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Malaria is a major public health problem of the world. An estimated 300-500 million cases and 1 to 2.7 million deaths occur each year due to malaria<sup>1</sup>. In India over the past two decades malaria incidence has been fluctuating between 2-3 million cases each year. India has 40% of all malaria cases outside Africa<sup>2</sup>. Effective Quinine monotherapy for malaria has been available for more than 350 years long before the causative organism of the disease were identified<sup>3</sup>. Chloroquine remains the chief drug as monotherapy which was later joined by amodiaquine, sulfadoxine-pyrimethamine and Mefloquine.

Resistance to antimalarials has been documented for *P. falciparum*, *P. vivax* and recently *P. malariae*<sup>4</sup>. In *P. falciparum*, resistance has been observed to almost all currently available antimalarials (Amodiaquine, Chloroquine, Mefloquine, Quinine and Sulfadoxine-Pyrimethamine) except for artemisinin and its derivatives<sup>4</sup>. *P. vivax* resistance to Chloroquine, Pyrimethamine has also been observed, though in Indian subcontinent it is still sensitive<sup>3,4</sup>.

Multi-drug resistance (MDR) is defined as resistance to three or more antimalarial compounds from different chemical classes<sup>4</sup>. Generally, the first two classes are 4-aminoquinolines (e.g. Chloroquine) and antifolate (Sulfadoxine-Pyrimethamine)<sup>4</sup>. MDR malaria presents as the biggest therapeutic challenge to health care in most malaria endemic area resulting in higher mortality, morbidity and increasing the burden of malaria. To counter the threat of resistance of *P. falciparum* to monotherapy and to improve the treatment outcome, combinations of antimalarials are now recommended by WHO for the treatment of falciparum malaria and may be used in other type of malaria<sup>4</sup>.

Antimalarial combination therapy is defined as the simultaneous use of two or more blood schizonticidal drugs with independent mode of action and thus unrelated by biochemical targets in the parasite<sup>4</sup>.

#### **Rationale for Antimalarial Combination**

Combination chemotherapy has been well established in TB, and Leprosy which has been recently applied to malaria<sup>3,4</sup>. The combination is often more effective. It prevents and delays the emergence of resistance by killing of mutant resistant parasite to one drug by the partner drug. To achieve this, the partner drug must be independently effective. The possible disadvantages of combination treatment are the potential risk or increasing adverse effect and increased cost<sup>4</sup>.

#### **What is not considered to be Combination Therapy**

Drug combinations such as Sulfadoxine-Pyrimethamine, Sulfalene-Pyrimethamine, Proguanil-Dapsone, Chlorproguanil-Dapsone and Atovaquone-Proguanil rely on synergy between the two components. The drug targets in the malaria parasite are linked. These combinations are operationally considered as single products and treatment with them is not considered to be antimalarial combination therapy. Multiple-drug therapies that include a non-antimalarial medicine to enhance the antimalarial effect of a blood schizonticidal drug (Chloroquine and Chlorpheniramine) are also not antimalarial combination therapy.

#### **ANTIMALARIAL COMBINATIONS**

There are two broad groups of antimalarial combinations.

1. Artemisinin based combination therapy (ACT)
2. Non-artemisinin based combination therapy (Non-ACT)

### Artemisinin Based Combination Therapy (ACT)

Artemisinin and its derivatives (artesunate, artemether, artemotil, dihydroartemisinin) produce rapid clearance of parasitemia and rapid resolution of symptoms. They act by inhibiting a *P. falciparum* encoded sceroplasmic endoplasmic reticulum calcium ATPase and not by inhibiting haem metabolic pathway as suggested earlier<sup>3</sup>. They reduce parasite numbers by a factor of approximately 10,000 in each a sexual cycle, which is more than other current antimalarials (which reduce parasite number 100 to 1000 fold per cycle). Artemisinin and its deriveatives are eliminated rapidly. When given in combination with rapidly eliminated compounds (tetracyclines, clindamycin), a 7-days course of treatment with artemisinin compound is required. But when given in combination with slowly eliminated antimalarials, shorter courses of treatment (3 days) are effective<sup>4</sup>.

