Keynote Lecture

01 CYTOKINES IN SLE: TRANSLATIONAL PERSPECTIVES 2019

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Systemic lupus erythematosus (SLE) is characterised by a dysregulated immune system, which leads to an ongoing autoimmune reaction. Many different cytokines are produced during an autoimmune response causing chronic inflammation, and studies in both animal models of lupus and patients with SLE have revealed a number of cytokine pathways important in the disease process.[1]Amongst these is the B lymphocyte stimulator (BLyS), which promotes B-cell survival and autoantibody production, the interferons that activates most immune cells, tumor necrosis factor (TNF), which contributes to organ inflammation and interleukin (IL)-17, which can induce the production of additional inflammatory cytokines and chemokines. Most cytokines have pleiotropic effects and can either positively or negatively affect the expression or function of other cytokines. Thus, a cytokine can both promote organ inflammation and at the same time down regulate a central autoimmune process. Furthermore, different cytokines may be operative during early or longstanding SLE, as well as in different disease subsets. Consequently, the precise role of a single cytokine in SLE as well as other autoimmune diseases has proved difficult to determine. Despite this difficulty, targeting cytokines in several rheumatic diseases, such as rheumatoid arthritis and ankylosing spondylitis, has been a remarkably successful approach. However, in SLE it has been far more difficult to demonstrate clinical efficacy with drugs targeting a single cytokine and a large number of studies have, after early promising results, failed in Phase III trials. At the moment only belimumab, a human mAb that binds to BLyS, is the only approved specific anticytokine treatment in SLE.[2] Targeting cytokine receptors or downstream signaling molecules, such as the Janus kinase-signal transducers and activators of transcription (JAK-STAT) pathway, is at the moment intensively studied as therapeutic possibilities.[3] Another approach is administration of a regulatory cytokine, and induction of regulatory T cells by low dose IL-2 is now explored as new therapy for SLE.[4] However, In order to be successful in obtaining remission in our patients, we need to better understand the cytokine network in the disease and stratify patients not only on organ manifestations, but also on involved molecular pathways.[5]

Learning objectives

- Understand the pleiotropic effects of cytokines and their possible role in autoimmunity
- Review key cytokines involved in the SLE disease process
- Discuss different possibilities to modulate cytokine effects in SLE

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Debate: New developments in Basic Science and Clinical Research: Defining SLE

01 WE NEED BETTER CLASSIFICATION CRITERIA FOR LUPUS

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Systemic lupus erythematosus (SLE) is a complex disease characterised by a wide range of clinical manifestations and autoantibodies and virtually any manifestation is considered to be possible in patients with SLE. Classically the disease has a relapsing remitting course and is characterised by damage accrual, increased morbidity and mortality, comorbidities. Early recognition of the disease could allow early intervention, prevent damage accrual and improve long term outcomes. However, the disease onset may be insidious, with clinically evident disease developing over years, and this can delay both the diagnosis and the classification of SLE; in addition some patients presenting with signs and symptoms of systemic autoimmune diseases will never develop SLE but will remain undifferentiated over time (UCTD, undifferentiated connective tissue diseases). Finally many different conditions may mimic SLE.

Classification is required to include patients in clinical trials and these difficulties suggest the need for classification criteria able to classify early disease. The existing classification criteria (ACR and SLICC) appear to have a lower specificity in early disease, with an increase after 5 years of disease.

New classification criteria for SLE have been developed to define a threshold above which experts could classify SLE for the purpose of research.[1-4] Clinical and serological characteristics of early SLE patients compared with mimicking diseases, were identified to inform the development of these criteria with the specific aim to develop classification criteria able to capture patients in the early disease.

