PHARMACOLOGY OF NEWER ANTIMALARIAL DRUGS: REVIEW ARTICLE

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ABSTRACT: Malaria is currently is a major health problem, which has been attributed to wide spread resistance of the anopheles mosquito to the economical insecticides and increasing prevalence of drug resistance to plasmodium falciparum. Newer drugs are needed as there is a continual threat of emergence of resistance to both artemisins and the partner medicines. Newer artemisinin compounds like Artemisone, Artemisnic acid, Sodium artelinate, Arteflene, Synthetic peroxides like arterolane which is a synthetic trioxolane cognener of artemisins, OZ439 a second generation synthetic peroxide are under studies. Newer artemisinin combinations include Arterolane(150mg) + Piperaquine (750mg), DHA (120mg) + Piperaquine(960mg) (1:8), Artesunate + Pyronardine (1:3), Artesunate + Chlorproguanil + Dapsone, Artemisinin (125mg) + Napthoquine (50mg) single dose and Artesunate + Ferroquine.Newer drugs under development including Transmission blocking compounds like Bulaquine, Etaquine, Tafenoquine, which are primaquine congeners, Spiroindalone, Trioxaquine DU 1302, Epoxamicin, Quinolone 3 Di aryl ether. Newer drugs targeting blood & liver stages which include Ferroquine, Albitiazolium – (SAR – 97276). Older drugs with new use in malaria like beta blockers, calcium channel blockers, protease inhibitors, Dihydroorotate dehydrogenase inhibitors, methotrexate, Sevuparin sodium, auranofin, are under preclinical studies which also target blood and liver stages. Antibiotics like Fosmidomycin and Azithromycin in combination with Artesunate, Chloroquine, Clindamycin are also undergoing trials for treatment of malaria. Vaccines - RTS, S– the most effective malarial vaccine tested to date.

KEYWORDS: CQ – chloroquine TF –taefenoquine, PM –primaquine, Q- quinine, MF-mefloquine, Pf –plasmodium falciparum, Pv-plasmodium vivax, DHA-dihydroartemisinin.

INTRODUCTION: Malaria remains one of the most prevalent and deadly infectious disease across Africa, Asia and America. WHO estimates 400-500 million cases of malaria every year throughout the world which results into approximately 1.5-2 million deaths each year.(1) Malaria is endemic in many parts of India and is one of major health problem. Thus National Malaria Control programme was started in 1958. Afteran initial decline in the incidence of Malaria there has been a significant increase in number of cases and malaria could not be eradicated. Currently it is again a major health problem. This has been attributed to wide spread resistance of the anopheles mosquito to the economical insecticides and increasing prevalence of drug resistance to plasmodium falciparum. Today first line medicines against malaria are Artemisins and its fixed dose combinations.(2) Newer drugs are needed as there is a continual threat of emergence of resistance to both artemisins and the partner medicines. There are four areas of focus of drug discovery.

1. In context of malaria eradication there is a need for medicines that can be administered as a single dose which will allow direct monitoring and they should have activity against all exiting resistant strains of parasite.
2. New medicines are needed that kill gametocytes and thus prevent transmission.
3. There is a need for medicines which prevent relapses of plasmodium vivax.
4. Need of molecules with longer half-life to give chemoprophylaxis or long term protection against reinfection. Most of the currently approved drugs are only effective against blood stages & young gametocytes this unfortunately does not cause complete clearance of mature gametocytes.

NEWER ARTEMISININ COMPOUNDS:

1. Artemisone – highly active antimalarial drug in phase2 trial is 10 times more potent than artesunate in invitromodels. It is also active in murine model of cerebral malaria[3]
2. Artemisnic acid – artemisinin is commercially produced by extracton from sweet worm wood.
3. A recent alternative production involves a yeast fermentation process that delivers the biosynthetic precusorartemisinicacid. This is converted to artemisinin using a photochemical oxidation process.[4]
4. Sodiumartelinate: ArtefleneA synthetic derivative of Yinghaosu was evaluated extensively against various drug-sensitive and drug-resistant Plasmodium falciparum in vitro and Plasmodium berghei in mice. Experimentally arteflene proved to be a highly effective antimalarial drug. The suppressive and prophylactic properties were comparable to chloroquine and superior to Qinghaosuartemether and artesunicacid. It was consistently rather more active against drug-resistant than against drug sensitive strains of Plasmodium falciparum. In vitro and in vivo studies with Chloroquine, Mefloquine and Quinine revealed an additive to synergistic effect with arteflene.[5]

