Reprints or correspondence: Dr. Robin K. Avery, Dept. of Infectious Diseases, S32, The Cleveland Clinic Foundation, 9500 Euclid Ave., Cleveland, OH 44195 (averyr@ccf.org).

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A Small, Randomized, Placebo-Controlled Trial of the Use of Antiviral Therapy for Patients with Chronic Fatigue Syndrome

Sir—We have presented controlled and observational data that are consistent with the hypothesis that subsets of cases of chronic fatigue syndrome (CFS) result from cardiac disease due to a single, persisting infection caused by Epstein-Barr virus (EBV) or, in turn, to a single, persisting infection caused by human cytomegalovirus (HCMV) in immunocompetent patients [1]. Patients who have a separate subset of CFS have simultaneous coinfection with EBV and HCMV. Cardiomyopathic changes are observed in right ventricular endomyocardial biopsy specimens obtained from such patients, and abnormal findings on Holter monitoring (e.g., oscillating abnormal T-wave flattenings and T-wave inversions) are "uniformly" present [2–4]. Left ventricular dysfunction is manifested by sinus tachycardia at rest, abnormal cardiac-wall motion, and decreased left ventricular ejection fractions (rest/stress) in those patients with CFS who are most ill [5]. These findings belie the relatively normal findings observed on standard 12-lead electrocardiograms [6].

In January 1995, a double-blinded, placebo-controlled, phase III crossover study of patients with CFS was initiated. Eleven patients who had CFS (10 of whom were women) were each followed for 18 consecutive months. The mean patient age was 42.7 years, and the mean duration of CFS was 35.1 months. Before antiviral nucleosides were administered, endomyocardial biopsies were performed. Cardiac tissues and blood samples tested negative for isolation of HCMV in cultures of human fibroblast tissues. Two cardiac biopsy specimens that were obtained from patients who had CFS tested positive for HCMV nucleic acids by means of PCR. No cardiac specimen that was obtained from a patient with CFS tested positive for EBV nucleic acids. (Cardiac tissue samples that were obtained from 4 of 21 control patients who had coronary artery disease but who did not have CFS also tested positive for HCMV nucleic acids.) Cardiomyopathic degenerative findings (e.g., myofiber disarray, interstitial fibrosis, increased intracellular granules, and interstitial fat) were noted in patients who had CFS. One patient who had CFS had myocarditis with focal lymphocytic infiltrates.

Patients with CFS had negative antistreptolysin O titers and no Lyme disease antibodies, IgM, or IgG, according to both ELISA and Western blot analysis. At the time of entry into the study, patients had positive HCMV IgG antibody titers with or without HCMV IgM antibody titers; both types of titer were tested by use of ELISA. Antibody titers to EBV, viral capsid antigen (VCA)–IgM, and EBV–diffuse early antigen (EBV-EA) were also tested. The patients in the treatment group received iv ganciclovir, 5 mg/kg given q12h for 30 days. Treatment with iv ganciclovir was followed by administration of oral ganciclovir, 1 g given q8h. At the completion of a 6-month period of observation after discontinuation of treatment with iv ganciclovir, if no improvement was observed and if elevated EBV antibody titers suggested the presence of coinfections, oral valacyclovir, 1 g given q6h, was added to oral ganciclovir treatment. Oral administration of antiviral nucleosides then continued for the remainder of the 18 months of the study. When 2 patients with CFS who were undergoing right ventricular endomyocardial biopsies experienced serious pericardial bleeding, the study was ended prematurely.

Measurement of HCMV and EBV antibody titers was repeated at 3- and 6-month intervals. Unchanging, high positive titers of HCMV IgG antibody were noted throughout the 18-month trial. At baseline, 1 of the 11 patients who had CFS had a positive HCMV IgM antibody titer. This HCMV IgM antibody titer was absent after the patient received 30 days of treatment with iv ganciclovir. Four of the 11 patients with CFS had coinfection with EBV, which was indicated by positive EBV-EA antibody titers. After administration of valacyclovir, EBV-EA antibody titers decreased or became negative in 3 of these patients who had CFS. The findings with regard to these serologic titers are consistent with incomplete herpesvirus multiplication of HCMV and, when present, EBV in patients who have CFS [7].

