Clinical Drug Trials

Drug resistance to chloroquine in *P. falciparum* was reported in India for the first time from Assam in 1973. Since then the foci of resistance have spread to many more states all over India. The situation has further deteriorated in the recent past due to parasite becoming resistant to other available drugs in addition to chloroquine. Sulphadoxine-pyrimethamine, a second line drug for *P. falciparum* is not effective for *P. vivax* malaria. Quinine is still effective but as oral monotherapy it has limited role in mild malaria because of 7-day regimen. Mefloquine and artemisinin have specific indications. Therefore, new drugs and treatment strategies need to be developed as a priority.

Development of new drugs involves extensive preclinical and toxicological studies followed by well planned clinical trials. At MRC, a number of new drugs have been screened in clinical trials for evaluation of safety and efficacy. Based on these data, the drugs have been registered with Drugs Controller General of India for commercial marketing and also for use in national programme under NAMP.

α,β-Arteether

Artemisinin is an active constituent of plant *Artemisia annua*, a Chinese herb (Qinghaosu). Artemisinin and its derivatives are most rapidly acting schizonticides valuable for emergency treatment of complicated malaria as well as multi-drug resistant falciparum malaria. Sodium artesunate, artemether and arteether are three formulations registered in India. Arteether is oil soluble ethyl ether derivative of artemisinin. α,β- Arteether (30:70 mixture racemic) was developed jointly by CIMAP and CDRI and clinical efficacy

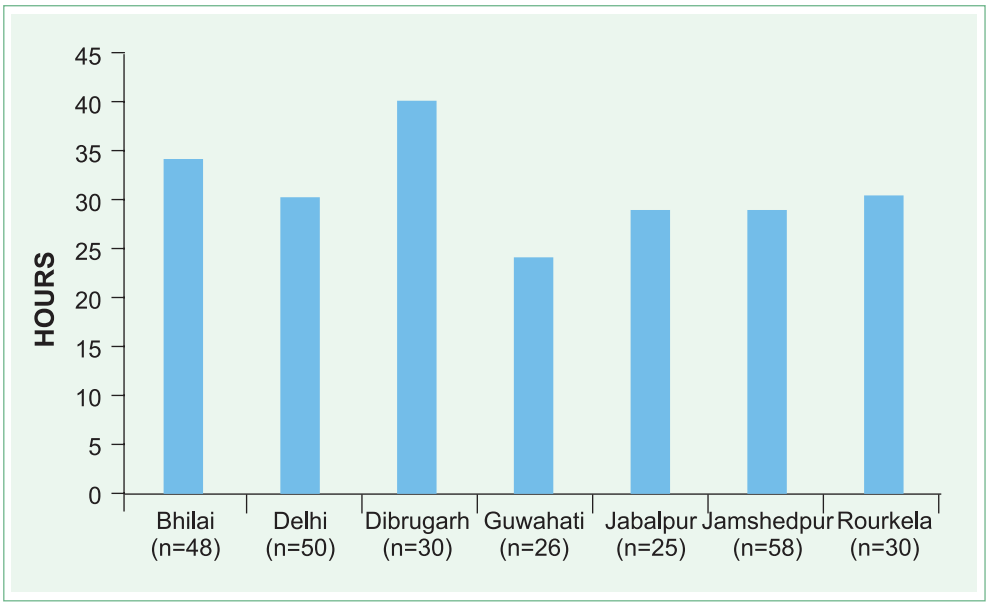

Fig. 3: **Mean parasite clearance time in uncomplicated *P. falciparum* malaria**

