

- Explain the characteristics and functions of renal myeloid cells in lupus nephritis

## 21 CYTOKINES IN SLE: BEYOND IFN

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Genetic, environmental and hormonal factors act on various elements of the innate and adaptive immune responses. The T-cell response to antigen is aberrant in terms of early and late signalling events and results in misbalanced production of cytokines including decreased interleukin (IL)-2 and increased IL-17. Distinct molecular events account for the opposite production of these two cytokines.<sup>1</sup>

IL-17-producing T cells also through distinct pathways acquire increased ability to invade tissues and contribute to the inflammatory response. IL-23 is crucial for the development of various autoimmune diseases by promoting Th17 cell-mediated tissue inflammation. A human monoclonal antibody that binds to the p40 subunit, which is shared by IL-23 and IL-12 provided early efficacy in patients with lupus.<sup>2</sup> IL-23 alters the function of kidney resident cells and causes their demise.<sup>3</sup>

Most Treg cells develop in the thymus, while some can develop in the periphery from naïve CD4+ T cells. The main contributor to the differentiation, survival and function of Treg cells is IL-2. People and mice lacking elements of the pathway that controls Treg cell development, i.e. IL-2, IL-2 receptor or FoxP3 invariably develop autoimmune disease. Metabolically Treg cells can switch between fatty acid and pyruvate oxidation or glycolysis. The effect of low-dose IL-2 has been studied in systemic lupus erythematosus (SLE) and several studies have shown biological (Treg cell induction) as well as clinical response. Other forms of IL-2 formulations with enhanced or specified receptor-binding capacities such as muteins or complexes with antibodies are in development. Restoration of immune tolerance by expanding and activating Treg cells is now extensively used as a novel approach to treat autoimmune diseases and native IL-2 is the first-in-class molecule. It needs to be studied in bigger trials how IL-2 can add to the current therapeutic landscape in curbing a pro-inflammatory state either as monotherapy in mild disease or in combination with immunosuppressives in active disease.<sup>4 5</sup>

### REFERENCES

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### Learning Objectives

- Explain the role of cytokine in autoimmune diseases, specifically SLE

- Describe the role of Treg cells in restoration of immune tolerance
- Discuss IL-2 as a therapeutic target for the treatment of autoimmune diseases

## 22 NEW AND APPROVED THERAPIES FOR SLE: ANIFROLUMAB

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Painstaking research over more than two decades has demonstrated the essential role that activation of the type 1 interferon system plays in a considerable subset of patients with systemic lupus erythematosus (SLE). Based on these observations down-regulation of this system became a logical therapeutic goal. Following limited success with anti-interferon monoclonal antibodies, the monoclonal antibody anifrolumab, which binds the type 1 interferon receptor and thereby interferes with the ligands' binding to that receptor, was developed successfully in a clinical trial program. The Phase 2 data and subsequent Phase 3 data, taken in aggregate, were accepted by regulators as sufficiently strong evidence for efficacy, and acceptable safety, for the compound to be approved for use in patients with active SLE. Several salient points from these trials include:

- Efficacy was more consistently demonstrated using the BICLA than with the SRI-4
- Efficacy was seen in both skin and joints, the most prevalent manifestations in these trials
- Among adverse events, herpes zoster seemed most clearly elevated for anifrolumab compared with placebo

More learnings from these trials, beyond initial efficacy and safety, have also been reported and will provide additional information in the future.

### Learning Objectives

- Describe the scientific rationale and mechanisms of action of anifrolumab
- Explain the main efficacy data from the anifrolumab clinical trials programme
- Explain of the main safety data from the anifrolumab clinical trials programme
- Discuss what additional learnings have emerged and will likely emerge from these clinical trials

## 23 NEW AND APPROVED THERAPIES FOR LUPUS NEPHRITIS: BELIMUMAB AND VOCLOSPORIN

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Our foray into novel therapies for lupus nephritis (LN) began in the first half of the 1990s. While the early development programmes ultimately failed, lessons learned from these studies paved the way for the successes of belimumab and voclosporin. The impetus to evaluate belimumab in LN was largely