Clinical Trials for Lupus
Are We There Yet?

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Systemic lupus erythematosus (SLE) is a complex autoimmune disease characterized by chronic inflammation of the vasculature and protean clinical manifestations. Sudden, life threatening illness initiated by both thrombotic and inflammatory events can occur without warning to any of the vital organs, including the brain, liver, kidney, lungs, and heart.1-11 The majority of patients survive for 20 or more years without this level of dramatic illness; however, accelerated atherosclerosis, the slow accumulation of organ damage, and the social sequelae of chronic illness have a dramatic impact on long-term morbidity and mortality.1,7-10 This may be true even in patients characterized as having mild-to-moderate disease.

Several studies support the notion that, although classic risk factors for atherosclerosis are common in the lupus population, there are additional risks for chronic, progressive arterial disease from lupus itself.7,8,10,12-14 Over and above the ubiquitous use of steroids that characterize this population. Therefore, it is suspected, but not known with certainty, that better control of lupus auto-immunity might have significant impact on the single major cause of mortality, which is atherosclerosis.9 Unfortunately, currently used immune suppressive drugs provide only sporadic and uncertain control, and their chronic use is limited by side effects.15-17 In this context the notion of immune rebalancing using relatively safe, finely targeted biologic therapies seems, at least in theory, to be an attractive alternative.

It has been more than 50 years since a new treatment was approved for lupus; three that are approved, hydroxychloroquine, prednisone, and aspirin, were grandfathered more than half a century ago without the evidence-base that would be required today. Since 1994, more than 20 rational, immune-targeted biologics have entered development, but so far all have failed. Even though all of these strategically designed treatments had dramatic effects in murine models, none of them met their primary outcomes in human lupus trials.16,17 Either we must begin to suspect that the murine models are fatally flawed or it can be hypothesized that the range of immune variables perturbed in our more complicated human patients are raising impediments to potentially effective treatments. If so, perhaps these impediments could be addressed.

Three problems that may have held back recent lupus trials have been identified: biologic insight relative to patient selection and treatment, disease activity scoring systems, and background medications. The first two are being tackled by increasingly sophisticated teams of industry and academic leaders.

Lack of Biologic Insight to Optimize Patient Selection and Dosing

Phase II trials have been invariably undertaken without ensuring that the type of inflammation in the various subsets of patients who participate in the study is relevant to the focused targets of the treatments. Even when this is the case, few trials have ensured biologic coverage of the targets prior to assessing clinical outcomes. There is now momentum to develop treatment-specific biomarkers for better patient selection and dosing strategies.16,17

Problematic Disease Activity Scoring Systems

The clinical outcome measurements for lupus are imperfect, particularly for use in treatment trials, since they were not designed originally for this purpose, but some new modifications and a better appreciation of how to design trials that avoid these pitfalls may improve efficacy detection in
In addition to work being performed in clinics by international groups, such as the SLICC (Systemic Lupus International Collaborating Clinics), the EULAR (European League Against Rheumatism) group, and a group chartered by the Lupus Foundation of America [which is working to optimize flare measurements and using both the SLEDAI (Systemic Lupus Erythematosus Disease Activity Index) and the BILAG (British Isles Lupus Assessment Group) instruments], data from recent industry-sponsored clinical trials support increased understanding of the strengths and weaknesses of each outcome measure.\textsuperscript{21,22} Evolving insights include the fact that trials using one new BILAG B (moderate disease) flare as a cutoff for non-response may be setting an impossibly high bar with less than optimal clinical meaning. Trials using the SELENA (Safety of Estrogens in Lupus Erythematosus National Assessment) SLEDAI index, may encounter a threshold effect, with minimal change in a moderately severe patient defining a severe flare, or moderate improvement going undetected when residual disease remains. These weaknesses do not invalidate the instruments, nor do they prevent robust trial designs, once the pitfalls are understood and addressed in the selection and application of specific outcome measure combinations.

**Background Medications**

Emerging data from recent trials suggest “background medications” could be one of the most important impediments to developing drugs for this population. The use of significant steroids in both the phase II rituximab and abatacept general lupus trials, which was useful in ensuring that patients who entered would have true active disease, resulted in significant improvements in the placebo-treated patients in both studies.\textsuperscript{21,22} Although no conclusions can be drawn from trials that failed to meet their primary or secondary outcomes, if the change in global disease activity in the placebo groups is considered from a pure trial-design point of view, irrespective of results in the treatment arm, it must be suspected that over treatment in a placebo arm might narrow the gap between any placebo and any treatment groups.

Furthermore, as is common in lupus trials, both studies required immune suppression at entry and each continued these treatments throughout the study. An exploratory analysis from the rituximab trial suggested different outcomes in patients on different immunosuppressive background treatments, although there had been dropouts by the time this became apparent, lessening the interpretability of these data.\textsuperscript{21,22} It should be kept in mind that background treatments may affect the biologic homeostasis of a given patient’s immune system at entry, the ability of a given targeted treatment to have impact on that immune balance, and, by introducing additional variables into an already complicated and heterogeneous disease, the measurement of meaningful outcomes in even the most carefully designed interventional clinical trial. Therefore, a better understanding of biology, both on and off background treatments, remains paramount in charting a course for future clinical trials.

The immune-suppressive treatments used most often in lupus trials are the standard of care for the disease today, but they are treatments neither approved by the Food and Drug Administration (FDA) nor well studied either alone or in combination with other lupus treatments. Although some papers have examined biomarkers in patients taking various immune suppressants,\textsuperscript{23-27} these studies were either performed too long ago to address currently understood mechanisms of lupus autoimmunity or were too small to support models of comparative background drug effects.

It will be important in the near future to examine the biologic impact of the most commonly used background treatments for lupus, especially those agents being used by patients either at entry or as background treatments during current clinical trials. Figures 1 and 2 present data from the Oklahoma Lupus Cohort, supporting the existence of various widespread immune pathways affected by lupus and the possibility that different (but at least identifiable) patterns exist even when on the same background medications. Therefore, there is likely a two-layered problem present, the heterogeneity of the disease and the variability of immune modulators interfering with the interpretation of clinical trials.

It would be surprising if there were no confounding effects of various immune suppressing treatments on the immune targets of the biologic treatments now in develop-
ment. It would be even more surprising to find that when a background treatment interferes with the targeted immune mechanism it would not also interfere with the clinical effects of a treatment. Although this concept seems obvious, it has not been examined, to date, in any strategic manner in the design phases of multicenter clinical trials for lupus. The potential impact of this problem is being recognized, and some have proposed study designs that withdraw certain background treatments, under coverage of steroid taper, at entry, with immediate rescue for flares. Even if such a design were used for some trials, an idea that is supported by this investigator, it will remain important to characterize the effects of the background medications at entry into a study so that optimal choices can be made about what and when to withdraw and so that the immunological consequences of withdrawal can be predicted in both placebo and treatment groups, then factored into the equation of patient selection and biologic coverage by the investigational agents.

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**References**


