Combination Therapy for Malaria: Mission Accomplished?

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(See the article by Hasugian et al. on pages 1067–74)

In the war against malaria, the tide turned dramatically in our favor in the mid-20th century with the development of chloroquine, a highly effective antimalarial drug that was the linchpin of a global campaign to eradicate malaria. But our brief ascendency was cut short when malaria parasites became resistant to chloroquine. For the next 50 years, we engaged in a long, hard slog against drug-resistant malaria, eventually losing on almost all fronts. Time and again, resistance emerged, and it spread more quickly than new drugs could be developed and deployed. Drug resistance has repeatedly arisen in Asia and then spread globally in inexorable sweeps that have left disease, death, and economic disability in their wake.

The battle may be turning once again in our favor with new antimalarial combination therapies designed to deter the emergence of resistance that are increasingly becoming the first line against malaria. The artemisinins are a new class of potent compounds derived from an ancient Chinese herbal remedy for malaria. These drugs exert a powerful, percussive blow, with extremely rapid killing of parasites at all stages of their life cycle, followed by equally rapid elimination of the drug from the body, thus avoiding the lingering subtherapeutic blood levels that create conditions conducive to selection of resistance after treatment with slower and longer-acting drugs. In hopes of delaying the emergence of resistance to the artemisinins, the World Health Organization (WHO) recommends that they be used exclusively in combination with partner drugs that attack malaria parasites through different mechanisms. Artemisinin-based combination therapies (ACTs) are now recommended by the WHO as first-line treatment for Plasmodium falciparum malaria in most countries where resistance has compromised the efficacy of older drugs [1].

ACTs are a formidable new weapon in the war against drug-resistant malaria. It is tempting to rely on these drugs to “shock and awe” drug resistance into submission. After all, artemisinins have been used as herbal remedies to treat malaria for at least 2000 years, and there is still no clinically significant resistance to them. Experts, advocates, and international donor agencies have mounted an aggressive campaign to persuade and induce countries to base their malaria treatment policies on ACTs [2, 3]. This campaign is inarguably justified by the proven fatal consequences of continued use of antimalarial drugs for which the efficacy has been severely compromised by resistance, as well as by the long history of countries failing to act in the face of persistently increasing resistance. Nevertheless, we should not simply deploy ACTs in an all-out blitz, using the same drugs in all settings and situations without anticipating what will come next. If we do not develop nuanced, integrated, and multivalent strategies to deter the emergence and to contain the spread of resistance, we could be faced with an even worse situation following an initial success.

Although the lion’s share of malaria-related morbidity and mortality occurs in sub-Saharan Africa, where P. falciparum is the predominant malaria species, in the other parts of the world where malaria is endemic, P. falciparum malaria usually coexists with Plasmodium vivax malaria, which is sometimes underestimated as a public health menace. P. falciparum malaria and P. vivax malaria may require different treatments because of the parasites’ different drug susceptibilities and because of the need to prevent relapse of P. vivax malaria by eradicating dormant liver parasites. To have the most public health benefit, malaria treatment policies must consider which malaria species are present locally and what their resistance patterns are. Optimal treatment plans must also consider the intensity of malaria transmission, because the likelihood of a new infection during the posttreatment drug-elimination phase means that there is a trade-off in benefit between shorter- and longer-acting partner drugs in ACTs:
when people are exposed to new malaria infection on a daily or weekly basis, complete elimination of parasites may be less important than a period of posttreatment prophylaxis, and this benefit may offset the potentially increased risk of selection of resistant parasites by longer-acting drugs. When transmission rates are low and the risk of acquiring new infection is small, radical cure is paramount, and a mismatch in kinetics between long- and short-acting partner drugs may not matter.

