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Pediatric Treatment for *P. vivax* Malaria: New Positive Data

The Tafenoquine Exposure Assessment in Children (TEACH) was a study to assess the pharmacokinetics (PK), safety, and efficacy of tafenoquine in the treatment of pediatric subjects with *Plasmodium vivax (P. vivax)* malaria. As the World Health Organization (WHO) is reviewing guidelines for the treatment of malaria, the TEACH study provides important data regarding the potential use of tafenoquine in the prevention of relapse of *P. vivax* malaria in children between 6 months and 15 years of age.

Context

Following a bite from an infected mosquito, the *P. vivax* parasite infects the blood and causes an acute malaria episode. It can also lie dormant in the liver (in a form known as hypnozoite), from where it periodically reactivates to cause relapses of malaria despite successful blood-stage treatment. Hence, a single *P. vivax* infection can give rise to multiple episodes of malaria, even in the absence of a new mosquito bite. These relapses can occur weeks, months, or even years after the initial infection. Radical cure entails treating both the acute blood-stage infection and the dormant liver stages of infection to prevent relapses.

Children are particularly at risk of *P. vivax* malaria; its prevalence peaks in children between 2 and 6 years of age. In 2019, children younger than 14 years of age accounted for 35 percent of relapsing *P. vivax* malaria cases in Colombia[i], 22 percent of cases in Brazil[ii], and 54 percent of cases in Peru[iii]. Malaria negatively affects the course of a child's development, with repeated episodes leading to cumulative severe anemia, physical and cognitive impairment[iv], and even death[v].

Tafenoquine is an 8-aminoquinoline drug. GSK and Medicines for Malaria Venture (MMV) have developed it as a single-dose treatment for *P. vivax* malaria. Single-dose tafenoquine, a non-patented drug, has been approved by the regulatory authorities in the United States, Australia, Brazil, Thailand, and Peru for the radical cure (prevention of relapse) of *P. vivax* malaria for use in adults and adolescents 16 years of age and older who are receiving chloroquine for acute *P. vivax* blood-stage infection. It is also under review by regulatory authorities in six endemic countries, including Colombia. Regulatory approval is a first and necessary step for countries looking to conduct feasibility studies on these tools.

At present, there are no WHO prequalified, age-specific, pediatric formulations for the prevention of relapse of *P. vivax* malaria in children. The current standard of care is primaquine and requires a 14-day course of treatment, as per WHO guidelines, although some country guidelines recommend

the same dosage over a 7-day course. Primaquine's 14-day treatment regimen is often associated with poor compliance, resulting in reduced effectiveness[vi,vii,viii]. Tafenoquine could help transform the treatment of *P. vivax* malaria, as it prevents malaria relapse with a single dose, potentially alleviating challenges with treatment adherence.

The study

TEACH has provided evidence to support the registration of a pediatric formulation of single-dose tafenoquine. The TEACH study investigated the use of a new, 50 mg tablet of tafenoquine, developed so that it can be dispersed in water to facilitate its use in children, and the approved 150 mg tablet of tafenoquine in children aged between 6 months and 15 years of age and weighing at least 5 kg. A total of 60 individuals were recruited into TEACH, from Colombia and Vietnam.

TEACH evaluated different dosages of tafenoquine based on weight in children and adolescents. All subjects received a single dose of tafenoquine and a course of chloroquine administered per local or national treatment guidelines to treat the acute blood stage of the illness. All subjects were screened for glucose-6-phosphate dehydrogenase (G6PD) deficiency prior to receiving tafenoquine and excluded from the study if they had under 70 percent G6PD enzyme activity levels.

There were no unexpected safety findings. The overall percentage of subjects reporting adverse events was similar to previous studies in adults and adolescents 16 years and older (37/60, or 62 percent). The most frequent adverse event was vomiting, which occurred in 12 subjects (12/60, or 20 percent). No drug-related, serious adverse events were reported. The recurrence-free efficacy rate of 95 percent at four months was in line with studies of tafenoquine in adults and older adolescents.

Data from TEACH would support the following weight-based dosing recommendations: children weighing between 10 kg and 20 kg should receive 100 mg in the form of two dispersible tablets; subjects between 20 kg and 35 kg should receive 200 mg in the form of four dispersible tablets; and subjects weighing over 35 kg should receive 300 mg in the form of two, 150 mg tablets, currently approved for older populations. Although no subjects were recruited into the lowest weight band (children between 6 months and 2 years of age, weighing between 5 kg and 10 kg), the pharmacokinetic (PK) modeling data from TEACH indicate a child in that weight band should receive a 50 mg dose of tafenoquine in the form of one dispersible tablet.

Moving forward in Latin America

Data from TEACH has supported the recent submission of pediatric tafenoquine for regulatory approval in Australia and will be used to support the regulatory submissions in malaria-endemic countries. If approved, and following a review of evidence by WHO, pediatric tafenoquine could be an important new tool for treating *P. vivax* malaria in children.

Research efforts are underway in Latin American and South East Asian countries to generate data that can be considered by WHO in making policy recommendations to inform countries in their decisions to adopt G6PD tests and tafenoquine, including planning for operational feasibility studies and cost-effectiveness and budget impact analyses, in close collaboration with national governments.

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