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03 TARGETING INTERLEUKIN 12/23

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10.1136/lupus-2019-la.15

Multiple novel approaches to treating systemic lupus erythematosus (SLE) in recent years have resulted in the approval of a single B-cell directed therapy, but also in the failure of several promising drug candidates. As many immunological pathways are disrupted in SLE,[1] it was recognized that immunomodulatory drugs approved for other conditions might also be effective in SLE. Grammer *et al*. employed a systematic analysis of existing drugs and found that the interleukin (IL)12/23 antagonist ustekinumab had a relatively high *a priori* likelihood of being effective in SLE.[2] Thus, IL12 plays an essential role in the activation and function of various T cell subsets seen in the inflammatory infiltrates in the tissues of patients with SLE, including follicular T-helper cells, T-helper-1 cells, and cytotoxic T cells; while IL-23 drives the expansion and survival of pathogenic T-helper-17 cells and decreases IL-2 production thereby diminishing regulatory T cell activity.[3] Moreover, in animal models of SLE, the selective deletion of the p40 subunit, which is shared by IL12 and IL23, resulted in decreased disease activity;[4] and several SLE-risk genes are related to the IL12 pathway. The IL12/23 antagonist monoclonal antibody ustekinumab binds the p40 subunit and thereby interferes with the activity of both IL12 and IL23. It has been approved in many countries for the treatment of psoriatic arthritis, psoriasis and Crohn's disease, and there is extensive clinical experience with the drug in patients with these diseases where the safety profile is considered favorable.

Based on these considerations, a Phase II clinical trial of ustekinumab was conducted in patients with active SLE despite conventional background therapy. The patient population in this trial was reflective of that seen in practice and in most clinical trials, with a large predominance of women and the most commonly affected organ systems being the skin and the joints. In the 24 week randomized, controlled portion of the trial, a statistically significant difference was seen in the response rate of patients on ustekinumab versus placebo. Thus, in the ustekinumab group 62% of patients achieved the SRI-4 *versus* 33% in the placebo group ($p=0.0057$).[5] Differences favoring ustekinumab were also demonstrated for some other outcomes such as the individual measures for skin and joint involvement and the number of flares. After Week 24, all patients continued on active ustekinumab treatment. At Week 48, the original ustekinumab group had maintained the responses, while the original placebo group showed improved outcomes. The safety and tolerability of ustekinumab in this relatively small trial were consistent with the much larger experience in other diseases and generally good. A Phase III clinical trial to confirm and extend these results is currently underway (NCT03517722).

Learning objectives

- Explain the significance of the IL12/23 pathway in the pathogenesis of SLE
- Describe the existing evidence for ustekinumab treatment in SLE
- Discuss the potential for IL12/23 blockade in the future treatment of SLE

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04 TARGETING NOVEL INTRACELLULAR PATHWAYS

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10.1136/lupus-2019-la.16

Systemic lupus erythematosus SLE is characterised by abnormalities in cellular and humoral immunity, while disturbances in cytokine production became very clear in recent years. Identification of increased IL-6, IL-17, IL-12 and IL-23, BAFF, and especially type I IFN production by different cell types, provided the rationale for targeting these cytokines and their corresponding cytokine receptors using biologics. Since these cytokine activate various intracellular pathways, such as Jak/Stat signaling, activation of the NfκB or using spleen tyrosine kinase (Syk), Bruton's tyrosine kinase (BTK), small molecules inhibiting these pathways are being investigated in various clinical studies. It should be emphasised that most of the above mentioned intracellular pathways may vary between different immune cells and tissues and can have interactions which have not been fully delineated. However, certain strategies target multiple key pathways along with inhibiting various cytokines (multiple targeting therapy)[1] which holds the promise to cover broadly heterogeneous SLE, a therapeutic principle that has already been introduced in antihypertensive and ant infectious treatment algorithms.

As a first example in patients with SLE, treatment with the Jak1/Jak2 blocking agent (jakinib) baricitinib showed improvements of skin and joint manifestations among patients with a daily dose of 4 mg/d but less pronounced under 2 mg/d in a Phase II trial over 24 weeks.[2] Another Phase Ib/IIa trial using tofacitinib as Jak1/Jak3 selective inhibitor in SLE has been reported without substantial safety concerns and early signs of efficacy.[3] In addition to jakinib in studies with SLE, there are also trials of inhibitors of other pathways (BTK, Syk etc.) that hold promise for a new era of more efficacious and well tolerated therapies that may address the current and substantial need for the effective treatment of SLE.

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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10.1136/lupus-2019-la.17

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