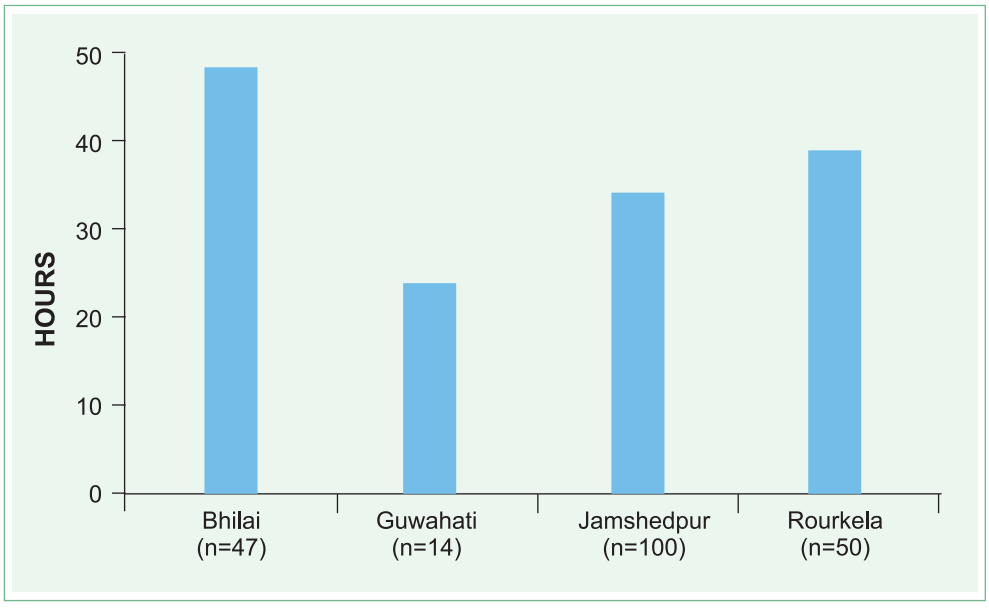

Fig. 4: **Mean parasite clearance in complicated *P. falciparum* malaria**

trials were conducted and coordinated by MRC. Phase III multicentric trial was conducted at seven centres in 267 uncomplicated falciparum malaria patients and 211 complicated falciparum malaria cases (Valecha *et al.*, 1997 & Asthana *et al.*, 1997). It was prospective, open, noncrossover study. Adult dose of drug was 150 mg once a day intramuscularly for three consecutive days. The cumulative cure rates ranged from 93–100% parasite clearance in 24–40 hours, while fever clearance was in 36–75.6 hours (Figs. 3 & 4). Based on the results of these Phase III trials the drug α, β-Arteether marketed by M/s. Themis, India as EMAL was registered for use in India in 1996. Now the drug has been included in the National Anti Malaria Programme.

Bulaquine (80/53)

Plasmodium vivax malaria constitutes 60–65% cases of malaria in India. Although mortality is low due to this infection, relapses occur due to persistence of hepatic forms. The only drug available for preventing these relapses is primaquine, which can cause haemolysis in G-6-PD deficient cases. In the quest for safer substitute, CDRI developed activated enamine of primaquine which is chemically N-(3-acetyl 4-5-dihydro-2-furanyl)-N-(6-methoxy-8-quinlinyl) 1,4-pentadiamine. This new drug is safer than primaquine as evidenced by toxicological and haematological studies in beagle dogs and *in vitro*. Phase III, double blind, prospective, noncrossover clinical trial was conducted at MRC, Delhi comparing placebo, primaquine and 80/53 for antirelapse activity during one year follow-up (Valecha *et al.*, 2001 & Adak *et al.*, 2001).

A total of 697 patients of *P. vivax* malaria were enrolled and drugs were given for 5 days after treating acute episode with chloroquine. The doses used were primaquine 15 mg and bulaquine15 mg orally daily. During one year follow-up; relapse rates in placebo group were 40.18%, in primaquine group 26.8%, while in 80/53 group 29.6%. This shows that bulaquine was better than placebo and as effective as primaquine in preventing relapses (Fig. 5).

The drug has been registered and marketed for use as antirelapse drug for *P.vivax* malaria in India. Further studies are being planned by MMV in collaboration with CDRI, MRC and Nicholas Piramel.