   Synthetic peroxides- they are proving to be useful substitutes of artemisinins.
5. Arterolane- synthetictrioxolane congener of AT. The 1st generation ozonide known as arterolane inhibits the growth of chloroquine resistant and sensitive strains. Orally active drug that has been developed in india and recently marketed in combination with piperaquine. It acts rapidly at all stages of asexual schizogony including multidrug resistant falciparum but has no effect on hepatic stage. It accumulates in the food vacuole of parasite and differs from other artemisinins which do not accumulate at this site. It has moderate gametocidalactivity. Half-life is 1-3hrs.[6]

OZ439 - OZ439 carries the hope of providing a single dose oral cure in humans when used in combination. OZ439 is a rapidly acting agent against asexual stage parasites, and will likely be developed for use in combination with a partner drug with a longer half-life than its own. Studies are underway to identify such a partner. This drug is currently undergoing Phase II a trials. It features an 8aryl rather than 8Alkyl group. It has a longer half-life. Provides single dose cure (20mg/kg).it has significant prophylactic activity. Theseozonides are synthesized from an oxime and ketone in presence of ozone. The stability of o-o bond toward Fe (11) is increased by 50 fold.[7]

NEWER ARTEMISININ COMBINATIONS:

1. Arterolane (150mg) + Piperaquine (750mg) (SYNRIAM) Arterolane acts rapidly at all stages of asexual schizogony including multidrug resistant falciparum but has no effect on hepatic stage. Piperaquine is bisquinolone. Congener of chloroquine with similar mechanism.it is high effective erythrocyticschizont with prolonged action but slow onset of action.it is effective against chloroquine resistant and sensitive strains. Half-life is 35days which may be beneficial in reducing the rate of relapse following the treatment. This combination provides >95%cure with fever and parasitemia clearance of 24-48hrs.[8]
2. DHA (120mg) + Piperaquine(960mg) (1:8) - DHA is derived from natural source. Combined with long acting Piperaquine.Trialsare going on in Indian population.[9]
3. Artesunate + Pyronardine (1:3) – pyronaridine is derived from mepacrine which is also known as yellow drug. It has been used in china for 40yrs. It is high efficacy erythrocyte schizonticide whose mechanism of action is similar to chloroquine. It is effective against chloroquine resistant and sensitive strains of plasmodium falciparum and vivax strains. Onset is slow with long duration of action. At high dose it has analgesic and antipyretic effect. Can used orally and parenterally, well tolerated. It is concentrated in RBC and metabolized with terminal half-life of 7days clinical efficacy of this combination has been tested in falciparum malaria in china, Thailand & Africa with >95% success& no recrudescence seen in 28 days. Clinical trials have completed in India with 95% cure rate. This combination has not yet approved for use in India.it is currently the only combination with regulatory approval for activity against plasmodium vivax.[10]
4. Artesunate + Chlorproguanil + Dapsone.
5. Artemisinin (125mg) + Napthoquine (50mg) single dose.
6. Artesunate + Ferroquine.
    - Newer drugs under development.
    - Transmission blocking compounds.

Primaquine congeners – currently the only fully effective gametocidal drug is primaquine which acts against gametocytes of all malarial species. Two major issues with its use is 14 days treatment & there is elevated risk of hemolysis in patients with G6PD deficiency. WHO recommended single dose 0.75mg/kg provided that the risk for acute hemolytic anaemia (in G6PD deficiency), the dose is lowered to 0.25mg/kg in 2012.[11]

Bulaquine – it is a primaquine congener developed with aim of drug with tissue schizonticidal activity which is safe inpatients with G6PD deficiency. It is developed at CDRI (Lucknow India). Bulaquine is a prodrug that is converted to primaquine. It is possibly well tolerated than primaquine in patients with G6PDdeficiency. It prevents relapses. It is given in dose of 25mg/day for 5 days together with chloroquine. They cannot be given parenterally.[12]

