Learning objectives

- Discuss the potential for novel therapeutic targets in SLE
- Explain the significance of the jak pathways and current treatment developments in SLE

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Keynote Lecture

01 NOVEL BIOMARKERS FOR MONITORING LUPUS ACTIVITY

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It is widely acknowledged that we need better biomarkers for management of patients with systemic lupus erythematosus (SLE). While many have been proposed, few new markers have yet made it into clinical practice due to lack of robust validation studies. Historically, antibody titres, complement proteins, immunoglobulin titres and acute phase markers are widely used in clinical practice, although the evidence base and utility of these is also limited.

The need for better biomarkers was highlighted in the recent EULAR guidelines for the management of SLE and for treating to target and it is worth considering these guidelines for questions that biomarkers should answer, and appropriate endpoints for clinical validation.[1]

In the EULAR guidelines for management of SLE a research agenda emphasised the need to predict susceptibility to develop SLE, involvement of particular organ systems over others, and response to specific therapeutic agents over others.[1] Several of the 2014 EULAR treat to target guidelines suggest the need for biomarkers too.[2] For example: prevention of flares is an objective that would be easier to meet if these could be predicted. Glucocorticoid tapering or withdrawal is recommended, but this may be difficult if we cannot predict which patients would flare. Finally, these guidelines state that treatment should not be escalated based on solely on persistent serological activity, highlighting the weakness of routinely used biomarkers.

In clinical validation studies, like outcome measures, biomarkers must be shown to demonstrate truth (e.g. they measure what they say they measure), discrimination (e.g. classifying patients correctly and predicting prognosis), and feasibility (e.g. use of standard samples types, transportation and reliable assays in clinically accredited laboratories). Additionally for biomarkers, there may be issues of pre-analytic validation.

Some of the most promising biomarkers in the field of SLE measure type I interferon (IFN) activity. type I IFN (i.e. IFN alpha, beta, kappa, epsilon and omega) are known to be important in lupus based on genetic susceptibility data. They are difficult to measure directly in serum due to binding to the abundant IFNAR receptor, and non-circulating sources. Instead, most assays measure cellular responses. The best validated of these measure expression of a set of genes known to respond to Type I IFN – an 'interferon signature'. Interferons are a complex system with many different ligands and responder cells. Recent data have shown that IFN stimulated genes cluster into subgroups with different clinical significance, rather than a single 'interferon signature'. This may improve their clinical utility. Gene expression assays for interferon have helped to stratify therapies that target interferon, and other therapeutic targets. These assays also predict clinical flares, glucocorticoid use. More recently, it has been shown that interferon scores can predict onset of SLE.[3] In this latter work, the separation of interferon-stimulated genes into subgroups was crucial.

The measurement of IFN-I status using whole blood IFN stimulated gene (ISG) expression has two key weaknesses in interpreting pathogenic processes. First, changes in expression may reflect expansion or contraction of certain circulating leukocyte populations that differ in their level of ISG expression.[4] This characteristically occurs in inflammatory diseases. In the case of SLE, lymphopenia is almost universally seen.[4] So any difference in whole blood gene expression may not necessarily indicate a change in production or exposure to IFN-I. Second, analysing whole blood ISG expression does not allow detection of key pathogenic processes among the noise of other, less relevant, effects of IFN-I on biology. For example, B cells are a key mediator in SLE. In these respects, flow cytometric biomarkers, such as memory B cell tetherin, may be advantageous, as they indicate the response to interferon in a particular cell type.

Another important area of biomarkers that also uses flow cytometry is monitoring of B cell numbers after rituximab therapy. It was initially thought that rituximab induced complete B cell depletion, which left the explanation for poor clinical responses unclear, and left no biomarker to guide retreatment decisions. These assumptions were reversed by assays optimised to reliably measure plasmablasts in a routine clinical context as well as other B cell subsets in lower numbers. Plasmablasts have low expression of CD20 and are not directly killed by rituximab. They have a short half-life in the circulation, so their continued presence in the absence of other B cell subsets after rituximab may indicate ongoing B cell activity in other tissues. Such 'highly sensitive flow cytometry' studies demonstrated first that B lineage cell depletion was often incomplete in non-responders, which has ultimately led to trials of more intensive B cell depletion therapies. Further, plasmablast repopulation has been shown to be a predictor of impending relapse after rituximab in several studies.

Other biomarkers with evidence of clinical validation include cell-bound complement, which may offer advantages of soluble complement product assays, other gene expression signatures, such as plasmablast and neutrophil signatures, and serum proteins, some of which may reflect interferon status.

The challenge in future years will be to harmonise measurement of these biologic parameters and implement into clinical practice.