Ayush-64

Ayush-64 is a combination of four plants namely *Alstonia scholaris* (aqueous extract of bark–1 part) *Picrorhiza kurroa* Royle (aqueous extract of rhizome–1 part), *Swertia chirata* (aqueous extract of whole plant–1 part) and *Caesalpinia crista* Linn (fine powder of seed pulp–3 parts).

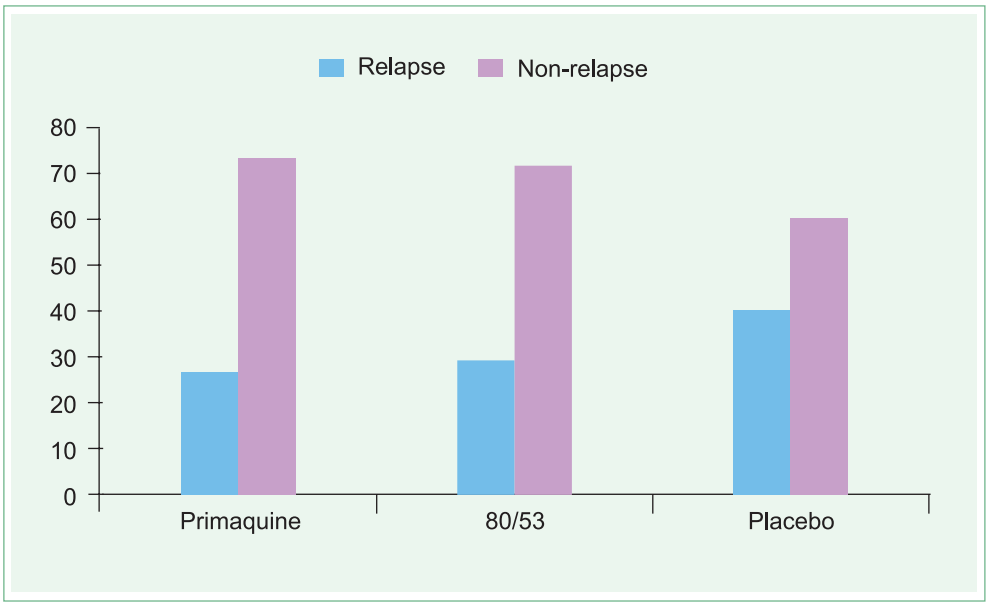

Fig. 5: **Per cent relapse rates in primaquine, 80/53 and placebo groups**

The drug was patented by the Central Council of Ayurveda and Siddha and to confirm the efficacy in well designed scientific trial, open prospective, noncrossover, randomized clinical trial was conducted in *P. vivax* malaria patients at the Centre in collaboration with NAMP (Valecha *et al*., 2000). Results showed that with Ayush-64 cure rate on Day 28 was 48.9% at a dose of 1 g three times a day for 5–7 days as against 100% with chloroquine 1500 mg over three days (Fig. 6).

Azithromycin

Azithromycin, an azalide antibiotic similar to erythromycin has been shown to possess good antimalarial activity in human malaria challenge studies. In addition, when used for treating other diseases the numbers of episodes of febrile parasitaemia due to *P. falciparum* were reduced. The drug has, therefore, been used in a number of studies and shown protective efficacy of 71–98% in falciparum and vivax malaria. The drug has an