Energy index point scores (EIs) and symptom scores were assessed at 30-day intervals [3]. A series of questions was used to calculate EIs (A.M.L. and R.G.D, unpublished data). An EI of 0 denoted a bedridden patient, whereas an EI of 10 denoted a healthy patient. At baseline, the mean EI for the entire group was 3.5. After 6 months, 4 patients with CFS who were receiving iv placebo had a mean EI of 3.9. When they were assessed 6 months after initiation of treatment with iv ganciclovir, they had a mean EI of 4.4. At this point in the study, as indicated by the presence of positive EBV, VCA-IgM, and/or EBV-EA antibody titers, valacyclovir was added to treatment and administration of oral ganciclovir was continued. At month 12 of the study, the mean EI for the 11 patients was 5.8, and at month 18, the mean EI was 6.1.

Symptom scores (e.g., chest pain, wooziness, palpitations, and muscle aches) were assessed at 30-day intervals. A symptom score of 1 denoted the presence of all 4 symptoms tested, whereas a symptom score of 0 denoted the absence of all 4 specific symptoms. At baseline, the mean symptom score was 0.81 for the 11 patients who had CFS. After 6

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months, 4 patients with CFS who were receiving iv placebo had a mean symptom score of 0.5. When assessed 6 months after initiation of treatment with iv ganciclovir, the entire cohort of 11 patients who had CFS had a mean symptom score of 0.38. At month 12 of the study, the mean cumulative symptom score was 0.28, and at month 18, the mean symptom score was 0.19.

This study is preliminary; however, either the protocol or a modification of the protocol may be helpful in a suitably sized, randomized, double-blinded, placebo-controlled trial of the use of antiviral therapy for patients with CFS [8].

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A. Martin Lerner,[1] Marcus Zervos,[1] C. H. Chang,[1] Safedin Beqaj,[1] James Goldstein,[1] William O'Neill,[1] Howard Dworkin,[1] Thomas Fitgerald,[2] and Robert G. Deeter[3]

[1]William Beaumont Hospital, Wayne State University School of Medicine, Royal Oak, and [2]University of Michigan School of Medicine, Ann Arbor, Michigan; and [3]Glaxo-Wellcome, Research Triangle Park, North Carolina

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Reprints or correspondence: Dr. A. Martin Lerner, 32804 Pierce Rd., Beverly Hills, MI 48025 (lerner@cdimed.com).

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Fascioliasis in Antalya

Sir—We read with interest the Brief Report by Mannstadt et al. [1] that describes triclabendazole therapy in the management of biliary obstruction due to *Fasciola hepatica* infection. The patient's history of travel to our region, Antalya, in Turkey, attracted our attention most. As you know, in travel medicine it is important to know the diseases to which the traveler might be exposed during his journey. We live and work in Antalya and want to share our experience with fascioliasis.

Fascioliasis is endemic in Antalya, and in 1998 we saw 2 cases with which we had the same difficulties in diagnosis and treatment that were described by Mannstadt et al. [1]. A 58-year-old man and his 27-year-old son who had been investigated for malignancies were referred to our clinic because of fatigue, anorexia, and right-upper-quadrant pain. Laboratory tests revealed the following for both patients: eosinophilia, high levels of acute-phase reactants, hepatic parenchymal heterogeneity and nonshadowing particles in the gallbladder visible on an ultrasonogram, and multiple hypodense structures within the liver visible on a CT scan. Because the 2 patients were members of the same family and had similar symptoms at the same time, our attention was directed to the possibility of infectious disease—particularly parasitic infections, because of the finding of eosinophilia. However, several microscopic examinations of stool samples revealed no ova or parasites. Although serological testing was not available at our university, the diagnosis of fascioliasis was made on the basis of microscopic examination of an aspirate obtained by means of ultrasonogram-guided gallbladder aspiration [2]. For treatment, Novartis Pharma AG provided the nonregistered compound triclabendazole. We then contacted the Department of Parasitology at Ege University in İzmir, Turkey, and sent them serum samples from the 2 patients. Results of serological tests for *F. hepatica* showed positive antibody titers.

We have since gained more experience with *F. hepatica* infection, and recently we have diagnosed 32 cases of fascioliasis on the basis of either the findings of radiology and serological tests or examination of stool samples. These patients' signs and symptoms have recently been reported [3]. Because fascioliasis is endemic in Antalya, we have planned a seroepidemiologic study to determine its prevalence.

Latife Mamıkoğlu and Rabin Saba

Department of Infectious Diseases and Clinical Microbiology, Akdeniz University Hospital, Antalya, Turkey

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