Epstein-Barr: New Therapeutic Target in SLE?

BY BRUCE JANCIN

SNOWMASS, COLO. — An effective vaccine against Epstein-Barr virus infection could conceivably turn systemic lupus erythematosus into a disease of historical interest within a few decades—but that's far easier said than done.

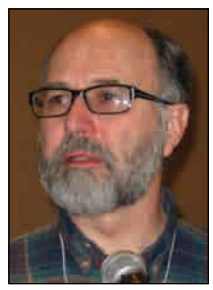
"There have been three trials of capsid-based EBV vaccines. All have failed because the vaccines didn't protect," said Dr. John B. Harley at a symposium sponsored by the American College of Rheumatology. Most people may be infected with five to nine substrains of the virus, he added. "We go through life possibly being reinfected by other strains as life progresses. Even the defenses that prevent us from getting mononucleosis over and over again are not sufficient to prevent reinfection. So finding a way to prevent the viral infection is going to be very complicated."

For decades, Dr. Harley has been developing the hypothesis that EBV (in conjunction with genetic predisposition) is the cause of SLE. The hypothesis initially went nowhere, but has gained traction as a result of mounting evidence that has converged from epidemiologic, immunologic, and genetic studies conducted in many different centers.

When he first zeroed in on EBV as likely having a causative role in SLE, Dr. Harley knew he would face scientific skepticism. For decades, it seemed that whenever researchers couldn't explain the pathogenesis of poorly understood diseases, they'd try to pin it on EBV. But not much has stuck to the Teflonlike virus.

"EBV . . . has been blamed for everything, and yet very little has been established as being causative," observed Dr. Harley, chair of the arthritis and immunology research program at the Oklahoma Medical Research Foundation in Oklahoma City.

Back in the 1980s, he laid the groundwork for his future studies of EBV when he recognized the unique research potential of the Department of Defense



Serum from the DOD repository showed increased anti-EBV titers in patients years before they developed SLE.

DR. HARLEY

(DOD) Serum Repository, which contains frozen serial specimens from more than 5 million armed forces personnel. He and his coworkers identified 130 individuals who developed SLE and for whom they found serum samples dating back to years before disease onset. This enabled the investigators to characterize—for the first time—the cascade of autoantibody production that often begins many years before SLE diagnosis (N. Engl. J. Med. 2003;349:1526-33).

The SLE patients tended to mount their immune response in a characteristic way. The first antibody to appear was directed against the viral protein EBV nuclear antigen–1 (EBNA-1). This antibody cross-reacted with the lupus-associated autoantigens Ro and Sm in lupus patients. Then, through molecular mimicry with self-antigens and the process of B-cell epitope spreading, the cross-reactive antibodies targeted non–cross-reactive autoepitopes and spread to a widening array of autoantigens, with generation of pathogenic autoimmunity. (Healthy individuals mount a far more limited immune response to EBV and EBNA-1 and do not produce cross-reactive antibodies.)

EBNA-1 is both immunogenic and antigenic. The researchers showed that nearly all military personnel who had SLE were seropositive for EBNA-1, whereas 12% of the military controls were not. This is consistent with the notion that, to lay the groundwork for SLE, an individual not only has to be infected with EBV but must also mount an immune response to EBNA-1.

"The host response to EBNA-1 is critical in the pathogenesis of SLE," stressed Dr. Harley, who is also the George Lynn Cross Research Professor at the University of Oklahoma Health Sciences Center. EBV is a strong candidate for having a pathogenic role in SLE because it is a ubiquitous infection, with 95% or more of adults in the general population being seropositive. The virus persists in the host for life as a latent infection with a viral reservoir in B lymphocytes. Low levels of lytic virus emerging in latency provoke persistent immune stimulation.

"It's remarkable that about 7% of our T-cell repertoire is directed against EBV," the immunologist continued.

Because EBV infection is so common in adults, Dr. Harley and coworkers studied seropositivity rates in a series of children and teens. The investigators demonstrated that 116 of 117 individuals with SLE (average age, 15.6 years) were seropositive against EBV, compared with two-thirds of controls. Indeed, EBV seropositivity was associated with a 50-fold increased probability of lupus (J. Clin. Invest. 1997;100:3019-26). Other investigators have independently replicated this work in more than half a dozen other cohorts.

There are additional differences between SLE patients and healthy controls in terms of response to EBV infection. Patients with SLE have 15- to 40-fold higher EBV loads, 10-100 times more EBV-infected B cells, and defective CD8 T-cell responses against EBV.