Etaquine - long acting - more potent analogue[13]

Tafenoquine - is anew long acting 8 amino quinolone exoerythrocyticschizonticide is being developed as a single dose antirelapse drug for vivax malaria with t1/2 of 16 – 19 days.TF is highly active against vivaxhypnozoites. It is also shown some activity against asexual erythrocytic stages of vivax & falciparum, but clearance &parasitemia were slow. it must be accompanied by CQ or other rapidly acting erythrocyticschizonticide. PQ has low therapeutic index, short half-life&

is associated with serious side effects & daily dosing is needed. TF was synthesized to overcome all these deficiencies. It has a potential to replace PQas a prophylactic agent. TQ acts by accumulating in food vacuole & inhibits the detoxification of haeme to haemzoin.TF via its hydroxyl metabolites stimulates the HMP shunt, increases methhaemoglobin production & decreases glutathione levels in the cell. The pro oxidant properties of its metabolite correlate with its exoerythrocytic & also erythrocyticschizonticidal action. TFin vitro also demonstrated gametocidal & sporonticidal activity suggesting a potential role in blocking transmission. In vitro studies also demonstrated an apparent synergism of blood schizonticidal activity with CQ & AT. Advantages of TQ include longer t1/2, better theraupetic index, greater activity against blood & liver stages, additional game tocidal & sporonticidal activity, better compliance because of single dose, potential drug of choice for travelers to endemic areas for short periods and can be stopped immediately upon leaving endemic are, chemoprophylactic property against vivax & falciparum& has potential for radical cure of P. vivax but it is not prescribed in G6PD deficiency due to risk of hemolysis & in pregnancy.[14]

Spiroindalone–these are emerging class of antimalarial drugs whose mode of action is to inhibit protein synthesis in the target parasite. Undergoing phase 2 trials. Studies have shown that it is more potent than artesunate & CQ & has 100%oralBA. It is given 3 daily doses of 50mg/kg or single dose of 100mg/kg which has given complete cure. It is also potent inhibitor of gametocy to genesis & blocks the transmission to mosquito. The medicine for malaria venture selected spiroindalone project as project of year 2009. Its mechanism of action is - the malarial parasite P. falciparum establishesin the host erythrocytic plasma membrane a new permeability pathways that mediate nutrient uptake into the infected cell. These pathways allow Na+ influx causing Na+ in the infected erythrocyte cytosol to increase to high levels. The intra erythrocytic parasite itself maintains a low cytosolic Na+ via unknown mechanism. The intra erythrocytic parasite actively extrudes Na+ against an inward gradient via P.fATP4 a parasite plasma protein. Spiroindalone cause a profound disruption in parasite Na+ homeostasis. Mutations in PfATP4 confer resistance to apotent class of antimalarial spiroindalone. It is 1st antimalarial not belonging to either AT or peroxide class.[15]

Trioxaquine DU 1302 – new antimalarial agent active on all erythrocytic forms including gametocytes. They are a synthetic hybrid molecules containing a trioxaquine motif which is responsible for antimalarial action linked to an aminoquinolone entity which is responsible for antiplasmodial properties. These trioxaquines are highly potent against young erythrocytic stages of P. f& exhibit efficient activity in vitro against chloroquine sensitive & resistant strains of P.f. TQDU1302 is prepared from alfaterpinene a cheap natural product. It is nontoxic & non genotoxic antimalarial agent. They are potent against gametocytes which would limit the transmission of malarial parasites are potentially very promising.[16]

Epoxamicin - it is proteosome inhibitor proteosome system plays a major role in overall protein turn over especially in fast dividing eukaryotic cells including plasmodia. Treatment with proteosome inhibitor arrests parasitic growth. This is a highly promising strategy to develop antimalarial effect. Studies have shown that epoxamicin kill all stages.24hrs after treatment was shown that total parasitemia clearance by 78%. Asexual parasites were decreased by 86% & gametocytes by 77%.

