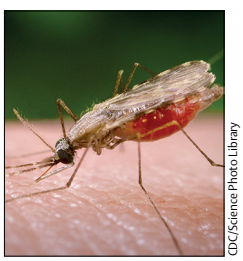
Widening the options for recurrent malaria



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The global need for new antimalarial drugs and new combinations is enormous and urgent,[1,2] but their successful delivery needs resilience to overcome the barriers imposed by expensive and lengthy clinical development plans. Attention is often directed to areas such as southeast Asia, where some antimalarial combinations are failing but transmission intensities are much lower than in sub-Saharan African countries. Children in Africa have frequent and life-threatening malaria infections as they grow up, and these need to be treated safely.

Pyronaridine–artesunate and dihydroartemisinin–piperaquine are two artemisinin combination therapies (ACTs) that exemplify the challenges that arise in the pathway towards licensure and wider implementation. These two drug combinations have a good track record of efficacy[3,4] and are approved by the European Medicines Agency (EMA). However, their introduction into first-line therapies in malaria-endemic countries, particularly in sub-Saharan Africa where the global malaria problem is worst, has been sporadic and slow. Questions about the safety of ACTS (ie, hepatotoxicity for pyronaridine–artesunate and cardiotoxicity for dihydroartemisinin–piperaquine) might have delayed their endorsement by WHO,[5] thereby obstructing adoption into national malaria-control programmes. They are also needed in southeast Asia where other antimalarial treatments are no longer effective when used in conventional doses.[6]

Adequate assessment of antimalarial drugs should not be restricted to investigating their ability to cure a single infection safely, but to rather account for their overall efficacy in decreasing the long-term cumulative incidence of disease and their prolonged safety when used repeatedly. In high-transmission, malaria-endemic areas, repeated symptomatic malaria infections are common until the acquisition of a degree of immunity against the disease. In highly endemic vivax transmission areas, relapses caused by hypnozoites frequently contribute to repeated clinical episodes of malaria. In *The Lancet*, Issaka Sagara and colleagues from the West African Network for Clinical Trials of Antimalarial Drugs (WANECAM) provide reassuring results on the safety and efficacy of pyronaridine–artesunate and dihydroartemisinin–piperaquine in a large, randomised, controlled trial undertaken in Mali, Burkina Faso, and Guinea.[7] For 2 years they followed up a longitudinal cohort of 4710 adult and paediatric patients aged 6 months and older with microscopically confirmed *Plasmodium* spp malaria to assess the safety and efficacy of pyronaridine–artesunate and dihydroartemisinin–piperaquine to treat recurrent malaria versus current recommended first-line (re)treatments with artemether–lumefantrine or artesunate–amodiaquine. All treatments were once-daily or twice-daily tablets or granules given orally over 3 days at the study centres, and patients were followed up as outpatients up to day 42.

The results of this large and complex trial[7] confirmed the non-inferiority of both pyronaridine–artesunate and dihydroartemisinin–piperaquine against the comparators for the primary endpoints of (1) 2-year malaria incidence rate in the intention-to-treat population (pyronaridine–artesunate *vs* artemether–lumefantrine [1·77, 95% CI 1·63–1·93 *vs* 1·87, 1·72–2·03; rate ratio (RR) 1·05, 95% CI 0·94–1·17] and *vs* artesunate–amodiaquine [1·39, 95% CI 1·22–1·59 *vs* 1·35, 1·18–1·54; RR 0·97, 0·87–1·07]; dihydroartemisinin–piperaquine *vs* artemether–lumefantrine [1·16, 95% CI 1·01–1·34 *vs* 1·42, 1·25–1·62; RR 1·22, 95% CI 1·06–1·41] and *vs* artesunate–amodiaquine [1·35, 1·21–1·51 *vs* 1·68, 1·51–1·88; RR 1·25, 1·02–1·50]); and (2) adequate clinical and parasitological response in uncomplicated malaria across all episodes assessed in the per-protocol population on days 28 and 42 (for *P falciparum* malaria, PCR-adjusted adequate clinical and parasitological response was greater than 99·5% at day 28 and greater than 98·6% at day 42 for all ACTs).