Learning objectives

- Describe the need for better biomarkers in SLE
- Explain how better understanding of IFN and SLE disease expression will improve patient outcomes
- Discuss the potential challenges of measuring biologic parameters in clinical practice

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Hot Topic Lecture

01 MIND ANTIBODIES AND CNS INVOLVEMENT IN SLE: DIFFERENTIAL DIAGNOSES

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Central nervous system involvement in systemic lupus erythematosus (SLE) is a highly important aspect of the disease that is not well understood. It involves several components of the immune system possibly related to certain conditions within the specialised brain compartment.

Important differential diagnoses include the growing spectrum of autoimmune encephalitides. Here, autoimmune mechanisms causing dysfunction of the brain are increasingly recognised and brought about a paradigm shift in neurology and psychiatry. Identification of numerous pathogenic autoantibodies against neuronal tissue resulted in unprecedented diagnostic and therapeutic opportunities. Current clinical and experimental data show that diverse neuropsychiatric abnormalities may be the sole symptoms of brain autoimmunity. Affected patients are at risk that such treatable etiologies are overlooked as rheumatic or psychiatric disorders. In some patients the diagnosis can be made by detection of specific auto-antibodies directed against neuronal or glial surface proteins. These epitopes include voltage-gated potassium channels or glutamate receptors, but also novel antigens not yet tested for autoimmunity, such as cell adhesion molecules or enzymes. The identification and recombinant production of disease-defining human monoclonal autoantibodies from these patients now allow detailed analyses of the pathogenic effects, of signaling cascades leading to neuropsychiatric symptoms and potential triggers of autoimmunity. It has become clear that the perpetual discovery of novel antibodies will continue and ultimately result in a better understanding of pathological mechanisms and therapies in patients with impairment of memory, cognition, affect and mood.

Learning objectives

- Understand important neuropsychiatric differential diagnoses of lupus, in particular autoimmune encephalitis and psychosis
- Review the role of anti–neuronal autoantibodies in autoimmune brain diseases
- Discuss why immediate immunotherapy is important for neuropsychiatric CNS symptoms

Roundtable: Treatment Challenges

01 WHEN AND HOW TO ESCALATE THERAPY IN AN IMPENDING FLARE

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Twenty to thirty percent of patients with systemic lupus erythematosus (SLE) patients experience a disease flare each year. Official definitions are available: The most used are based on physician decisions to change treatment; if treatment is added or escalated, that defines flare. Much research has focused on detecting flares before symptoms occur. The most effective and available is a decline in serum complement levels (C3 or C4), which often precedes symptoms; a recent study showed falling complement has a positive predictive value of 0.74 (very good) and a negative predictive value of 0.90 (excellent).[1] Other biomarkers include rising titers of anti-dsDNA, falling platelet counts and for nephritis increase in proteinuria and appearance of red blood cells in the urine. Other blood markers, less available but probably better, include increased proportions of activated monocytes and naïve B cells, increases in levels of serum cytokine/chemokines ICAM-1 and IP-10, and increased numbers of RBC, platelets or B cells binding the complement split product, C4d. Several urinary biomarkers are likely to predict flares of nephritis, including MCP, NGAL and TWEAK, but these are not consistent across studies. As soon as symptoms of flare begin, the patient saying s/he is flaring is the best sign and is usually accompanied by changes in the laboratory values associated with that individual, such as falling platelet, WBC or RBC counts, increase in proteinuria, rising erythrocyte sedimentation rate, etc. Prevention of flare is a major goal of therapy and the effective treatments that induce improvement also reduce flare rates, including hydroxychloroquine, glucocorticoids, cyclophosphamide, mycophenolate, azathioprine, belimumab, rituximab, and calcineurin inhibitors.

The physician must also rule out other causes of the 'flare' that are NOT SLE. In my experience, fever in an SLE patient is more often a sign of infection than of lupus flare (presence of shaking chills and of very high levels of C-reactive protein are more likely in infection); the urinary tract is the most common source of infection, followed by upper respiratory tract infection and pneumonia, septicemia is also common.[2 3] Appropriate cultures should be obtained before escalating immunosuppression. Risk of infection will be lower if the patient has received all appropriate immunisations and is taking preventive medications while immunosuppressed. Similarly, ischemia of heart, brain, gastrointestinal tract can result from clotting with or without vasculitis, and you may consider anticoagulation while evaluating for active SLE. Serositis can result from uremia. When the physician decides SLE is flaring there are several approaches that suppress flare; probably the quickest is to give an intramuscular dose of long-acting glucocorticoid, such as 40–80 mg of triamcinolone acetonide or 20–40 mg of methylprednisolone acetate, which usually suppresses flare and lasts 2–4 weeks. If flare recurs, increase the daily glucocorticoid dose (patients often do this themselves – before consulting the physician). If there is still disease activity and you cannot taper prednisolone/prednisone to less than 10 mg