Systemic Lupus Erythematosus (SLE) is a condition familiar to dermatologists and is characterized as an autoimmune disease in which the immune system attacks self-nuclear antigens in multiple organ systems including skin, joints, kidneys, heart, and brain. SLE exists as a differential diagnosis for many cutaneous findings including: malar/papulosquamous/discoid rashes, as well as alopecia and vasculitis. Patients with SLE most commonly suffer with relapses and remissions associated with non-uniform responses to treatments. Many patients with SLE relay stories about various changes in lifestyle/diet/environmental (LDE) exposures that seem to be associated with either worsening or improvement of their disease state. However, many of these LDE exposures seem to be accompanied with inconsistent, non-linear, changes in disease state within different patients as well as within individual patients at various points in time.

WHY A CAS APPROACH

A literature review discovered that the commercial reagents used as target tissue to test for autoantibodies in lupus are often calf thymus.5,6 Other reagents used for target tissue include tissue from rodent, fowl, sheep, and various microorganisms.5-10 HEla cell lines are perpetually reproducing cervical cancer line wherein HPV viral DNA segments are included.5,11,12 These tests have been demonstrated to correlate with antibody to self-DNA as well as disease activity. Nevertheless, they also demonstrate antibodies to the exogenous DNA of the target tissue. Current literature cannot confirm if the suspect DNA in the immune complex is fully human in origin. Our hypothesis is that subpopulations of lupus patients may not only form antibodies against the patient’s own DNA, but also form antibodies that are directed against ingested animal or microbial products that correlate with these target tissue reagents. We suspect that molecular mimicry exists in SLE to certain antigenic segments of the animal, microbial, and human nucleic acids, in a manner similar to the role of molecular mimicry to streptococcal antigens in rheumatic heart disease. Thus, intermittent exposure in selective lupus patients to any of these antigens that express molecular mimicry may be the reason for increased disease activity.13,14 Studies have shown that SLE patients who adopt vegan diets experience an improvement in symptoms.1,4,15,16 The exact cause of this improvement has not been established. The authors evaluating these patients suggest a mechanism based on immunosuppression secondary to malnutrition while fol-
lowing vegan diet. None of these authors noted any tests to confirm the prevalence of malnutrition or immunosuppression among those patients. On the other hand, DNA recognizable to its food source can be found in circulation in humans within one hour of ingestion.\textsuperscript{17-19} This could provide a source of an exogenous antigen to those SLE patients whose autoantibody testing demonstrated antibodies to this species. These data support the hypothesis that animal source foods with cross-reacting DNA segments may enter circulation and form immune complexes with the patient’s autoantibodies. These ANA immune complexes, achieved through molecular mimicry, thus would become capable of evoking clinical symptoms in prone SLE patients.

Additionally, SLE patients’ antibodies react to Epstein-Barr viral protein (EBNA-1).\textsuperscript{20-22} EBV as a herpes virus remains in the human host after infection. It usually is dormant but may become active under unclear stimuli. One proposed mechanism for activity is low Vitamin D levels.\textsuperscript{23-25} EBV infection reactivated in immune-suppressed or vitamin D deficient individuals may explain disease fluctuation in some SLE patients. Depending on the reagents used, Leishmaniasis antigens also cross react with positive autoantibodies to DNA.\textsuperscript{26,27} In areas where Leishmaniasis is endemic, this may affect the state of lupus flares.

Another avenue associated with disease flare may be variable UVA exposures. Direct time in the sun and exposure to UVA through auto window glass affect disease flares. Moreover, these behaviors and the degree of flare may be modulated by the ingestion of foods that naturally contain psoralens, such as celery, parsnips, lemons, and limes combined with topical applications of fragrances containing extracts of psoralens and other UVA absorbing agents. Interestingly, Zhou, et al report that psoralens bind the calf thymus DNA.\textsuperscript{28,29}

Due to this complexity, use of traditional one-dimensional linear statistical analysis for each variable fails to account for or test the hypothesis that LDE exposures affect treatment response in pattern arrays that are time independent. Thus, we believe patients with SLE would benefit from treatment management derived using complex adaptive systems (CAS) science with continuous quality improvement assessments (CQIA). This incorporates non-linear, multi-dimensional, and time independent array analyses to identify subpopulations with arrays of SLE factors interacting over differing time periods.

In order to apply the science of CAS-CQIA to the treatment of SLE, one needs to interact with hundreds to thousands of SLE patients globally capturing the minucia of their LDE exposures over longitudinal time periods of months to years. In that an individual’s genetic background, weather, cultural, and local geography may contribute to disease state, interacting with SLE patients globally using their native language becomes critical. An initial survey is utilized to capture disease state in light of demographics, medical history, SLE treatments and treatment compliance, concomitant diseases and treatments, environmental exposures, social behavior, diet, and other lifestyle factors. On a monthly basis, SLE patients update the changes from the initial survey in order to capture variations in disease status, as well as LDE factors. CAS-CQIA recognizes that the analysis will need to include a myriad of interacting variables over varying time intervals. Thus, non-linear array statistical analysis through recurrence quantification will be performed in order to identify patterns and subpopulations in which similar outcomes are associated with similar exposures. Patients will be kept current to patterns identified, creating a dynamic system of potential continuous improvements. This will ultimately help to individualize and optimize treatment plans for each patient over given time intervals and could ultimately reduce costs and the overall burden associated with the treatment of SLE.\textsuperscript{30-34}

To test our hypothesis further, we will conduct a study to isolate the DNA from DNA-antibody complexes in SLE patients undergoing disease flares. Serum will be processed to separate the DNA-Anti DNA immune complexes. The genetic origin of the sequence of DNA will be compared to the DNA database in order to identify other biological sources containing the same epitope. Results will be correlated with environmental and food history so that specific triggers that cause disease relapse can be identified and ultimately avoided for disease control. If non-human antigens are identified in the immune complex analyses, the patients’ exposures from whatever sources to these antigens and correlation of the exposure with disease activity will be tracked through CAS-CQIA.\textsuperscript{34}
(Continued from page 40)


