Epstein-Barr May Be Therapeutic Target in SLE

BY BRUCE JANCIN

SNOWMASS, COLO. — An effective vaccine against Epstein-Barr virus could conceivably turn systemic lupus erythematosus into a disease of historical interest within a couple of 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) causes SLE. The hypothesis initially went nowhere, but it has gained considerable traction as a result of mounting evidence that has converged from epidemiologic, immunologic, and genetic studies conducted in many centers.

When he first zeroed in on EBV as likely having a causative role in lupus, Dr. Harley understood that he would face scientific skepticism. For decades, it seemed that whenever researchers could not explain the pathogenesis of various poorly understood diseases, they'd try to pin it on EBV, which "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 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).

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DR. HARLEY

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 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," he said. ■

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

Presentation of Lupus Differs Before and After Age 50

BY DOUG BRUNK

SAN DIEGO — Although an estimated 80% of patients with systemic lupus erythematosus acquire the disease before age 50 years, beware of ruling out the potential for diagnosing new cases in older patients.

"It certainly can happen," Dr. Bevra H. Hahn said at the annual meeting of the North American Menopause Society. "It's not rare, so it's okay to let it cross your mind."

The clinical presentation of SLE that develops before the age of 50 differs from that of disease that occurs later in life, said Dr. Hahn, chief of rheumatology at the University of California, Los Angeles, Ronald Reagan Medical Center. SLE that develops before age 50 is marked by development of nephritis, anti-DNA antibodies, malar rash, and/or discoid lupus. This relatively early-onset form of SLE causes less organ damage in general. Mortality in this patient population "is primarily from active lupus or from infections that relate to being sick and having immunosuppressive therapies," Dr. Hahn said.

SLE that develops after age 50 is marked by cardiac and pulmonary problems. "I see a lot of patients who present with heart failure or with pericarditis, or arrhythmias, and they have a strongly positive antinuclear antibody, so it's fine to screen for ANA in that situation," she said.

Compared with their younger counterparts, patients who develop SLE after age 50 are also more likely to have arthritis, Sjögren's syndrome, and a high damage index.

Compared with their younger counterparts, patients who develop SLE after age 50 are also more likely to have arthritis, Sjögren's syndrome, and a high damage index. "Their mortality is more from coronary artery disease or stroke, some from infection, and less of it from antilupus medications," said Dr. Hahn, who is also a professor of medicine at UCLA. "For this group, preventive care is very important for the coronary artery disease."

Several clinical studies have shown that the use of the antimalarial drug hydroxychloroquine reduces damage over time, whether the lupus is mild or severe. "We think most people should be on [hydroxychloroquine] if there is not a contraindication," she said. Hydroxychloroquine use has a slight risk for associated retinal damage, Dr. Hahn added.

Dr. Hahn's approach to treatment involves first determining whether the disease threatens life or organs. If the disease is mild, she will consider a number of different agents to lessen pain, fatigue, and rash, including NSAIDs; topical agents, such as steroids or tacrolimus; sunscreen with SPF 50; antimalarials, such as hydroxychloroquine at a dose of 200-400 mg/day or quinacrine dosed at 100 mg/day; DHEA (dehydroepiandrosterone) dosed at 100-200 mg/day; or low-dose prednisone.

She cautioned that the use of NSAIDs "can bump creatinine levels and cause aseptic meningitis in patients with lupus. It's not common, but it happens."

"The three phases of treatment for severe SLE are induce improvement, maintain improvement, and prevent damage," she said. For these patients, high-dose prednisone "saves lives. It causes cataracts, osteoporosis, and diabetes, but it really is life saving."

Other options to consider for patients with severe lupus include antimalarials and the cytotoxic agents mycophenolate mofetil (CellCept), azathioprine (Imuran), and cyclophosphamide (Cytoxan). Other agents showing promise include rituximab, which is a monoclonal antibody against the protein CD20, and belimumab, an investigational human monoclonal antibody.

One certainty of the disease is that infections are common. Dr. Hahn said that 60% of the time, fever that occurs in SLE is the result of infection; the other 40% result from flare. "If you think these patients have an infection, treat it as early as possible," she advised.

Survival rates in SLE patients have improved in recent decades. Currently, Dr. Hahn said, the 10-year survival for SLE patients without nephritis stands at about 95%, whereas the 10-year survival for SLE patients with nephritis stands at about 88%.

"This is so different from 20-30 years ago," she remarked. "We've had tremendous improvement in our therapies and our diagnoses." ■

Disclosures: *Dr. Hahn had no relevant financial disclosures.*