

Antimalaria drug development & pipeline

Abstract

Increasing incidence of artemisin resistance endangers very foundations of current guideline based antimalarial therapy. There is an unmet need to develop newer strategies, targeting novel pathophysiology to set high standards in antimalaria care. Of late, the antimalarial drug pipeline is becoming increasingly robust, and promises healthier outcomes. We discuss few drugs currently under pre-clinical development that have shown encouraging results.

Keywords: artemisin, resistance, malaria, novel drugs

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Abbreviations: NCE, new chemical entity; PfCRT, *P. falciparum* chloroquine resistance transporter; IPT, intermittent preventative treatment; MMV, medicines for malaria ventures

Discussion

Artemisinin-based combination therapies (ACTs) are currently the gold standard treating uncomplicated malaria. Primaquine also eliminates liver hypnozoites, and is the only registered drug active against the mature gametocyte. However, resistance against existing antimalarials is well documented, and troubling due to the emerging resistance to artemisinins. A rising incidence of drug resistance requires new drugs with novel disease targeting strategies. The challenge is to demonstrate:

- Faster onset and longer duration of drug action,
- Safe for children and pregnant women and
- Ideally be amenable to a single-dose administration.

Artemisinin have traditionally cleave the peroxide bond by Fe(II) found in heme proteins, thus generating toxic oxygen radicals. Synthetic peroxides, thus are proving to be useful substitutes for artemisinin. The first-generation ozonide OZ277, known as arterolane,¹ has been found to inhibit the growth of chloroquine-resistant (K1) and chloroquine sensitive (NF54) parasite strains. In 2012, the combination of arterolane maleate and piperazine phosphate was released as a 3-day treatment in India.² The second-generation peroxide OZ439 (EC₅₀ = 3.4–4.0 nM) is now undergoing Phase IIa studies. It features an 80-aryl rather than an 80-alkyl group causing higher stability of the O–O bond towards Fe(II) increasing by 50-fold, presumably because of steric reasons. This in turn translates into a much longer half-life in both rats (t_{1/2} = 20 h for OZ439 vs. 1h for OZ277) and humans (t_{1/2} = 25–30h for OZ439).³

Tetraoxanes (also stabilizes O–O bond), has been employed in the drug candidate RKA 182, which has displayed good activity against *P. falciparum* 3D 7 strain and K1 strain (chloroquine sensitive and -resistant, respectively).⁴ However, RKA 182 was not found curative in a single dose. The Central Drug Research Institute, Lucknow, India, is investigating a new chemical entity (NCE) trioxane CDRI-97/78, currently in Phase I studies. It has 'trioxane core' and singlet oxygen to yield a peroxide compound.⁵

P. falciparum chloroquine resistance transporter (PfCRT) mutations result in increased efflux of chloroquine from the acidic digestive vacuole to the cytosol of the parasite. Ferroquine has

been found to be active against chloroquine-resistant strains, and is currently undergoing Phase II clinical trials. Ferroquine, unlike chloroquine, accumulates in the digestive vacuole of the chloroquine resistant parasites, enabling PfCRT inhibition.⁶ Amodiaquine has been found active against most chloroquine resistant strains, however, two reactive metabolites are formed, namely imine and aldehyde, and are the likely causes of reported hepatotoxicity and agranulocytosis, respectively.⁷

N-tert-Butyl isoquine (GSK369796) has been designed to avoid the formation of quinone imines, and has entered Phase I studies. It is potent in vitro, including in the chloroquine resistant strain K1 and is active in vivo, thus being comparable to amodiaquine. However, its development was discontinued due to exposures insufficient to demonstrate drug safety superior to chloroquine.⁸

Walter Reed Army Institute of Research screened for analogs with a lower brain penetration, and have identified WR621308, which has a substantially lower permeability across MDCK cell monolayers than mefloquine, suggesting lower brain exposures.⁹

Cycloguanil and pyrimethamine demonstrate inhibition of dihydrofolate reductase (DHFR). Inhibition of DHFR therefore arrests DNA replication, but resistance is widespread due to mutations in the enzyme.¹⁰ P218, another DHFR inhibitor has been found to be active against all clinically relevant mutations. It combines the pyrimidine ring of pyrimethamine which brings potency, and the linker of the DHFR inhibitor WR99210, which tolerates mutations due to its flexibility. P218 is more potent than pyrimethamine against DHFR in the wild-type strain TM4 as well as in the quadruple mutant strain V1/S.¹¹

About 125 million pregnancies are at risk of malaria every year, and 10,000 women and 200,000 babies die as a result. An intermittent preventative treatment (IPT) has been recommended for pregnant women, but drug-resistance to the currently adopted IPT (sulfadoxine–pyrimethamine) poses an issue.¹² Azithromycin and chloroquine have demonstrated safety in children and pregnant women over a number of years. Notably, the azithromycin–chloroquine combination has been designed to be synergistic against chloroquine-resistant strains of *P. falciparum*, and was shown to be synergistic in the treatment of symptomatic malaria in clinical trials, with a maximum antiparasitic effect occurring only after two cycles of intra-erythrocytic development (one cycle of invasion, development, and egress lasts 42–48h). Finding azithromycin analogs with improved activity in mouse models of malaria has been challenging.¹³

Spiroindolones as a novel chemotype series, has been optimized to deliver NITD-609, are now currently in Phase II trials.¹⁴ The target was identified to be the cation channel PfATPase4. NITD-609 has an excellent potency, with 100% orally bioavailability in mouse and rat. It is also a potent inhibitor of gameto-cytogenesis, and blocks transmission to mosquitoes. The Medicines for Malaria Ventures (MMV) selected the spiroindolone project as the 'Project of the Year 2009'.¹⁵

Albitiazolium (T3 or SAR97276) is a drug that has reached Phase II clinical trials. It acts primarily by inhibiting the transport of choline into the parasite. An important property of albitiazolium is that it accumulates irreversibly in the *Plasmodium* up to 1000-fold. Albitiazolium inhibits parasite growth and halts disease progression in mice without recrudescence.¹⁶ DSM265 (Phase I) inhibits PfDHODH (Dihydroorotate dehydrogenase (DHODH) is the enzyme which catalyzes the rate-limiting step of the de novo pyrimidine biosynthetic pathway) selectively over its human counterpart. It demonstrated good oral bioavailability in rats and was efficacious *in vitro* and in mouse.¹⁷ Benzimidazole inhibiting PfDHODH (IC₅₀ = 40nM) and parasite growth, has a decent bioavailability in rat (49%).¹⁸

Genz-668764 inhibits *P. falciparum* *in vitro* and is active in mouse at doses of the order of 100mg/kg/day.¹⁹ It is also active against the chloroquine resistant strain Dd2. Similarly, ML238 has been a potent NCE, being highly water soluble and not cytotoxic.²⁰

ACT-213615 has been established as fast-acting molecule against all asexual erythrocytic stages, currently being tested with encouraging results.²¹ Notably, ACT-213615 completely cured *P. berghei*-infected mice with three consecutive oral daily doses of 750mg/kg. Benzoxaborole has also emerged as a promising starting agent.²² TDR84420 was identified as a potent screening hit WHO Special Programme for Research and Training in Tropical Diseases (TDR).²³

Conclusion

There have been significant advancements in antimalarials drug development in the preclinical setting, with few molecules showing exceptional properties. It will be interesting to see how many of these replicate such results in human trials.

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Conflicts of interest

The authors declare no conflicts of interest related to this article.

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