Our understanding of the pathophysiological mechanisms in systemic lupus erythematosus (SLE) has increased over the years and with that came the hope that more effective therapies could be developed; however, progress in the therapeutic area has been slow. An appreciation of the important role of autoantibody producing B-lymphocyte-derived plasma cells in SLE led to the development and subsequent approval of a B-cell specific biological therapy, belimumab.¹⁻³ As could have been expected, this treatment was shown to be most effective in patients with anti-DNA antibodies and complement activation.⁴ Perhaps surprisingly, the efficacy of this treatment in lupus nephritis, the manifestation of SLE most closely associated with the highly specific anti-DNA antibodies, remained incompletely established until a recent large randomised clinical trial demonstrated convincing efficacy when belimumab was added to standard background treatment in patients with progressive lupus nephritis.⁵ Moreover, improved understanding of the cellular processes involved in nephritis and the development of proteinuria supported the development of voclosporin, which demonstrated efficacy in a Phase 3 clinical trial.⁶

Meanwhile, other pathophysiological pathways in SLE also attracted attention. Both interleukin (IL)-12 and IL-23 were shown to be involved in aspects of SLE, and a Phase 2 clinical trial demonstrated efficacy for the IL-12/23 inhibitor ustekinumab. Blocking multiple cytokines using the JAK inhibitor baricitinib was also effective in a Phase 2 trial.⁷

The role of the type 1 interferon (IFN) pathway in SLE has been under intense scrutiny for many years. Pioneering work by Rönnblom and other investigators demonstrated the presence of interferon and interferon-related gene activation in the majority of patients with SLE,⁸ and identified the plasmacytoid dendritic cell (pDCs) as the source of excessive IFN in this disease. An etiological link between defective clearance of nuclear breakdown products and excess IFN may be the most central immunological deviation in this complex disease. Following a successful Phase 2 trial, two Phase 3 trials of the IFN-receptor antagonist anifrolumab demonstrated efficacy in a range of outcomes.⁹ Early studies with a monoclonal directed against the pDC marker BDCA2 also showed clinical efficacy.¹⁰

Based on these developments taken together, it is now correct to say that for understanding and treating SLE, a new era is dawning.

**Learning Objectives**

- Demonstrate understanding of the key pathophysiological mechanisms in SLE
- Describe the different therapeutic targets in SLE and the importance of new drug development aimed at these
- Discuss how the therapeutic landscape in SLE may evolve in the near future

**References**


**New Developments in Basic Science and Clinical Research: Defining SLE**

**DEBATE: A MAJORITY OF LUPUS PATIENTS (WILL) NEED A BIOLOGIC!**

David Isenberg. University College London, UK

The mortality figures for lupus have improved from 50% 4-year survival in the 1950s to approximately 85% 15-year survival now. This change has resulted from the judicious use of steroids, immunosuppressive drugs, concomitant therapies, dialysis and transplantation; however, there seems little prospect that these figures will improve further. A Canadian study showed that lupus patients are still, overall, three times more likely to die than the rest of the population¹, a figure which increases to twelve times in those aged under 40 years old. A UK study showed the premature mortality gap in lupus has not closed in a recent 16-year period.²

In addition to mortality, morbidity linked to the disease, concomitant diseases and treatment side-effects remain a big problem. Steroids in particular are a major culprit. As an example, myocardial infarction, infection and some cancers remain increased in lupus patients.

In this debate, I will try to persuade you, using both data and the works of Cornelis Escher and Kathe Strenitz, that to improve both the longevity and quality of life of lupus patients, we must embrace new treatment paradigms including biologics and small molecules and whatever comes next! Biological drugs such as rituximab have shown great benefit in the treatment of lupus³ and in reducing, even abolishing, the need for concomitant steroids.⁴ Other drugs like belimumab have