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Nanotechnology applied to the treatment of malaria ☆

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ABSTRACT

Despite the fact that we live in an era of advanced technology and innovation, infectious diseases, like malaria, continue to be one of the greatest health challenges worldwide. The main drawbacks of conventional malaria chemotherapy are the development of multiple drug resistance and the non-specific targeting to intracellular parasites, resulting in high dose requirements and subsequent intolerable toxicity. Nanosized carriers have been receiving special attention with the aim of minimizing the side effects of drug therapy, such as poor bioavailability and the selectivity of drugs. Several nanosized delivery systems have already proved their effectiveness in animal models for the treatment and prophylaxis of malaria. A number of strategies to deliver antimalarials using nanocarriers and the mechanisms that facilitate their targeting to *Plasmodium spp.*-infected cells are discussed in this review. Taking into account the peculiarities of malaria parasites, the focus is placed particularly on lipid-based (e.g., liposomes, solid lipid nanoparticles and nano and microemulsions) and polymer-based nanocarriers (nanocapsules and nanospheres). This review emphasizes the main requirements for developing new nanotechnology-based carriers as a promising choice in malaria treatment, especially in the case of severe cerebral malaria.

Contents

Abbreviations: ACT, artimisinin-based combination therapy; AE1, anion transport protein; AM, artemether; AS, artesunate; AT, atovaquone; AUC, area under the curve; CD, cyclodextrin; CHEMS, cholesteylhemesuccinate; CHOL, cholesterol; C_{max}, plasma maximum concentration; CQ, chloroquine; CQR, chloroquine resistance; CRT, chloroquine resistance transporter; CSA, chondroitin sulfate A; CTP, phosphocholine cytidylyl transferase; DFO, desferrioxamine; DHA, dihydroartemisinin; DHFR, dihydrofolate reductase inhibitor; DHPS, dihydrofolate synthesis inhibitor; DMPC, dimyristoylphosphatidylcholine; DPPC, dipalmitoylphosphatidylcholine; DPPG, dipalmitoylphosphatidylglycerol; DPPE, dipalmitoylphosphatidyletanolamine; DPPE–PEG, dipalmitoylphosphatidyletanolamine conjugated to poly(ethyleneglycol); DSPC, distearoylphosphatidylcholine; DSPE, distearoylphosphatidyletanolamine; ECC, encoded erythrocyte choline carrier; ECG, electrocardiogram; ED_{50}, effective dose to kill 50% of parasites; EPC, egg phosphatidylcholine; Hf, halofantrine; HIV, human immunodeficiency virus; HSPC, hydrogenated soya phosphatidylcholine; IPT, intermittent preventive treatment in pregnancy; IRS, indoor residual spraying of insecticide; LD_{50}, lethal dose for 50% of animals; LD_{100}, acute lethal dose; Lf, lumefantrine; LLIN, long-lasting insecticidal nets; LUVs, large unilamellar vesicles; MHC, major histocompatibility complex; MLVs, multilamellar vesicles; MPS, mononuclear phagocyte system; NaDC, sodium deoxycholate; Nanoject, AM-NLC; NanOsorb, solid microemulsion pre-concentrate; NC, nanocapsules; NE, nanoemulsions; NLC, nanostructured lipid carriers; N-LCT, long chain triglycerides; NPPs, new permeability pathways; NS, nanospheres; O/W, oil-in-water emulsion; PA, phosphatydic acid; PBS, phosphate buffer solution; PC, phosphatidylcholine; PCL, poly-ε-caprolactone; PE, phosphatidyletanolamine; PEG, poly(ethyleneglycol); PG, phosphatidylglycerol; PVP, polyvynilpyrolidone; Pgh1, P-glycoprotein homologue 1; PLA, poly(lactic acid); PLGA, poly(lactic-co-glycolic acid); PQ, primaquine; PS, phosphatidylserine; QN, quinine; RBCs, red blood cells; SLNs, solid lipid nanoparticles; SMEDDS, self-microemulsifying drug delivery systems; TDR, Diseases Research Programme of the World Health Organization; Tf, Transferrin; TQ, Tafenoquine; WHO, World Health Organization; W/O/W, water-in-oil-in-water emulsion.

