1736

HEMOGLOBIN DECLINE IN G6PD NORMAL *PLASMODIUM VIVAX* PATIENTS TREATED WITH CHLOROQUINE AND TAFENOQUINE OR PRIMAQUINE IN THE PHASE 3 TAF112582 (DETECTIVE) STUDY

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Tafenoquine (TQ) is a novel 8-aminoquinoline in development for radical cure of *Plasmodium vivax* malaria but like all 8-aminoquinolines can cause haemoglobin decline in G6PD deficient individuals. TAF112582 (DETECTIVE Part 2, NCT01376167) was a phase 3 randomised, double-blind, placebo-controlled study. This multi-centre study recruited 522 G6PD normal patients with *P. vivax* malaria. Patients in all three treatment arms received chloroquine and were randomised to receive TQ 300mg single-dose (N=260), placebo (N=133) or primaquine (PQ) 15mg daily for 14 days (N=129). We report a *post-hoc* regression analysis of haemoglobin decline in the study to investigate a possible excess of haemoglobin declines from baseline observed in TQ group (5% TQ vs 1% placebo and 2% PQ patients with >3g/dL decline). The outcome of interest was maximum haemoglobin decline from baseline over the first 15 days post treatment. The covariates used in the final model were baseline haemoglobin, G6PD enzyme activity and baseline *P. vivax* parasite count. Other explanatory variables explored were geographical region, gender, age and baseline urea. Results: There was an overall decline in haemoglobin in all treatment groups. The maximum decline in haemoglobin was 1.22 g/dL (95% CI 1.13 - 1.30 g/dL) in the TQ arm, 1.02 g/dL (95% CI 0.90, 1.14 g/dL) in the placebo arm, and 1.11 g/dL (95% CI 0.98 - 1.23 g/dL) in the PQ arm. Haemoglobin declines in G6PD normal patients in the study were partly due to higher baseline haemoglobin and parasite count and lower G6PD enzyme activity. After adjusting for baseline haemoglobin, parasite count and G6PD enzyme activity, although there was a larger decline in haemoglobin in patients treated with TQ compared to placebo this treatment difference was only 0.19 g/dL [95% CI 0.04 - 0.34 g/dL], and thus not considered clinically significant.

1737

DEALING WITH INDETERMINATE OUTCOMES IN ANTIMALARIAL EFFICACY TRIALS: A COMPARISON BETWEEN COMPLETE CASE ANALYSIS, MULTIPLE IMPUTATION AND INVERSE PROBABILITY WEIGHTING

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Antimalarial clinical efficacy studies for uncomplicated *Plasmodium falciparum* malaria frequently encounter situations in which parasite molecular typing is unable to discriminate between parasitic recurrence, either new infection or recrudescence. The current WHO guideline recommends excluding these individuals with indeterminate outcomes in a complete case (CC) analysis. Data from the four artemisinin-based combination trial was used to compare the performance of multiple imputation (MI) and inverse probability weighting (IPW) with the standard CC analysis for dealing with indeterminate recurrences. A total of 3,369 study participants with molecularly defined parasitic recurrence treated with three artemisinin-based combination therapies were used to represent a complete dataset. A set proportion of recurrent infections (10, 30 and 45%) were reclassified as to missing using two different mechanisms: a completely random selection (mechanism 1); missingness dependent on treatment and transmission intensity (mechanism 2). The performance of MI, IPW and CC approaches in estimating the Kaplan-Meier (K-M) probability of drug efficacy was then compared. Performance measures (bias, relative bias, standard error and coverage) were reported as an average from 1,000 simulation runs. The CC analyses resulted in absolute overestimation of drug efficacy by up to 1.7% and were associated with reduced precision and poor coverage across all the missingness scenarios studied. Both MI and IPW method performed better (unbiased and greater efficiency) compared to CC analysis. The widely used CC approach overestimates antimalarial efficacy. The IPW and MI procedures provided efficient and unbiased estimation of antimalarial efficacy and should be considered when reporting the results of antimalarial clinical trials, especially in the areas of high transmission where the proportion of indeterminate outcomes could be large.

1738

THE PHARMACOKINETICS OF PRIMAQUINE AND ITS METABOLITES IN HEALTHY CAMBODIAN ADULTS WITH VARIOUS CYP2D6 GENOTYPES

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The Cambodian government declared elimination of *Plasmodium vivax* in 2025, which will require increased administration of primaquine for *P. vivax* radical cure. Recent research suggests the hepatic CYP450 2D6 enzyme to be responsible for metabolism of primaquine to the active metabolites required for hypnozoite clearance. The effects of different 2D6 genotypes on the pharmacokinetics of primaquine in populations living in vivax endemic areas are not well characterized. We previously reported on the various CYP2D6 genotypes prevalent in a subset of 40 Cambodians and found 55% allelic frequency of the reduced activity 2D6*10 allele, most often paired with a normal activity allele or another reduced allele. In 2017, we re-consented 27 of the 40 volunteers to participate in a primaquine pharmacokinetic study. Using the CYP2D6 AS-A scoring system, 1 volunteer was found to have a score of 2, 13 volunteers had a score of 1.5, 12 had a score of 1.0 and 1 Undetermined (UNDET) with a genotype of *5/*10 DUP, which could lead to scoring as either 0.5 or 1.0. Thus, all of the volunteers were predicted to be Extensive Metabolizers (EMs), except the UNDET volunteer, who could be predicted to be either an EM or Intermediate Metabolizer (IM) phenotype. Primaquine (PQ) and its metabolite levels were measured in blood and urine by UPLC-MSMS over the subsequent 24 hours after oral administration of single dose primaquine (15 mg) in order to correlate CYP2D6 genotype with metabolite concentrations and phenotype. Initial results show the plasma PQ C_{max} values were 65.2 61.6, and 101.2ng/ml for AS-A scores of ≥1.5, 1.0, and UNDET, respectively, which suggested the AS-A scores of 1.5 and 1.0 metabolized similarly and the UNDET had an IM phenotype. T_{max} results were similar for all 3 AS-A scores and to results seen previously (range 2-3.1 hours). Carboxyprimaquine, the major metabolite generated through the monoamine oxidase pathway, showed similar C_{max} values for all (452.0, 460.8 and 451.7ng/ml) and T_{max} of 7.7, 8.8 and 6 hours AS-A scores of ≥1.5, 1.0, and UNDET, respectively. Full pharmacokinetic analysis of primaquine metabolites in both blood and urine will be presented.