. (1),

$$
\begin{aligned}
\frac{dR_B}{dt} &= \lambda_B + \sigma_1 R_B - \beta\left(\frac{R_B M}{1+c_0 A}\right) - \sigma_1 R_B M_o M - \mu_B R_B,\\
\frac{dI_{RB}}{dt} &= \beta\left(\frac{R_B M}{1+c_0 A}\right) - k_{iB} T I_{RB} - \mu_{iB} I_{RB},\\
\frac{dM}{dt} &= N\mu_{iB} I_{RB} - k_m T M - k_f N_F M\left(\frac{I_\gamma}{I_\gamma + K_\gamma}\right) - \beta\left(\frac{R_B M}{1+c_0 A}\right) - k_o M_o A M - \mu_m M,\\
\frac{dA}{dt} &= n_1\left(\frac{I_{12}}{I_{12}+K_{I_{12}}}\right) + n_2\left(\frac{M}{M+K_M}\right)T - \mu_A A,\\
\frac{dT}{dt} &= \lambda_T + \left(\rho_0\frac{N_F}{N_F+K_0} + \rho_1\frac{I_\gamma}{I_\gamma+K_\gamma} + \rho_2\frac{M}{M+K_M}\right)T - \mu_T T,\\
\frac{dM_o}{dt} &= \lambda_o + \left(p_0\frac{M}{M+H_0} + p_1\frac{I_{RB}}{I_{RB}+H_1}\right) - \mu_{mo} M_o,\\
\frac{dM_I}{dt} &= \beta\left(\frac{R_B M}{1+c_0 A}\right) + \frac{\eta N I_{RB}}{1+c_1 T}\left(1 - \frac{M_I}{M_I+H_3}\right) - N\mu_{iB} I_{RB} - N_T k_{iB} T I_{RB} - \mu_{mi} M_I,\\
\frac{dI_\gamma}{dt} &= \gamma_1 M + \gamma_2 T + \gamma_3\left(\frac{I_{12}}{I_{12}+K_{I_{12}}}\right) - \mu_\gamma I_\gamma,\\
\frac{dN_F}{dt} &= \alpha_1 M + \alpha_2 T + \alpha_3\left(\frac{I_\gamma}{I_\gamma+K_\gamma}\right) - \mu_f N_F,\\
\frac{dI_{12}}{dt} &= \kappa_0 M_o + \kappa_1\left(\frac{M}{M+K_M}\right) - \mu_{I_{12}} I_{12}.
\end{aligned}
\tag{1}
$$

The first equation describes the dynamics of red blood cells (RBCs). Antibodies specific to malaria parasites (merozoites) inhibit invasion of erythrocytes by merozoites as modelled by the term $\frac{1}{(1+c_o A)}$, where c_o represents the efficiency of antibodies in reducing erythrocyte invasion [4]. This term implies that as antibody activity increases the number of RBCs that are infected by the merozoites are reduced.

The second equation models the dynamics of merozoites infected RBCs (IRBCs). The second term of this equation represents the killing of IRBCs due to T specific immune response at rate k_i through lysis. We associate lysis of IRBCs with the death of