Quinolone 3 Di aryl ether - it is a new class of antimalarial drug. ELQ 300 is an experimental antimalarial medication. It is endochinlikequinlone. It will act as an inhibitor of the mitochondrial cytochrome bc1 (in electron transport chain). In preclinical studies with mice it was found to be highly active against Pf &P.v at all life cycle stages i,e target both liver & blood stages as well as forms that are crucial for disease transmission i,e gametocytes, zygote, oocyst.it has good oral bioavailbility.[17]

Newer drugs targeting blood & liver stages.

Ferroquine -it is a novel antimalarial drug and 1st organometallic drug, a ferrocenyl group covalently flanked by a 4 aminoquinolone & a basic alkylamine. FQis able to overcome CQ resistant problem. The ferrocene group itself has no antimalarial activity. Metabolized into one major metabolite (N monodemethylated) is also highly active in vitro. Well tolerated upto 800mg once daily for 3 days. Safety profile is upto 1600mg.mild side effects are seen prolong. QT interval. FQ was more active against Pf in vitro. FQ was active than CQ, Q, MF, PQ, but less active than artesunate. FQ like CQ forms complexes with haematin & is even stronger inhibitor of beta haematin formation than CQ. Due to it hiherlipophilicity FQ targets lipid sites more efficiently than CQ & is able to generate ROS whereas CQ is not under-going phase2 trials. CQ resistant parasites expel CQ more rapidly from RBC which catalysed by P, f membrane protein (Pf CRT) FQ block PFCRT through its lipophilic properties acting like a resistant reversing agent.so far no resistance of P, f to FQ has been found in vitro.[18]

Isoquine– amodiaquine is a 4aminoquinolone that causes adverse effects agranulocytosis&liver damagedue to the formation of 2 electrophilic metabolites (quinoneimine& aldehyde) which causes hepatotoxicity &agranulocytosis. N tert-butyl isoquine was designed to avoid the formation of quinine imines & entered phase1 clinicaltrial.[19]

Albitiazolium – (SAR – 97276) - choline uptake inhibitor, acts by inhibiting the transport of choline into parasite which requires choline to generate phosphatidyl choline, the main lipid of its cell membrane as it replicates & forms new membrane. An important property of albitiazolium is that it accumulates irreversibly in the plasmodium. Notably single injection is curative which is observed even at high parasitaemia levels also effective orally but BA is low.[20]

Older drugs with new use in malaria- all these drugs are undergoing preclinical studies. Betablockers - propranolol prevent the entry of p.f into RBC.G proteins in RBCwere shown to be used by the parasite to enter the RBC.it has been shown that Gprotein subunit Gs concentrates around the malarial parasite during infection. Several laboratory models of malaria have demonstrated that blocking the Gs signal resulted in receptors decreased malarial infection. 2 major Gs associated receptors beta adrenergic & adenosine receptors are known to be present in RBC. Stimulating these receptors with an agonist increases the infection of P. f whereas betablockers which are antagonist prevented the P. f parasite from entering the RBC. Because these drugs are directed against host target there is less chance of rapid emergence of resistance to these drugs.[21]

Methotrexate – inhibition of DHFR arrests DNA replication. Low dose methotrexate has inhibited P, v DHFR.[22]

Dihydroorotate dehydrogenase inhibitors– (DSM265) –unlike its human host P.f cannot salvage pyrimidine & depends on their denovo biosynthesis. DHOH is the enzyme which catalyses

the rate limiting step of denovo pyrimidine pathway. It converts dihydrotate to orotate. This represents potential target for antimalarial therapy. DHOH is the critical enzyme for survival of the parasite DSM265 approach was awarded the MMVproject of year 2010.[23]

Sevuparin sodium – a heparin derivative that block resetting (key event in severe malaria). Act by preventing & reversing infected cell ability to block blood vessel, can be used in severe malaria & uncomplicated falciparum malaria. Completed preclinical studies, entered phase1trial.

