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EDITORIAL
AMODIAQUINE AND COMBINATION CHEMOTHERAPY FOR MALARIA

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Antimalarial drug resistance is becoming an increasingly important public health problem.[1] There is a consensus among malariologists that combination chemotherapy is the best way to treat malaria, which is resistant to current drugs, and to mitigate the emergence of resistance to new drugs.[2,3] But there is no consensus about which antimalarial drugs to combine. The paper by Zongo and others,[4] in this issue, should elicit a serious discussion of the issues involved.

Combination antimalarial therapy works for two reasons. First, some antimalarial combinations contain component drugs that potentiate each other, like sulfadoxine-pyrimethamine[5] and atovaquone-proguanil.[6] The second reason has to do with resistance. Mutations that confer resistance occur spontaneously at a small but finite rate ($\sim 10^{-6}$ per generation). When exposed to two drugs, parasites would need to develop mutations at two resistance loci simultaneously, and the likelihood of this occurring (i.e., $10^{-6} \times 10^{-6} = 10^{-12}$) becomes extremely small.[7]

Partnering of artemisinins with other drugs, dubbed artemisinin combination therapy (ACT), has been heralded as the next great weapon in our fight against malaria.[8] While ACTs, such as artesunate-mefloquine and artemethether-lumefantrine (Coartem®), have been extremely effective in Southeast Asia,[9] they might not be appropriate for sub-Saharan Africa for two reasons. First, artemisinin derivatives have very short half-lives; when used as a partner to a long-half-life drug, patients may have subtherapeutic concentrations of the latter drug alone in their plasma for days or weeks. In Southeast Asia, where the risk of new infection is rare, this may not be a problem. However, in sub-Saharan Africa, people may be subjected to infectious mosquito bites on a daily basis. Thus, parasites could easily be exposed to subtherapeutic concentrations of single antimalarial agents, an ideal scenario for the development of resistance.

A second strike against ACTs is the possible reproductive toxicity of artemisinin derivatives.[10] Artesunate, at normal therapeutic doses, was found to cause fetal death and malformations in pregnant rodents in the equivalent of the first trimester of pregnancy. In light of the fact that the average woman in sub-Saharan Africa gives birth 5.7 times,[11] women between ages 15 and 45 might simply be ineligible for this treatment.

What other combinations can be used? As suggested in Zongo and others[4] one possibility is the combination of amodiaquine with other antimalarials. Amodiaquine was developed during World War II by the US Army-sponsored program to develop alternatives to quinine.[12] It became widely used both prophylactically and therapeutically. In the 1980s, amodiaquine prophylaxis was found to be associated with agranulocytosis, neutropenia, and hepatitis, and its use was halted.[13] Later, it was reintroduced for therapeutic use only. To date, there is no evidence for serious toxicity associated with amodiaquine therapy.[14] This is reminiscent of the situation with sulfadoxine-pyrimethamine (SP).[15]

Another advantage of amodiaquine over the artemisinin derivatives is the long half-life of its principal active metabolite (9–18 days).[16] Thus, if it were partnered with another drug with a long half-life (such as SP), there would be little chance of exposing parasites to subcurative concentrations of a single antimalarial.

What about amodiaquine resistance? Very little is known about the mechanism or epidemiology of amodiaquine resistance. *In vitro* studies have found that resistance to chloroquine and amodiaquine are correlated; however, chloroquine-resistant strains appear to have lower levels of resistance to amodiaquine.[17–19] There is also evidence that amodiaquine is effective against chloroquine-resistant malaria *in vivo*.[20–22] However, amodiaquine resistance does occur in areas where it has been used regularly.[23] More work on this topic is clearly needed.

The paper by Zongo and others[4] evaluates the combination of amodiaquine with SP in Burkino Faso in a randomized placebo-controlled clinical trial (RCT). This study was performed using the best available methodology—28-day follow-up using polymerase chain reaction (PCR) to correct for reinfection. No matter how failure is defined (parasitologically, clinically, or both), amodiaquine-SP performed better than SP alone. A large number of studies by this group and others have also shown the increased efficacy of this combination.[8,24–34] Both amodiaquine and SP are inexpensive and readily available, so a policy switch from SP, for example, to amodiaquine-SP can be made quickly and easily. Even though SP and amodiaquine resistance may preexist, SP-amodiaquine could be of great benefit for the short term.

How compelling are the arguments for switching to SP-amodiaquine? In the current study, amodiaquine-SP appeared to be more than twice as efficacious as SP alone—only 4.2% of patients failed amodiaquine-SP (by any definition) compared with 9.1% of SP patients.[4] Are these improvements significant enough to warrant policy change from SP to amodiaquine-SP? This study, like many of the others, was analyzed on a per-protocol basis as opposed to intention-to-treat. This means that patients who were lost to follow-up or excluded during the course of the study were dropped from the final analysis. Most randomized trials rely on intention-to-treat analyses, meaning that these patients who drop out are defined as failures. This is done for two reasons. First, the randomization of patients, made on admission into the trial, minimizes selection bias and confounding. Since patients might not drop out randomly, per-protocol analyses permit these to creep back in. Second, intention-to-treat analyses make a clinical trial more like an effectiveness study and more relevant to policy makers.[35–37] If a certain percentage of pa-

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tients drop out of an RCT, then it is safe to say that the same percentage or higher will drop out when the treatment enters clinical practice. When we recalculated the data from Zongo and others[4] on an intention-to-treat basis, then the failure rates for amodiaquine-SP and SP would be 15.5% and 21.0%, respectively. Would this difference merit a policy change? Probably not. But, given the cost and availability of both drugs, the combination might still be useful in the short-term.

In summary, the paper by Zongo and others strongly suggest that amodiaquine combination therapies for malaria should be evaluated. Further analyses (both intention-to-treat and cost-benefit) need to be performed to make the results more relevant for policy makers.

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