CORRESPONDENCE

Artemisinin-Based Treatments in Pregnant Women with Malaria

TO THE EDITOR: The Pregnancy Artemisinin-Based Combination Treatments (PREGACT) Study Group compared the polymerase-chain-reaction (PCR)–adjusted "recrudescence" rates of *Plasmodium falciparum* infection after treatment and suggest that this indicates the failure to eradicate the initial infection (March 10 issue).[1] However, analysis of the PCR-adjusted and PCR-unadjusted survival curves of time to "treatment failure" (Fig. S1 in the Supplementary Appendix, available with the full text of the article at NEJM.org) suggests that the curves are equally well explained by a constant rate of new infections, a proportion of which are misclassified as recrudescent. The percentage of infections classified as recrudescent is 9.9% (68 of 686) across the cohort (Table 2 of the article) and does not differ significantly among the four drug regimens ($P=0.64$ by the chi-square test). Nor is there evidence of an early clustering of PCR-adjusted infection, as might be expected from treatment failure.[2,3] In fact, the only significant difference between drugs appears to be their duration of post-treatment prophylaxis. It is important to clarify terminology, because assuming that all PCR-adjusted infections indicate failure to eradicate existing parasites may exaggerate estimates of the recrudescence rate and therefore of drug resistance. Parasite genotyping may perform poorly in areas of high transmission,[4] and consideration of the underlying infection kinetics can provide additional insights.

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No potential conflict of interest relevant to this letter was reported.

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THE AUTHOR REPLIES: In our trial, women were actively followed for 9 weeks, so it was necessary to genotype recurrent infections, to distinguish between new infection and recrudescence, the

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latter considered to be a "true" treatment failure. Our main hypothesis was that the four treatments would have similar efficacy, and indeed the differences between the PCR-adjusted cure rates were within the prespecified equivalence margin of 5 percentage points. Genotyping was carried out according to standard methods,[1] whose limitations, particularly where transmission is intense, were mentioned in the Discussion section of our article. Adekunle et al. state that the recrudescence rate equates to resistance. However, it is well known that this is not true, because observed therapeutic failure may be due to factors other than parasitologic resistance (e.g., malabsorption and rapid or abnormal metabolism),[2] and this may be particularly true for pregnant women.[3] We have also stated that there are major differences in the duration of the post-treatment prophylaxis between treatments, and this is shown by the PCR-unadjusted cure rates.

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Since publication of his article, the author reports no further potential conflict of interest.

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Trimethoprim–Sulfamethoxazole for Uncomplicated Skin Abscess

TO THE EDITOR: Talan et al. (March 3 issue)[1] slightly misstate the findings of an earlier summary to which I contributed.[2] My fellow authors and I concluded that prior studies of antibiotics administered in patients with uncomplicated abscesses were underpowered because the authors of those studies could not rule out the 5 to 10% superiority of antibiotics suggested in our review. The current study was well designed to address this concern. Comment is also warranted regarding the trial guidance provided by the Food and Drug Administration (FDA) on an early end point that is required as the primary end point for registrational studies and was a secondary end point in the study by Talan et al. The FDA guidance indicates that patients are considered to have been treated successfully even if 80% of their infection remains unresolved after 3 days of therapy. Space limitations here preclude a thorough discussion of this objectionable end point.[3] The trial by Talan et al. is at least the second randomized, controlled trial (RCT) that has shown that the early end point does not correlate well with test-of-cure success.[4] Furthermore, the current trial adds to the data that show that an "end-of-therapy cure" end point is sensitive to the efficacy of the antibiotic for skin infections.[5] In my opinion, the early end point should be abandoned.

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Dr. Spellberg reports receiving consulting fees from Adenium Biotech, Cempra, the Medicines Company, MedImmune, PTC Therapeutics, Tetraphase, AstraZeneca, and Merck, serving as a member of a data safety and monitoring board for Dipexium, and holding stock in Motif, BioAim, and Synthetic Biologics. No other potential conflict of interest relevant to this letter was reported.

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TO THE EDITOR: Talan et al. reported higher per-protocol cure rates for abscesses treated with tri-