Auranofin – clinically established antiarthriticmetallo drug behaves as potent inhibitor of mammalian thioredoxinreductases causing severe intracellular oxidative stress. Antiplasmidial effect is due to direct inhibition of P.fthioredoxinreductase.[24]

Calcium channel blockers -Verapamil - When used in combination with CQ-enhances the accumulation of CQ within the parasticvacuole, rendering it incapable of detoxifying itself &making it more susceptible to death.[25]

HIV protease inhibitors- have been shown to have direct anti-parasite effects. Directly interfere with Plasmodium growth in vitro, in vivo and have chloroquine-resistance reversing properties.Saquinavir and ritonavir behave synergistically with chloroquine and mefloquine, against chloroquine sensitive and resistant strains of P. falciparum. Synergy might result from HIV protease inhibitors reducing levels of specific enzymes and products (GSH and glutathione) used by the parasite to detoxify by-products of hemoglobin digestion.[26]

ANTIBIOTICS IN MALARIA: Fosmidomycin - antibiotic originally isolated from culture broths of bacteria of genus streptomyces. It specifically inhibits key enzyme DOXP (1-deoxy D-xylulose 5phosphate) reductoisomerase key enzyme in nonmevalonate pathway of isoprenoidbiosynthesis. The discovery of non-mevalonate pathway in malarial parasite has indicated the use of fosmidomycin as antimalarial drug.FM is effective but it needs tobe given for > 4 days when given alone. It is combined with clindamycin which is protein synthesis inhibitor. Antimalarial effect of clindamycin has not been established but has shown to act on 70s ribosome.[27]

COMBINATIONS: Fosmidomycin+Clindamycin - act synergistically undergoing phase 2 trial, combination is safe & Welltolerated short course regimen, achieved high efficacy in children with P. f. Fosmidomycin+ Artesunate - studies have shown that fever and parasite clearance in 24hrs.

Azithromycin – is presumed to target the plasmodial ribosome.AZ is also a weak base, like CQ raise.

The pH of digestive vacuole &inhibits beta haemitin formation.[28]

COMBINATIONS: Azithromycin (250mg) +Chloroquine (155mg) once daily 3day regimen is undergoing phase3 trial.it is the promising alternative for treatment for malaria in region with CQ resistance. This combination considered to be safe in children & pregnancy.[29]

Other new target – Falcipains-cysteine proteases that hydrolyze host hb to provide AA for parasite protein synthesis. They are difficult to develop as drug candidates because of selectivity issues

Vaccines - RTS, S– the most effective malarial vaccine tested to date is RTS,S, a hybrid protein particle formulated in multi component adjuvant ASO1.intial vaccine constructs of tandem repeat region of circumsporozoite protein mainly copies of 4AA sequence NANP showed very low level of efficacy, but expressing the central repeat (R) fused to "C" terminal region known to contain T cell epitopes (henceT) fused inturn to hepatitis B surface Ag (S) yielded a yeast expressed protein called RTS. However to generate immunogenic particles, RTS protein needed to be co-expressed with large amounts of unfused S protein to yield RTS,S. it was tested withseveral adjuvant formulations. The highest protective efficacy was observed in volunteers who received vaccine with an adjuvant containing the immune stimulants. When combined with this adjuvant known as ASO2 or related adjuvant ASO1 which contains liposomes. RTS,S has shown sterile efficacy of 30-50% in healthy volunteers. Immunological analysis has demonstrated the remarkable ability of this vaccine to induce a very high concentration of Ab that target the conserved repeat region of cicumsporozoite protein. The level of efficacy achieved by RTS, S in challenge studies was a clear breakthrough. In many epidemiological studies RTS, S can reduce the rate of clinical malaria by 30-50%. The end point most widely accepted is reduction in clinical episodes or during 1st 12 months of follow up. RTS, S/ASO1 is in phase3 clinical trial. However some important questions remain about the efficacy, utility, duration of protection provided by the vaccine & cost effectiveness.[30]

Future targets of malaria vaccine. 80% protection against clinical malaria, persistence of protection for 4 years& new efforts include transmission blocking vaccine (mosquito stage vaccine), vaccine against plasmodium vivax, combination vaccines (RTS, S (clear sporozoites before they enter liver cell) + vector vaccine (clear infected liver cells).[31]

CONCLUSION: New drugs ideally should addressdrug resistance, have rapid onset of action, safe in children & pregnancy & provide single dose cure. The challenge is to find a drug that addresses all these features It is our hope that with rich variety of new chemical entities, such a drug will be discovered.[32]

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