Potential Benefits of Retreatment Highlight the Need for Additional Lyme Disease Research

To the Editor:

We are responding to Klempner et al1 regarding our statistical review of the National Institutes of Health—sponsored antibiotic retreatment trials for Lyme disease.2,3 Our primary finding is that the trials did not prove retreatment is ineffective. A basic concept in statistical science regarding randomized controlled trials is that one can only conclude treatment is ineffective when the treatment effect and confidence interval exclude and are below the minimum clinically important difference. None of the trials showed this. Two trials actually demonstrated evidence of improvement in patients with severe symptoms at baseline. The trials without significant findings did not incorporate interactions between treatment and baseline severity in their statistical analysis. The only valid conclusion is that treatment may be beneficial, which is the conclusion we drew.

Our review used a common definition of minimum clinically important difference—the smallest difference that patients perceive as beneficial and that would mandate, in the absence of troublesome side effects and excessive cost, a change in the patient’s management. The published minimum clinically important difference literature for the Short Form-36 Health Survey is robust, including anchor-based physical and mental component score estimates relevant to our study population, and studies by a coauthor of the trials by Klempner et al.1,3-5 These published minimum clinically important difference estimates, calculated apart from risks, are intended for use in clinical trials. Minimum clinically important difference estimates for the trial by Krupp et al6 also were examined. Although research on minimum clinically important difference estimates for the Fatigue Severity Scale (FSS-11) and Alphabet Arithmetic (A-A) test is limited, the few studies estimating the Fatigue Severity Scale 11 minimum clinically important difference support Krupp et al’s fatigue effect size choice (references available on request). We are unaware of literature supportive of tripling the observed placebo effect for a minimum clinically important difference.

Our objective was to evaluate biostatistical elements of the randomized controlled trials; we purposefully omitted risk—benefit analyses as attempted by Klempner et al.1 Such analyses are performed after all data are collected and results are validated, are subjective, and deserve their own careful and transparent analysis.

Contrary to the authors’ suggestion, no support exists for a placebo effect in the trials. Because similar proportions of patients taking placebo worsened and improved in the trials by Klempner et al,1 it is impossible to disentangle placebo effects from natural variability. Significant changes in placebo arms simply may be due to practice effects or desire to please the study team. Defensible estimates of placebo effects compare randomized, blinded placebo groups with unblinded control groups (references available on request).

Our careful statistical analysis of the antibiotic retreatment trials demonstrates a lack of scientific support for claims that retreatment was ineffective. Furthermore, we identified groups that clearly benefitted from retreatment. Given the heterogeneous patient population, the limited number of trials, and the need for safer, less costly regimens, we not only stand by our conclusions, but also renew our call for additional research. That is, after all, how science is supposed to work.

Allison K. DeLong, MSa
Barbara Blossom, BAb
Elizabeth Maloney, MDc
Steven E. Phillips, MDd
aDepartment of Biostatistics
Center for Statistical Sciences
Brown University
Providence, RI
bDepartment of Statistics
Colorado State University
Fort Collins
cPartnership for Healing and Health, Ltd
Wyoming, Minnd
dGreenwich Hospital
Greenwich, Conn

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