In 3-day ACT regimens, the artemisinin compound is present in the body during only two a sexual parasite life-cycles (each lasting 2 days, except for *P. malariae* infections). This exposure to 3 days of artemisinin treatment reduces the number of parasites in the body by a factor of approximately one hundred million ( $10^4 \times 10^4 = 10^8$ ). However, complete clearance of parasites is dependent on the partner medicine being effective and persisting at parasitocidal concentrations until all the infecting parasites have been killed. Thus, the partner compounds need to be relatively slowly eliminated. As result of this, the artemisinin component is protected from resistance by the partner medicine, provided it is efficacious and the partner medicine is partly protected by the artemisinin derivative. Courses of ACTs of less than 3 days are not recommended as they are less efficacious, and provide less protection of the slowly eliminated partner antimalarial<sup>4</sup>.

The artemisinin compounds are active against all four species of malaria parasites that infect humans and are generally well tolerated. The only significant adverse effect to emerge from extensive clinical trials has been rare type 1 hypersensitivity reactions (manifested initially by urticaria). These drugs also have gametocidal effect. This helps in preventing transmissions of malaria<sup>4</sup>. The evidence of their superiority in comparison to monotherapies have been clearly documented<sup>3-5</sup>.

Currently, there are four ACTs which have been recommended by WHO for treatment of uncomplicated *P. falciparum* malaria. They are:

1. Artemether + Lumefantrine (AL)
2. Artesunate + Mefloquine (AS + MQ)
3. Artesunate + Sulfadoxine–Pyrimethamine (AS +SP)
4. Artesunate + Amodiaquine (AS + AQ)

All the above four regimens are effective with minor differences in their potency and adverse effect (Table 1)<sup>4,5,8-10</sup>. But all are superior as antimalarial therapy in comparison to monotherapy<sup>3,4</sup>. A systematic review has observed statistically insignificant rise at detection of parasite on 28 days. But fewer side effects with AL in comparison to AS + MQ.<sup>8</sup> However, one study has shown irreversible hearing impairment with AL<sup>3</sup>.

Artesunet + doxycycline/tetracycline/clindamycin for 7 days has been considered as a second line regimen for uncomplicated *P. falciparum* malaria<sup>4</sup>.

### Non-artemisinin Based Combination Therapy (Non-ACT)

- I. Sulfadoxine-Pyrimethamine + Chloroquine (SP +CQ): Chloroquine interferes with parasitic hem-degradation pathway and thereby prevents detoxification harmful products of metabolism whereas Sulfadoxine and Pyrimethamine inhibits dihydropteroate synthase (DHPS) and dihydrofolate reductase (DHFR) respectively, resulting in prevention of folic acid in parasite<sup>3</sup>.  
However, there is no convincing evidence that SP + CQ provides any additional benefit over SP, hence not recommended<sup>3,4,6</sup>.
- II. Sulfadoxine-Pyrimethamine + Amodiaquine (SP + AQ): The mechanism of action of AQ is similar to chloroquine. In a recent systematic review SP + AQ combination has resulted in significantly lower risk of treatment failure than SP or AQ monotherapy. Serious adverse effects are rare<sup>6</sup>. WHO recommends its use in uncomplicated *P. falciparum* malaria where more effective ACT is not available<sup>4</sup>.
- III. Quinine + tetracycline / doxycycline: tetracycline and doxycycline probably act by inhibiting the binding of aminoacyl tRNA to the ribosome of parasite. Tetracycline and doxycycline maintain activities against MDR malaria parasite. The combinations have been advocated as a second line therapy for uncomplicated *P. falciparum* malaria. Tetracycline and doxycycline are not recommended in pregnancy and children.
- IV. Quinine + clindamycin: The combination is effective against MDR malaria. Both of them have short half life thereby reducing the selection of

**Table 1:** Dose schedule of currently available ACT

Name of Regimen	Dose	Duration
Artemether + Lumefantrine	1.5 mg/kg/dose +9.0 mg/kg/dose	0, 8, 24, 36, 48, 60 (hr)
Artesunate + Mefloquine	4 mg/ kg/day + 15 mg/kg/day + 10mg/kg/day	Once daily for 3 days On 2nd day On 3rd day
Artesunate + Amodiaquine	4 mg/kg/day + 10 mg base/kg/day	Once daily for 3 days Once daily for 3 days
Artesunate + Sulfadoxine – Pyrimethamine	4 mg/kg/day + 25 mg/kg/day – 1.25 mg/kg/day	Once daily for 3 days Once on 1st day

resistance parasite. Clindamycin is preferred in pregnancy and children. It is considered as second line drug for uncomplicated *P. falciparum* malaria.

