Reply to Parvu and Parvu

To the Editor—In their letter [1], Parvu and Parvu question our approach to statistical analysis in our recent study [2]. We would point out that the study of post-Lyme disease symptoms has particular challenges. First, the numbers of patients who have persistent symptoms following antibiotic treatment of erythema migrans (EM) is relatively small. Second, the term “post-Lyme disease symptoms” probably consists of >1 syndrome with >1 pathogenic mechanism. Therefore, we anticipated that patients would probably need to be subgrouped for analysis based on clinical or laboratory findings.

In our manuscript, we studied the largest group of patients available who were evaluated for EM, treated with 2 weeks of antibiotic therapy, and followed prospectively for 1 year thereafter [3, 4]. Of the 510 patients enrolled, 62 (10%) had post-Lyme disease symptoms. Our study group of 86 EM patients included all 45 patients with post-Lyme disease symptoms in whom serum samples at the appropriate time points were still available, and a randomly selected control population of 41 patients who did not have post-Lyme disease symptoms. The analysis of 26 cytokines and chemokines showed significant differences between the groups only for the T17-associated chemokines CXCL9 and CXCL10, and the T17-associated cytokine interleukin 23 (IL-23). Although multiplying the P values by 26 would negate statistical significance, clinical correlations suggested that these findings had biologic relevance. First, these experiments demonstrated a dichotomy between T11 and T17 responses. Second, IL-23 responses often persisted in the postantibiotic period. Finally, post-Lyme disease symptoms tended to be more common in patients with detectable levels of IL-23.

Because of these clinical correlations, we examined more thoroughly the occurrence of post-Lyme symptoms in the subgroup of 41 patients with detectable levels of IL-23. Importantly, within this subgroup, IL-23 levels were significantly higher in patients who developed post-Lyme symptoms than in those who did not. Moreover, all 7 patients with the highest levels of IL-23 (≥230 ng/mL) experienced posttreatment symptoms, suggesting that the magnitude of the response is the important clinical variable. Furthermore, IL-23 levels correlated directly with the height of antibody responses to endothelial cell growth factor (ECGF), a recently identified autoantigen in Lyme disease [5], and anti-ECGF antibodies were more common in patients with post-Lyme disease symptoms. Taken together, these findings strongly suggested that the key factor in the correlation between IL-23 and post-Lyme symptoms is the magnitude of the T17 immune response.

We concluded that these findings offered a new paradigm for the study of patients with post-Lyme disease symptoms. Namely, we hypothesize that a subgroup of patients with EM has an immune response to Borrelia burgdorferi sensu lato tilted toward a T17 response. Patients with low levels of IL-23 may not have an increased frequency of untoward events. However, in the subgroup of patients with high IL-23 levels, T17 immune responses may have disadvantageous aspects, including the development of autoimmune phenomena and post-Lyme disease symptoms. It will be important to explore this hypothesis further in future studies.

Note

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

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.

Klemen Strle,1 Daša Stupica,2 Elise E. Drouin,1 Allen C. Steere,3 and Franc Strle1
1Center for Immunology and Inflammatory Diseases, Division of Rheumatology, Allergy and Immunology, Massachusetts General Hospital, Harvard Medical School, Boston; and 3Department of Infectious Diseases, University Medical Center Ljubljana, Slovenia

References


Correspondence: Klemen Strle, PhD, Center for Immunology and Inflammatory Diseases, Massachusetts General Hospital, 55 Fruit St, CNY149/8301, Boston, MA 02114 (kstrle@partners.org).

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