clinically valuable for prediction of TB treatment outcome on an individual basis, which will be necessary to detect improvement over the current treatment protocol with its recurrence rate of around 5%.

We believe the inclusion of host factors could increase sensitivity over microbiological testing alone, particularly as the majority of patients with TB are sputum culture negative after 3 months but may still experience TB recurrence. The host immune system is intricately linked with TB disease pathogenesis, and changes in the immune response can be observed during treatment [2–4]. Immunosuppression that is present at diagnosis in patients with TB is reduced by therapy, with a concomitant reduction in the proportion of regulatory T cells [5]. We have already identified host biomarkers that associate with treatment response [6], and our transcriptomics study was performed to identify new candidate biomarkers.

The issue concerning the time point of testing in the recurrent group is one that we have been considering for a long time. The majority of HIV-negative people who are infected with Mycobacterium tuberculosis never succumb to disease, and the majority of treatment-adherent patients with active TB do not have TB recurrence. We therefore believe that this recurrent group represents people who are highly susceptible to TB disease and therefore were a good target group to identify our biomarkers. People who have TB relapse after conventional treatment after infection with drug-sensitive organisms are likely to be such highly susceptible individuals. We believe the strength of our study is the demonstration that groups of patients with TB can be classified using host gene expression in blood.

To test the predictive value of biomarkers in a prospective study, large numbers of patients must be recruited because of the expected 5% TB recurrence rate. This is logistically challenging, but we have now collected samples from such patients and will test the correlation of expression of our biomarkers with treatment outcome.

Optimal time points during treatment can also be identified. Such samples may also be used for the identification of further biomarkers using microarray technology, now that we have established proof-of-principle. We hope that the publication of the data from our cross-sectional pilot study will allow other investigators to test them in different geographical locations and situations.

An issue that Davies et al. do not address is the one of matching. This shows the complexity of the topic. Does one match for clinical characteristics known to be associated with recurrence, such as cavitation on chest x-ray? Or are such characteristics dependant on whatever underlying cause there may be for recurrence, and by matching one thereby introduces a bias that will obscure the relevant markers?

Ultimately, we expect an algorithm to be developed that will combine host and microbiological biomarkers, together with clinical factors such as extent of disease at diagnosis, to reliably predict TB recurrence after treatment. Such an algorithm would then need to be rigorously tested in a clinical trial setting as described by Davies et al., to determine whether it is useful as a surrogate marker of cure.

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References


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Randomized, Controlled Trial of Treatments for Second-Stage Sleeping Sickness

To the Editor—The trial reported by Bisser et al. [1] is a carefully conducted study undertaken in the challenging field of human African trypanosomiasis (HAT) and adds data that may influence future studies and policies. These data are amenable to alternative methods of analysis for several reasons.

The trial’s stated aim was to assess equivalence between 3 alternative treatment regimens and standard melarsoprol therapy, using relapse as an effectiveness criterion and an equivalence margin of 15%. It is apparent that any improvement in efficacy would be welcomed, particularly given that all of the alternative regimens are easier to administer than standard melarsoprol. Therefore, the 15% margin should not be applied symmetrically but only on the inferiority side, rendering noninferiority a more appropriate approach than equivalence. In fact, the statistical analyses undertaken by Bisser et al.
Figure 1. Increase (95% confidence interval [CI]) in the percentage of patients with relapse or treatment failure for 3 alternative regimens (B, 10-day incremental melarsoprol; C, nifurtimox; and D, melarsoprol-nifurtimox), compared with that for standard melarsoprol. Wilson's test (with no continuity correction) was used to calculate the 95% CIs. The shaded area indicates the zone of noninferiority. The black and white symbols represent analyses in terms of relapse and treatment failure, respectively. The no. of relapses, deaths, and total patients with complete data (those with follow-up to 24 months or treatment failure) were, respectively, as follows for each group: for A, 7, 5, and 49; for B, 17, 6, and 60; for C, 24, 3, and 60; and for D, 0, 6, and 52. Three deaths in group B that were attributed to causes other than human African trypanosomiasis or its treatment were not included in the analysis.

are classical tests of superiority without reference to the prespecified margin of 15%.

The decision to analyze relapse and mortality as separate outcomes is also open to debate. Incorporation of mortality into the main analysis is critical because, in stage 2 HAT, drug regimens may influence mortality via differing efficacy or toxicity, particularly encephalopathy. Given that the study was not powered to assess mortality (indeed, sample size based on relapse rate was not achieved), the lack of a significant difference in mortality rates between groups is unsurprising. It may be preferable to analyze these data in terms of a combined outcome of treatment failure that includes both death possibly attributable to HAT or its treatment and relapse.

We have reanalyzed the data accordingly and undertaken a standard noninferiority analysis using both relapse only and treatment failure at 24 months as outcome measures, applying a noninferiority margin of percentage increase in relapse or treatment failure of 15%, compared with that for standard melarsoprol (figure 1). For regimens B and C (10-day incremental melarsoprol and nifurtimox, respectively), the 95% confidence interval (CI) crosses the noninferiority margin irrespective of the end point assessed; hence, it is not possible to conclude whether these regimens are noninferior or inferior to standard therapy on the basis of a 15% noninferiority margin. Regimen D (melarsoprol-nifurtimox) is clearly noninferior, because the entire 95% CI lies to the left of the noninferiority margin, irrespective of the outcome assessed. Furthermore, the 95% CI for increase in relapse lies entirely to the left of zero, demonstrating that regimen D is superior to standard treatment by this outcome measure. However, the 95% CI for increase in treatment failure (including deaths) crosses the zero line; statistical evidence for the superiority of regimen D in terms of treatment failure remains lacking. Taken together, these data nevertheless provide support for the accompanying editorial’s call for a trial comparing melarsoprol-nifurtimox with the updated standard melarsoprol regimen (2.2 mg/kg daily for 10 consecutive days) [2].

The alternative analysis presented here is not designed to detract from the conclusions of the original article but rather to present these important, carefully collected data in a format that is most consistent with the trial’s original hypothesis and that is in line with recently updated guidelines promoted by the CONSORT group [3].

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References


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