These findings highlight that all four ACTs are robust in some of the highest pockets of malaria transmission globally and they exemplify the cumulative advantages of using drug combinations that include partner drugs with longer elimination half-lives, such as piperaquine (around 4 weeks in dihydroartemisinin–piperaquine) or pyronaridine (10–13 days in pyronaridine–artesunate). Indeed, the crude effects of dihydroartemisinin–piperaquine on the 2-year incidence of malaria compared with artemether–lumefantrine or artesunate–amodiaquine probably reflect the better long-term and cumulative effects of post-treatment prophylaxis with piperaquine

in preventing new infections, a finding that has implications for the current malaria-elimination agenda.[8]

Additionally, the WANECAM study[7] confirmed the good tolerability of single and repeated treatments of pyronaridine–artesunate and dihydroartemisinin–piperaquine. For pyronaridine–artesunate, this finding ratifies the revision in 2015[9] of the initial 2012 EMA approval,[10] which originally limited the treatment possibilities both individually (to just once in a lifetime) and geographically (to low-endemic settings with high risk of artemisinin resistance). The 2015 revision has removed all restrictions on repeat dosing, on use only in areas of high resistance and low transmission, and on requirements for liver function monitoring. The results from the WANECAM study[7] should enable rapid inclusion of pyronaridine–artesunate into WHO's malaria treatment guidelines.[5]

The WANECAM trial did confirm an increased risk of liver transaminitis in some recipients of pyronaridine–artesunate. However, the absence of any clinical implication, the transient nature of the increases in all cases, and the absence of an incremental effect in those receiving repeated doses are reassuring, and support the wider use of pyronaridine–artesunate for the treatment of malaria. The safety of pyronaridine–artesunate should continue to be monitored, including its use in HIV-infected individuals, as this particularly vulnerable population was excluded from participating in the trial—an important limitation for the generalisation of the results. A large study of pyronaridine–artesunate in which HIV infection is not an exclusion criterion is ongoing (NCT03201770).

The WANECAM trial also shed light on other safety concerns, particularly prolongation of the QT interval and the consequent increased risk of life-threatening arrhythmias. The findings suggested that the incidence of QTcF prolongation was higher after dihydroartemisinin–piperaquine versus artemether–lumefantrine and pyronaridine–artesunate, but no differences were noted between dihydroartemisinin–piperaquine and artesunate–amodiaquine. There were no clinical symptoms or complications associated with the prolongation, and retreatment did not seem to make these findings worse, although the numbers studied were small.

Manufacturers recommend that dihydroartemisinin–piperaquine should be taken under fasting conditions to minimise the risks of a food effect that increases plasma concentrations of piperaquine and cardiac effects. In the WANECAM study,[7] dihydroartemisinin–piperaquine was administered without first imposing a fast, providing further reassurance about safety. The results from this study are also consistent with the opinions of an expert panel convened by WHO to review the cardiotoxicity of antimalarial drugs,[11] and with the conclusions of a meta-analysis reviewing the safety of repeated use of dihydroartemisinin–piperaquine.[12] They further support the continued use of dihydroartemisinin–piperaquine in malaria-endemic areas.

Rigorous safety assessments of any new drug are necessary to safeguard patients. Generally, risk–benefit analyses of antimalarial drugs also need to account for the life-threatening potential and continuing morbidity associated with malaria. The findings from the WANECAM study support upscaling the use of pyronaridine–artesunate and dihydroartemisinin–piperaquine in sub-Saharan Africa so that they can contribute even more effectively to the global fight against malaria.

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We are both members of the WHO Malaria Treatment Guidelines Group. This group produces global guidance on the treatment of malaria and this includes decisions about pyronaridine–artesunate. The views expressed by the authors are personal opinions and do not represent the recommendations of WHO.

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