ASAQ, A NEW FIXED-DOSE COMBINATION OF ARTESUNATE-AMODIAQUINE: PROGRESS TO DATE AND CHALLENGES AHEAD

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Background

Malaria is a leading cause of childhood morbidity and mortality in Africa. In response to growing parasitic resistance to commonly used antimalarials, the 2006 WHO guidelines urged the use of artemisinin-based combination therapies (ACTs) in uncomplicated *P. falciparum* malaria and in fixed-dose combinations whenever possible. One of the most widely-used ACTs is a 3-day regimen with artesunate and amodiaquine (AS+AQ), but treatment involves taking these drugs separately as loose formulations or in co-blister packs, involving a large number of tablets. In 2002, the FACT Project was initiated by MSF (and then DNDi in 2003) and TDR to develop two fixed-dose combinations (ASAQ and artesunate-mefloquine) with the aim of simplifying the dosing regimen (including paediatric formulations), improving compliance, and making the drugs available without patent and at a more affordable price for developing countries.

Methods

The key partners in the FACT Project (Tropival, Bordeaux University, France; Oxford University, Centre for Tropical Medicine, UK; Drug Research Centre, Universiti Sains Malaysia; Mahidol University, Faculty of Tropical Medicine, Thailand; Instituto de Tecnologia em Fármacos (Farmanguinhos), Brazil; Tropical Disease Research Programme (TDR), Switzerland; Centre National de Recherche et de Formation sur le Paludisme (CNRFP), Burkina Faso) conducted critical pharmaceutical, preclinical, and clinical research and development. The pharmaceutical company, sanofi-aventis, was the partner for industrial scale-up, registration, distribution, and post-marketing surveillance. This presentation will discuss results demonstrating the bioavailability of ASAQ, a field study comparing combinations of AS and AQ in Burkina Faso, a meta-analysis examining efficacy and safety data from 31 clinical trials, and the progress and challenges of this partnership to develop, test, and register ASAQ.

Results

Across age categories and several African countries, the combination of AS and AQ showed improved efficacy over monotherapy. Results of clinical studies, including one conducted in Burkina Faso children <5 years and a multinational trial in Cameroon, Madagascar, Mali, and Senegal, have shown fixed-dose ASAQ, (4 mg/kg and 10.8mg/kg) which requires only one daily dose over 3 days, to have a PCR-corrected, day-28 cure rate of >95%. A comprehensive review of 31 studies, with a combined enrollment of approximately 12 000 patients (including >5000 patients receiving AS and AQ), found the combination of AS and AQ to be well tolerated and more effective than monotherapy or non-artemisinin-based combinations. However, in areas with significant AQ resistance and/or high reinfection rates, other ACTs may be superior.

Conclusion

With their simplified regimens and paediatric formulations, these drugs could improve compliance, accessibility, and therefore, long-term efficacy at a time when African patients desperately need a high quality, easy-to-use antimalarial. The partnership with sanofi-aventis is critical to making these drugs available in the field and will be discussed.