In this issue of Clinical Infectious Diseases, Hasugian et al. [4] report a clinical trial designed to guide the choice of antimalarial treatment drugs in Papua, Indonesia, where both P. falciparum and P. vivax are common, where resistance of both species to chloroquine is prevalent, and where mixed infections with both species are frequent. Their study compared 2 ACT regimens, artesunate-amodiaquine (a WHO-recommended combination) and dihydroartemisinin-piperaquine (a newer ACT), in an open-label, randomized trial of safety and efficacy. These combinations differ mainly with respect to the nonartemisinin partners. Amodiaquine is shorter acting and has somewhat diminished activity against chloroquine-resistant P. falciparum. Piperaquine has a longer half-life, and relatively little is known about its activity against P. vivax malaria.

The trial was stopped early because of the better efficacy of dihydroartemisinin-piperaquine. Treatment with both ACTs resulted in parasite clearance and resolution of fever within 48 h in 99% of cases, illustrating the rapid action of the artemisinins. However, dihydroartemisinin-piperaquine treatment was followed by 3-fold lower rates of recrudescence P. falciparum infection and of new P. falciparum infection and a 4-fold lower risk of recurrent P. vivax infection. Dihydroartemisinin-piperaquine also reduced the rate of posttreatment anemia and carriage of P. vivax gametocytes and was better tolerated. Thus, this study shows a clear superiority of dihydroartemisinin-piperaquine for treating malaria in this setting.

Several features of the design of this clinical trial add to its value. The standard duration of follow-up in malaria drug efficacy trials has been 28 days. In this study, many of the recurrences of P. falciparum infection and most of the recurrences of P. vivax infection occurred 28–42 days after starting treatment. A shorter study would have missed most of these treatment failures and underestimated the benefits of dihydroartemisinin-piperaquine therapy. The use of survival analysis to assess efficacy means that there is no wasted information, as is the case with standard intention-to-treat and per-protocol analyses—an important consideration in studies that use longer follow-up times with higher rates of attrition. The figures that show the cumulative risk of treatment failure present the study results in a way that should be clear and meaningful to policy makers.

The authors draw a distinction between treatment efficacy and posttreatment prophylaxis: the former refers to resolution of the presenting clinical illness and elimination of the parasites that are causing it, and the latter refers to prevention of new infection with either malaria species, as well as prevention of relapse of infection caused by the liver stages of P. vivax. They allude to a possible trade-off of more selection pressure for resistance being exerted by the long half-life drugs that provide the most posttreatment prophylactic benefit, and they call for monitoring for loss of efficacy. All of the ACTs presently recommended by the WHO rely on partner drugs that are already compromised by resistance. As ACTs are rolled out, optimizing their effectiveness will require more such trials that help target the right drugs to the right settings and that consider the broader impacts of different treatment regimens. These will include longitudinal trials, which take a step beyond extending the duration of follow-up after a single treatment and assess the longer-term health benefit of treatment regimens by assigning participants to receive the same treatment each time they get malaria over the course of a year [5]. In addition to the standard assessment of efficacy, longitudinal trials measure any loss of efficacy or selection for resistance after repeated treatments, as well as long-term prophylactic efficacy, safety, and tolerability with repeated dosing and cumulative incidence of malaria treatment episodes, anemia, and severe malaria.

Because new policies are made on the basis of good clinical research—like that reported in this issue of the journal—the mission to replace failed malaria drugs with more efficacious ACTs is being accomplished. However, maximizing the benefit and prolonging the life of ACTs will also require learning from the past. New strategies are needed to prevent ACTs from following chloroquine’s trajectory. Can better understanding of mechanisms of action, pharmacokinetics, and pharmacodynamics be used to design combination therapies that provide prolonged prophylactic efficacy while still deterring resistance? Can drugs be rotated to preserve or resuscitate their efficacy [6]? Can selective pressure for resistance be reduced by using multiple ACTs in parallel, instead of serially replacing failing drugs? Can use of ACTs in combination with insecticide-impregnated bednets, residual spraying, and, eventually, vaccines reduce malaria transmission and block the dissemination of resistance when it arises? As the campaign to push ACTs to the front line of the war on malaria succeeds, answering some of these questions may help us to contain the insurgency of drug resistance.

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References