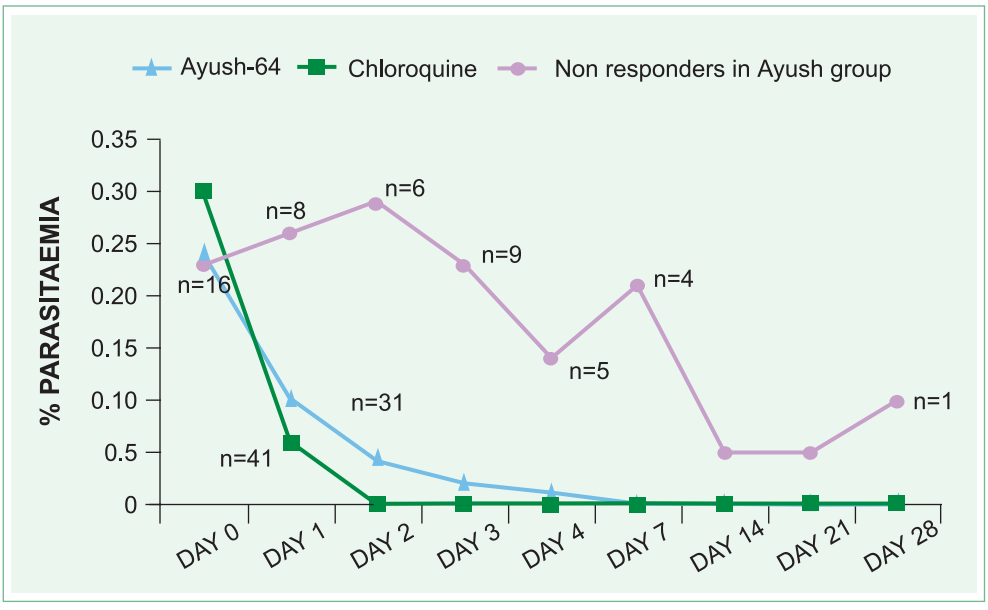

Fig. 6: **Comparative parasite clearance time with chloroquine and Ayush-64**

additional advantage that it can be given to pregnant women and infants.

Considering the potential of the drug and the limitations of existing drugs to treat malaria, a randomized, double blind, comparative GCP study was undertaken to explore antimalarial activity of azithromycin in the dose of 1g/day for 3 days in vivax malaria in comparison to standard chloroquine treatment in the dose of 1500 mg over 3 days. The results in 98 vivax malaria patients show that although the clinical and parasitological recovery on Day 3—74% and 44% in azithromycin group was low but it increased to 88 and 84% on Day 7. In chloroquine group the values were 95–100% on these days. Both the drugs were well tolerated and there were no recrudescences in either group up to Day 28.

This shows that azithromycin is well tolerated, safe and can be curative in vivax malaria in approximately 85% cases when used as monotherapy but is slower acting than chloroquine. Studies in falciparum malaria using azithromycin in combination with chloroquine in 48 patients have shown no recrudescence over 28 days.

Combination Therapy

Combination therapy is based on the synergistic or additive potential of two or more blood schizontocidal drugs with independent modes of action and different biochemical targets in the parasite. The objective of combining antimalarial drugs is to improve efficacy and delay the development and subsequent selection of drug-resistant parasites, thus prolonging the useful therapeutic life of drugs in the combination. The advantages of artemisinin-based combination therapy (ACT) relate to the unique properties and mode of action of the artemisinin component, which include rapid reduction of the parasite biomass, rapid resolution of clinical symptoms, effective action against multidrug resistant *P. falciparum* and reduction of gametocyte carriage rates (which may reduce transmission of resistant alleles specially in areas with low or moderate malaria transmission). Therefore, in Indian scenario studies have been planned to evaluate the role of combination therapy in malaria.

A study was conducted in microscopically confirmed patients of uncomplicated falciparum malaria in Madhya Pradesh in areas where resistance to first line/second line drugs has been reported. The combination used was chloroquine or SP with artesunate orally and parasite and fever clearance was compared with chloroquine or SP treatment alone Subjects fulfilling inclusion criteria were enrolled. Safety and tolerability of combination therapy was first established in 12 patients by recording detailed physical, haematological and biochemical parameters before and after treatment. Subsequently 60 patients were enrolled randomly by open design in different treatment groups (monotherapy or combination therapy). Clinical and parasitological parameters were evaluated during 28-day follow-up period.

None of the patients had early parasitological or clinical failure. All the patients tolerated the drugs well. The parasite and fever clearance was faster with combination therapy than monotherapy. No major adverse effects were observed in any of the groups. n