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1. Introduction

Malaria, the most prevalent parasitic disease in the world, is caused by the apicomplex protozoan of the *Plasmodium* genus. Malaria is present all over the tropics, where four species, *Plasmodium falciparum*, *Plasmodium vivax*, *Plasmodium malariae* and *Plasmodium ovale* are transmitted to humans by the bites of the female mosquito vector of the *Anopheles* genus. In 2008, 109 countries were endemic for malaria, 45 of which are in Africa [1]. There were an estimated 247 million malaria episodes in 2006. Around 86% of these cases occurred in Africa, causing over 1.25 million deaths [2]. The reason for such high morbidity and mortality stems from the fact that (i) the majority of the infections in Africa are caused by *P. falciparum*, the most dangerous of the four malarial parasites that infect humans, and (ii) the most effective malaria vector and the most difficult to control (*Anopheles gambiae*) is widespread in that continent. Approximately 80% of malaria cases in Africa were in 13 countries, and over half of them occurred in Nigeria, The Democratic Republic of the Congo, Ethiopia, Tanzania, and Kenya [3]. Among the cases that occurred outside Africa, 80% occurred in India, Myanmar, Bangladesh, Indonesia, Papua New Guinea and Pakistan [1]. After Africa, India and Brazil are currently the regions of highest malaria endemicity in the world, being affected also by other *Plasmodium* species. Despite causing less mortality than *P. falciparum*, *P. vivax* is a widely distributed infection that has an enormous socioeconomic impact, being prevalent in South America, Asia and Oceania. There were approximately 881,000 malaria deaths in 2006, of which 91% were in Africa [1,2,4,5] and 85% were of children under 5 years of age. The majority of children experienced their first malaria infection during the first few years of life, when they have not yet acquired adequate clinical immunity [1]. For all, the efforts of the several not-for-profit partnership initiatives in the world, along with The Tropical Diseases Research Programme of the World Health Organization (TDR/WHO), malaria can still be considered a neglected disease because it suffers from insufficient research and development in therapy and vaccines worldwide, costing millions of lives. As shown in Fig. 1, South-East Asia and the African regions are the most affected areas in the world, with a combined population of more than 700 million. Currently, eighty countries are in the phase of malaria control; twelve countries are making the transition to an elimination programme; eleven countries are operating a malaria elimination programme, and six countries are actively engaged in preventing the reintroduction of malaria (Fig. 2). The latter are located along the edges of the global malaria distribution map (Fig. 1) [6].

Even though chemotherapy has been successful to some extent, failures are frequent and due to a variety of factors [7]. First, the intrinsic characteristics of the disease, related to the conditions of transmission and the difficult control of spreading through tropical areas [1,8]. Primary factors are the complexity of the parasite life cycle and the development of drug resistance [2,6,9,10]. Another critical factor is the increasing number of immune-compromised patients that suffer from malaria and human immunodeficiency virus (HIV) co-infections [11]. Reports suggest that the anti-malaria treatment failure is more common in HIV-infected adults with low CD4-cell counts than in HIV-uninfected patients. On the other hand, acute malaria episodes cause a temporary increase in the viral replication of HIV and consequently of the plasma viral load [12]. One study showed that HIV-infected children with advanced immune-suppression have more episodes of clinical malaria and higher parasite densities than HIV-infected children without advanced immune-suppression [13]. Another study showed a clear tendency to increased mortality in children with co-infection [14]. Together, these infections cause more than 4 million deaths a year.

Furthermore, the complexity of the recommended regimens, which are usually based on a combination of two or more drugs, increases the cost and reduces patient compliance, due to the severe side effects found (Table 1). In addition, extrinsic factors such as technical and operational failures in implementing campaigns to fight malaria, the poor quality of medicines distributed in different countries, drug interactions, the unavailability of less toxic drugs, resistance of the vector to insecticides and socioeconomic conditions of affected populations aggravate the difficulties for the eradication of malaria in the world [7].

The combination of tools and methods to arrest the widespread dissemination of malaria includes measures for the prevention of infection through the elimination of the mosquito using long-lasting insecticidal nets (LLIN) and indoor residual spraying of insecticide (IRS), and treatment with artemisinin-based combination therapy (ACT). As a last resort, intermittent preventive treatment with antimalarial drugs in the case of pregnancy (IPT) has been used to reduce the impact of malaria infection on the foetus during pregnancy [1]. Despite the fact that the most cost-effective measure for reducing the intolerable global burden of malaria would be the vaccination of the endemic population, an effective vaccine to control malaria is still not commercially available [15]. However, new vaccines that prevent malaria infection have been recently reported [16]. These vaccines, known as RTS,S/AS01B and RTS,S/AS02B, are undergoing phase I and II clinical trials and contain liposome-based and water-in-oil-based emulsion adjuvants, respectively. Both systems contain the immunostimulants monophosporyl lipid A and QS21, a triterpene glycoside purified from the bark of *Quillaja saponaria* [17].