In an interview, Dr. Harley predicted that as EBV's role in the pathogenesis of SLE becomes more fully understood, "there will be new opportunities for treatment." For example, once the specific T-cell responses to the virus in SLE are better grasped, clinical studies of anti–T-cell therapies directed at those mechanisms will be appropriate.

"If you accept the idea that the virus is a necessary condition in order to develop lupus—just hypothetically—then if a way was developed to rid the body of the virus and the virus' presence was needed to sustain the disease, then that would be a new therapeutic approach. The virus has been adapted to human beings for something like 20 million years. So it has found a wonderful niche in our peculiar environment, and it has many presumably unknown ways of sustaining that infection," he said. ■

Disclosures: *Dr. Harley disclosed that he is on the board of directors of IVAX Diagnostics Inc., and JK Autoimmunity Inc. He is also a consultant to UCB and Bio-Rad Laboratories Inc.*

Alglucosidase Alfa Improved Function in Late-Onset Pompe's

BY MARY ANN MOON

Enzyme-replacement therapy with recombinant human alglucosidase alfa "has a positive, if modest, effect on walking distance and pulmonary function" in patients who have late-onset Pompe's disease, according to Dr. Ans T. van der Ploeg of Erasmus University, Rotterdam, the Netherlands, and associates.

Pompe's disease is a rare, autosomal recessive, progressive neuromuscular disorder caused by a deficiency of acid alpha-glucosidase, which leads to deposition of glycogen primarily in skeletal and respiratory muscles.

The late-onset form of the disease is characterized by limb-girdle myopathy and respiratory insufficiency that often eventually proves fatal.

Enzyme-replacement therapy using recombinant human alglucosidase alfa was approved for use in classic infantile-onset Pompe's disease in 2006.

Preliminary studies of the agent's use in children and adults who have the late-onset form of the disease showed "some positive effects," but those studies were small and uncontrolled, the investigators wrote.

To address those shortcomings, the investigators conducted a randomized, controlled trial involving 90 patients with late-onset Pompe's disease, which is a large population for a clinical trial of an orphan disease but "relatively small when the goal is to judge the progression of a clinically heterogeneous" disorder.

VITALS

Major Finding: Patients who received active treatment showed a mean increase of 25.1 m on the walk test, whereas those who received placebo showed a decrease of 3.0 m, for a differential effect of 28.1 m. Those who received active treatment showed a increase of 1.2 percentage points in predicted FVC, while those who received placebo showed a decrease of 2.2 percentage points, for a differential effect of 3.4 percentage points.

Data Source: A randomized, controlled trial involving 90 patients with late-onset Pompe's disease.

Disclosures: Dr. van der Ploeg and most associates in this study reported receiving support from Genzyme. Some associates reported receiving support from numerous makers of drugs, devices, and technologies. The study was designed and funded by Genzyme Corp., maker of alglucosidase alfa.

The study subjects were between 10 and 70 years of age at enrollment, and all had developed symptoms while between 2 and 59 years of age (mean age of onset, mid-20s). All had "substantially diminished" health status, but all were able to walk at least 40 m on the 6-minute walk test, with assistive devices permitted, and they had a percentage of predicted forced vital capacity (FVC) of 30%-80% while upright.

Of the 90 study participants, 60 were randomly assigned to receive biweekly infusions of alglucosidase alfa (20 mg/kg of body weight) and 30 to receive placebo infusions.

The dual primary end point was increase in distance walked on the walk test and percentage of predicted FVC after 78 weeks of therapy.

Patients who received active treatment showed a mean increase of 25.1 m on the walk test, while those who received placebo showed a decrease of 3.0 m, for a differential effect of 28.1 m.

Similarly, patients who received active treatment showed a increase of 1.2 percentage points in predicted FVC, while those who received placebo showed a decrease of 2.2 percentage points, for a differential effect of 3.4 percentage points, Dr. van der Ploeg and colleagues said (N. Engl. J. Med. 2010;362:1396-406).

These results were consistent and robust across several methods of data analysis and in all subgroups studied. The findings "indicate that alglucosidase alfa has a positive effect on the complex process that leads to impaired ambulation and respiratory failure in late-onset Pompe's disease," according to the investigators.

"Patients in the two groups had similar frequencies of adverse events, serious adverse events, treatment-related adverse events, and infusion-associated reactions. Most adverse events were mild or moderate in severity and were not considered to be related to the study drug," the investigators said. ■