Lupus nephritis (LN) is a common manifestation of systemic lupus erythematosus (SLE) that can lead to irreversible renal impairment. Lupus nephritis is initiated by the deposition of immune complexes involving nucleic acid-containing material in the glomeruli, which triggers the engagement of complement, the activation of renal stromal cells and the recruitment of circulating pro-inflammatory cells. Disease progression is associated with tubulointerstitial hypoxia, metabolic dysfunction of the tubular epithelium, tubulointerstitial capillary rarefaction, accumulation of mixed lymphoid infiltrates and fibrosis. Each of these abnormalities may require different therapeutic approaches. In addition, loss of renal homeostatic programs contributes to morbidity including anemia, hypertension and increased cardiovascular risk.

Forty percent of patients with moderate to severe renal lymphoid infiltrates progress to end stage renal disease over 2–5 years. Immune infiltrates in LN kidneys can occupy several niches. Glomerular infiltrates consist mainly of macrophages, with T cells present in the more severe crescentic forms. Glomerular macrophages are recruited from the pool of circulating monocytes and include both classical and non-classical subtypes. Endothelial cells that are activated via nucleic acid-sensing toll-like receptors (TLRs) such as TLR 7 preferentially recruit non-classical monocytes. Macrophages change their phenotype upon glomerular entry and take on a phagocytic phenotype that is associated with disease activity.

Mixed tubulointerstitial leukocyte infiltrates, sometimes with features of lymphoid organisation, are found in LN, particularly in chronic disease. B cell and T cell clones are present in LN tissue, and T peripheral helper cells that express high amounts of inducible T-cell costimulator and interleukin (IL)-21 are located next to B cells in the renal infiltrates. Lupus nephritis kidneys also contain large numbers of CD8 T cells and natural killer cells that produce interferon (IFN)γ. Interestingly a predominance of B cells over T cells is associated with a better prognosis. The presence of antigen presenting cells such as myeloid dendritic cells (DCs) and plasmacytoid DCs, is associated with more advanced disease in LN.

In addition to infiltrating cells, the kidneys have a network of tissue resident macrophages located around glomeruli and in the tubular interstitium that are involved in immune surveillance. Peritubular renal macrophages are particularly susceptible to immune complex-mediated activation owing to their anatomic location near to small peritubular vessels that lack an intervening basement membrane. These cells expand and become both inflammatory and pro-fibrotic during LN, suggesting a dysregulated repair process.

Overall, many types of immune cell are found in the kidneys of individuals with LN. A better understanding how each infiltrating cell type contributes to renal injury is now needed so that pathogenic cells can be targeted, whereas those involved in organ protection and repair can be spared.

REFERENCES

Learning Objectives
- Describe the heterogeneity of immune cells in lupus nephritis kidneys
- Discuss the spatial organization of immune cells in lupus nephritis kidneys
Abstracts

• 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.1

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.2 IL-23 alters the function of kidney resident cells and causes their demise.3

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.4 5

REFERENCES

Learning Objectives
• 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