COMMENTARY: Defeating lupus starts with a diagnosis

BY PETRA BUDDE AND PETER SCHULZ-KNAPPE OF PROTAGEN

AUTOIMMUNE DISEASES ARE more widespread than many might appreciate: systemic lupus erythematosus (SLE) for example, affects as many as five million people worldwide[1], yet remains without any significant therapeutic options. The underlying cause of SLE is yet to be deciphered, but it is known that B cells play a central role in its pathogenesis, which includes antibody-dependent and antibody-independent mechanisms, such as the presentation of autoantigens, T cells and the production of proinflammatory and regulatory cytokines[2]. High circulating levels of autoantibodies that are reactive with DNA/RNA molecular complexes, and the deposition of such autoantibody-immune complexes, can induce the activation of dendritic cells, which can promote the progression of SLE and organ damage[3]. Symptoms can vary between patients, yet the vast majority of those living with SLE have to cope with joint pain and swelling, leading to arthritis in many cases. More severe symptoms can affect the brain and nervous system, kidneys, digestive tract, vascular system and internal organs.

One of the challenges at the heart of tackling this disease is the intense difficulty associated with reaching an accurate diagnosis early in the disease. This is due to the first symptoms of SLE often overlapping with other rheumatic diseases or resembling other disorders and infectious diseases. While R&D in the pharmaceutical industry has continued despite this highly diverse disease presentation, approval for novel medicines for SLE has lagged behind that of other autoimmune diseases such as rheumatoid arthritis (RA). In fact, the FDA has approved only one novel treatment for SLE in the past 50 years (Benlysta). This isn't due to any sort of relaxed approach to R&D, but rather a collection of hurdles in front of the developers:

- The pathogenesis of SLE is multifactorial, including genetic, environmental and hormonal factors.
- There are differences among ethnic groups relating to disease prevalence, disease activity, clinical manifestations, autoantibody serology and efficacy of treatments[4].
- The natural course of disease with periods of relapse and remission strongly affects clinical outcome regardless of treatment.
- SLE patients treated with placebos (in addition to standard of care) show significant response rates, and different disease activity indices (e.g. SLEDAI and BILAG) often yield different drug and placebo response rates[5]. This makes demonstrating superior efficacy over a placebo very difficult, and predicting treatment response essential for efficient clinical development and regulatory approval.

The heterogeneity amongst SLE patients is a major obstacle for pharmaceutical development and remains something that the industry needs to overcome before work on identifying effective and curative therapies will succeed. Clearly, there is a need for new technologies and biomarkers that allow for the definition of more homogeneous subgroups of SLE patients who are more likely to respond to a new treatment. Using the full power of biomarkers for SLE patient stratification and treatment response prediction should therefore prove essential for efficient clinical development and regulatory approval.

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The diagnostic gap

Existing diagnostics (Dx) for SLE are somewhat limited, lacking a highly sensitive but disease-specific test. The detection of antinuclear antibody (ANAs) staining patterns in patient blood using immunofluorescence microscopy is the most commonly applied starting point. The problem with these tests lies in their relatively low degree of specificity. ANA tests, for example, will produce a positive result in approximately 98 percent of SLE patients. While this may seem like a highly promising test, approximately 20 percent of healthy individuals also receive the same positive result[6,7]. Therefore, despite ANAs having an excellent level of sensitivity for SLE, the conversely low degree of specificity makes using ANAs in isolation suboptimal due to the risk of overdiagnosis, or even misdiagnosis[8,9].

An alternative to ANA tests are anti-extractable nuclear antigen (ENA) antibody tests and anti-double-stranded DNA (anti-dsDNA) antibody tests which are also established criteria of the American College of Rheumatologists' (ACR) SLE classification. Anti-dsDNA antibodies are found in up to 70 percent of SLE patients at some point during the course of the disease—even prior to the onset of clinical symptoms[10]. However, anti-dsDNA titres tend to fluctuate in SLE patients[11], and today's commercial tests differ in their sensitivity and specificity in detecting SLE.

The anti-cyclic citrullinated peptide (CCP) antibody, an established marker in the diagnosis and prognostication of RA, can also be useful in SLE patients. SLE patients occasionally develop an erosive arthritis similar to that of RA. Recent research has shown that the anti-CCP antibody can be employed as a highly specific marker of erosive arthritis in SLE[12].

Throwing the diagnostic kitchen sink at SLE

To help overcome the deficits in existing methods, an array approach is preferable. This makes it possible to combine the strengths of individual tests while mitigating some of their known weaknesses. Together, it becomes possible to build up an accurate composite picture of the type of SLE and even disease severity in a patient. Lupus nephritis, for example, is associated with particular levels of anti-C1q and anti-dsDNA antibodies that tend to precede flare-ups of disease activity. Anti-U1-RNP autoantibodies are associated with Raynaud's phenomenon and a reduced probability of nephritis. Autoantibody profiles like these make it possible to diagnose or even predict SLE-associated organ damage.

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Disease activity and severity can be similarly determined by assessing distinct autoantibody profiles that are characteristic of different aspects of the disease (*e.g.* combined anti-Ro/La antibodies are associated with secondary Sjögren's syndrome (SjS) and photosensitivity, but a lower risk of nephritis).

A suite of autoantibody assays that extend traditional Dx, such as anti-dsDNA tests, offers clinicians the ability to define subgroups of SLE patients. The recently developed SLE stratification array (NavigAID SLE, from Protagen) distinguishes between four main groups of SLE patients. Groups range from a highly reactive patient group who have a high disease activity score and possess broad and homogenous positive autoantibody reactivity, through to a smaller group of patients who have comparatively low levels of autoantibody reactivity. These distinct groups were defined via the analysis of over 1,000 SLE patient samples with different disease states and ethnicities. This has generated a distinct collection of SLE-specific autoantibody profiles that provide the framework for future diagnostic research into not only SLE, but autoimmune diseases in a much broader sense.

Early steps toward better Dx and better treatment

With these diagnostic foundations in place, there is now the capacity to begin implementing array techniques that enable accurate diagnoses of SLE patients and the prediction of an individual's disease state and severity. The subgroups of SLE patients generated from autoantibody profiles raise the possibility of defining different SLE immunotypes, and thus the rationale for assigning patients to certain therapies. Such a therapeutic response prediction can be beneficial to the subsequent development of companion diagnostics (CDx). It is hoped that pharmaceutical companies will eventually begin to align CDx development with clinical programs for SLE treatment, allowing those trials to benefit from the highly relevant patient stratification. Implementation of CDx combats the "one-size-fits-all" approach to drugs used in the treatment of autoimmune diseases, and form part of a market that has already been identified as having significant potential for revenue generation. In addition to patient health and possible financial benefits, a drug-CDx co-development model during clinical trials could result in the earlier identification of possible side effects, a shortening of overall trial lengths, improved success rates to reach the patient and numerous improvements to drug efficacy and safety.

For now, diagnostic arrays facilitate highly useful definitions of homogenous groups of SLE patients. Such Dx allow for accurate diagnoses, patient stratification, response prediction and potentially form the basis of autoimmune CDx. ■

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