Reappraisal of the Efficacy of a Simplified Artesunate Regimen in Falciparum Malaria

To the Editor—Kremsner and colleagues report a pharmacodynamic comparison of standard 5-dose intravenous artesunate with a simplified 3-dose regimen (same total dose) in hospitalized African children with malaria [1]. Graphical display of the primary outcome data (Figure 1) shows that the 3-dose regimen is probably worse than the 5-dose standard regimen, yet the article states that the 5-dose regimen does not confer any pharmacodynamic advantage over the 3-dose regimen. This apparent contradiction led us to examine key elements of the trial methodology in the context of established guidelines on the conduct and reporting of randomized controlled trials [2–4].

This was a noninferiority trial, a design that aims to show whether a new treatment is worse than an established treatment. The key decision is "how much worse can the new treatment be

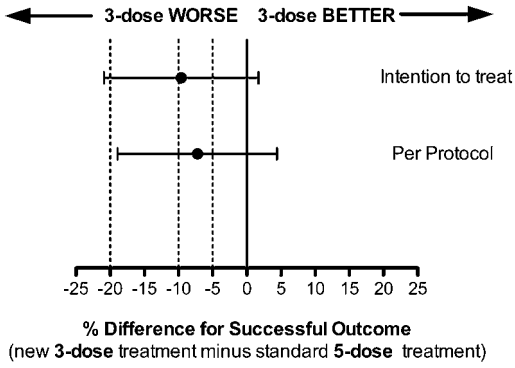

Figure 1. Observed difference in pharmacodynamic efficacy of 3-dose (simplified) vs 5-dose (standard) artesunate regimens (data from Kremsner et al [1]). Success in terms of primary outcome was defined as 99% parasite clearance at 24 hours. Error bars indicate 2-sided 95% confidence intervals. The dotted lines indicate noninferiority margins (delta values) referred to in the text.

and yet still be acceptable?" This is the margin of noninferiority, or delta [4]. The 20% value of delta used in this study is, in our view, too high. Severe malaria carries a high mortality that is reduced substantially by artesunate when compared with the previous standard regimen (quinine) [5]. Because even a small fall in pharmacodynamic efficacy could result in extra deaths, it is hard to see how a worse outcome in one-fifth of patients can be considered acceptable. The ill-defined nature of the relationship between the study endpoint (parasite clearance) and mortality demands even greater caution. A delta value of 5%–10% would have been preferable, although only partially reassuring, given the surrogate nature of the endpoint. At these levels the trial clearly failed to demonstrate noninferiority (Figure 1).

The interpretation of noninferiority also required a "per-protocol" (PP) analysis to move the lower confidence interval marginally inside delta (Figure 1). CONSORT guidelines do describe the use of alternative analyses in noninferiority trials but only in the context of checking for type I errors (false conclusions of noninferiority) sometimes resulting from intention-to-treat (ITT) analyses in this form of trial [4]. This did not apply here because the ITT analysis did not show noninferiority. CONSORT counsels that all exclusions after randomization are troubling, because any erosion over the course of a trial from the initially unbiased groups can only harm the careful process of randomization [6]. Postrandomization exclusions here appear to have involved arbitrary and/or potentially confounding rules. Adequate antimalarial treatment within 24 hours prior to admission was a prospectively defined exclusion criterion at trial registration, but, inexplicably, patients with quinine pretreatment up to 72 hours before study drug administration were actually removed for the PP analysis. Another reason for exclusion was a dosing error of >10%, an inherently confounding step given that the 2 arms involved different numbers of doses before the primary efficacy endpoint. The number of exclusions in each arm is unfortunately not provided in the trial flow, so these were deduced from the percentage data: 7 patients in the standard 5-dose arm (all primary outcome successes) and 4 patients in the simplified 3-dose arm (2 successes, 2 failures) were excluded. Given this imbalance in exclusions (an indicator of potential bias in itself [3]), the concerns regarding specific exclusion rules, and the difficulty in determining when such rules are stipulated [6], the PP analysis would be better labeled as a nonrandomized, observational comparison [3] and the ITT analysis considered the primary analysis. ITT also provides a pragmatic assessment of efficacy under "real life" conditions [7].

The way in which clinical trials are reported is critical to clinical decision making [3], and it is because of this that the CONSORT group has provided an extended statement covering noninferiority trials that describes precisely the scenario where an excessive noninferiority margin hides a true state of inferiority [4]. Here the biological significance of the trial data is, we argue, clouded by the article's emphasis on postrandomization exclusions and ultimately lost within an unacceptably broad noninferiority margin of 20%. When the data are presented graphically (Figure 1), readers can observe directly how the upper 95% confidence interval for the difference in efficacy between 3-dose and 5-dose regimens lies just above zero. This means that the simplified artesunate regimen is very likely to be inferior to standard (around 9 chances in 10) with, it must be assumed, an accompanying likelihood of clinical detriment in the form of increased mortality. In this clearer light, omission of the 12-hour artesunate dose from the current regimen looks like a backward step for severe malaria treatment.

Note

Potential conflicts of interest. All authors: No potential conflicts of interest.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

Charles J. Woodrow[1,2] and Walter R. J. Taylor[1]

[1]Mahidol-Oxford University Tropical Medicine Research Unit (MORU), Bangkok, Thailand; and [2]University of Oxford, Centre for Tropical Medicine, CCVTM, Oxford, United Kingdom

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Correspondence: Charles J. Woodrow, Mahidol-Oxford University Tropical Medicine Research Unit (MORU), 420/6 Rajvithi Rd, Bangkok, Thailand (charlie@tropmedres.ac).

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