Learning objectives

- Describe the variability of the clinical picture of SLE and describe the characteristics of early SLE
- Highlight the difficulties for early diagnosis of SLE
- Differentiate early SLE from mimicking conditions
- Discuss the development of the new EULAR/ACR criteria and their performance in early SLE

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02 WE NEED A DIFFERENT APPROACH: A MOLECULAR CLASSIFICATION FOR CONNECTIVE TISSUE DISEASES

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Systemic lupus erythematosus (SLE) is a heterogeneous disease with unpredictable patterns of activity measured using mostly SLE disease activity index (SLEDAI). However, patients with similar SLEDAI scores have different molecular abnormalities and prognosis. We reported the longitudinal stratification of SLE into three clusters based on correlation between gene expression and SLEDAI.[1] Each of the clusters showed differences in the molecular pathways involved, the clinical manifestations, and how cell populations evolved with activity. In two clusters, the SLEDAI increase was linked to neutrophil increases, while in the third it was linked to increased lymphocyte counts. The neutrophil-driven clusters showed increased risk to develop proliferative nephritis. This presentation will show how the stratification was estimated and its clinical utility.

For drug analysis we used two cohorts from previous work[1] selecting gene expression data of one visit/patient with active SLE (SLEDAI>5). We compared patient gene signatures with drug derived gene signatures from the CLUE database, giving a connectivity score. The magnitude of the score reflects the potential efficacy of the drug.

Patient stratification based on drug connectivity scores revealed the same cluster structure previously described,[1] implying that differential treatment depends on the cluster to which patients belong. Drugs commonly used in SLE showed different connectivity values for each cluster and this depend on the cell-specific expression of the drug targets, suggesting that expression of target genes may provide insight in the prioritization of compounds. New drugs were also found.

We next constructed a model to classify patients to inform on drug use and predict nephritis applied to three new longitudinal cohorts. A meta-analysis showed a significantly higher incidence of nephritis in patients classified to a neutrophil-driven cluster.

Learning objectives

- Describe the possibility of stratifying patients with lupus using molecular transcriptome data
- Discuss how stratification of lupus can be of clinical use and help identify and prioritize new drugs
- Describe the most recent results on disease stratification
- Explain how unsupervised clustering integrating transcriptome and methylome data can be used to stratify SLE and other systemic autoimmune diseases

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Plenary I: Lupus Manifestations and Comorbidities: How Have Our Strategies Improved?

01 CARDIOVASCULAR OUTCOMES AND SLE IN 2019

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The prevalence of atherosclerotic vascular events (AVE) in a systemic lupus erythematosus (SLE) inception cohort in published literature is 10%.[1] However this represents only clinically diagnosed events and gives no indication of the predisposition to such events. Furthermore there has been no study of changing prevalence of AVE over the past decades to the present.

In this presentation the past prevalence AVE in the University of Toronto Lupus Cohort (UTLC) and the SLICC inception cohort will be described.[2] It will then review the approaches for detecting subclinical atherosclerotic changes in SLE patients, which are the possible precursors to clinical events.[3] Then the occurrence of AVE in patients with SLE prior to their diagnosis or in the first 2 years after their SLE diagnosis will be presented.[4 5]

Studies of incidence AVE in the systemic lupus international collaborating clinics (SLICC) cohort are dramatically lower than previously reported. However this cohort includes only inception cohorts seen in the current millennium. The UTLC was then studied for inception patients seen in two eras 1975–1987 and 1999–2011 and then followed for 6 years thus mirroring the SLICC cohort. Similar to the SLICC results the late UTLC revealed a four-fold decrease in AVE compared to its earlier cohort. This will be shown to be due in large part to the more effect management of the classic cardiovascular risk factors in the modern era. This offers significant hope for reducing the impact of this co-morbidity in patients with SLE.

Learning objectives

- Describe the extent of clinical, subclinical and preclinical AVE in patients with SLE.
- Discuss the magnitude of the improvement in the incidence of AVE in patients with SLE in the modern era
- Explain the importance of effectively managing the classic cardiovascular risk factors in patients with SLE to minimize the occurrence of AVE

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