### PROMISING COMBINATIONS

Dihydro-artemisinin–Piperaquine is highly efficacious and inexpensive treatment which needs further studies before WHO recommends it<sup>4,7</sup>.

Ateovaquone with proguanine and fosmidoxycine with Clindamycins are also promising<sup>3,4</sup>.

### Current Clinical Practice Guidelines or Treatment of Malaria by WHO<sup>4</sup>

For uncomplicated plasmodium falciparum malaria any one ACT of Table 1 is preferable. In South-east Asia artesunate + mefloquine (AS + MQ) or artemether + Lumefantrine (AL) should be preferred, whereas artesunate + sulfadoxine-pyrimethamine (AS + SP) and artesunate + amodiaquine (AS + AQ) to be preferred in Africa in view of wide spread resistance of SP in South-east Asia and intolerance of MQ among African People. In the event of failure of one ACT regimen another ACT regimen should be used. The alternative second line regimens were artesunate (2 mg/kg/day) for 7 days + tetracycline (4 mg/kg/hr) for 6 hourly or Doxycycline (3.5 mg/kg/day) or clindamycin (10 mg/kg) twice daily for 7 days or quinine (10 mg/kg) 8 hourly for 7 days + tetracycline/doxycycline or clindamycin in the previous doses for 7 days to be used in order of preference.

In severe *P. falciparum* malaria artesunate (2.4 mg/kg) in 0 hr, 12 hrs and then daily for 7 days with

tetracycline/doxycycline/clindamycin should be preferred over quinine + tetracycline/doxycycline/clindamycin<sup>4,11</sup>.

In vivax malaria, chloroquine with primaquine is still effective but ACT can be used except AS + SP.

Multidrug resistant malaria parasite has forced the use of combinations antimalarial regimen. Artemisinin based combinations are preferred until better combination regimens are found. There is no place monotherapy in malaria.

### REFERENCES

1. WHO, 2000. WHO expert committee on malaria. Twentieth report World Health Organisation, Geneva, Technical Report Series, No. 892.
2. Pareek A, Nandy A, Kocher D, Patel KH, Mishra SK, Mathur PC. Efficacy and safety of a/b Artemether for treatment of acute Plasmodium Falciparum Malaria. American Journal of Trop Med Hyg 2006; 75(1):139-42.
3. Kreamsner PG, Krishna S. Antimalarial combinations. Lancet 2004;364:285-94.
4. WHO, Geneva, guide lines for the treatment Malaria. World Health Organisation 2006;1-253.
5. Adjui M, et al. Artesunate combination for treatment of Malaria: Meta Analysis. Lancet 2004;363:9-17.
6. Hwang J, Bitara Kwate, et al. Choloquine or Amodiaquine combined with Sulfadoxine-Pyrimethamine for uncomplicated Malaria; a systematic review. Tropical Medicine and International Health 2006;11(6):789-99.
7. Smithuis F, Kyaw MK, et al. Efficacy and effectiveness of dihydro artemisinin-paiperaqueine versus artesunate-mefloquine in falciparum Malaria; an open label randomised comparison, Lancet 2006;367:2075-85.
8. Omari A, Gamble C, Garner P. Artemether-lumefantrine for treating un complicated falciparum malaria. The Conchrane Library issue 4, 2004.
9. Mohamed AO, Eltaib EH, et al. The efficacies of artesunate-sulfadoxine pyrimethamine and artemether lumenfantrine in the treatment of uncomplicated, plasmodium falciparum malaria, in an area of low transmission in central Sudan. Annals of Tropical Medicine and parasitology 2006;100(1):5-10.
10. Guthman JP, Ampyero J, et al. Antimalarial efficacy of chloroquine, amodiaquine, sulfadoxine - pyrimethamine and combination of amodiaquine + artesunate and sulfadoxine-pyrimethamine+artesunate in Huamto and Bie provinces, Central Angola. Transaction of Royal Society of Tropical Medicine and Hygiene 2005;99:485-92.
11. South-east Asian Quinine Artesunate Malaria Trial (SEAQUAMAT) group. Artesunate versus quinine for treatment of severe falciparum malaria : A Randomized Trial. Lancet 2005; 366:717-25.