Abstracts

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

21 CYTOKINES IN SLE: BEYOND IFN

George C Tsokos. Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA, USA
10.1136/lupus-2022-la.21

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

22 NEW AND APPROVED THERAPIES FOR SLE: ANIFROLUMAB

Ronald van Vollenhoven. Amsterdam University Medical Centers, and Amsterdam Rheumatology and Immunology Center, The Netherlands
10.1136/lupus-2022-la.22

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

Richard Furie. Zucker School of Medicine at Hofstra/Northwell, New York, USA
10.1136/lupus-2022-la.23

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

fueled by a post-hoc analysis of the BLISS-52 and BLISS-76 datasets that suggested improvement of kidney parameters in those patients who entered the Phase 3 programme with kidney abnormalities and who were randomized to belimumab.1 BLISS-LN was the largest LN study ever performed and introduced several unique design features. The primary and key secondary endpoints were all successfully achieved.2 3

The successful use of calcineurin inhibitors in LN justified studying voclosporin for this disease. Voclosporin had unsetting beginnings with a Phase 2 study where the mortality rate in the lower of the two dose groups was extraordinarily high.4 Despite the observed efficacy, the safety signals created some degree of anxiety in moving forward. However, there was no uniform pattern to the deaths and furthermore, excessive mortality was not seen in the higher dose group. The Phase 3 study, known as AURORA, attained its primary endpoint as well as all key secondary endpoints.5

In December 2020 the US FDA approved belimumab for the treatment of LN. This was a historical event in that belimumab was the very first drug approved for LN. One month later in January 2021, voclosporin received FDA approval. Not only will the availability of these two drugs improve LN response rates, their successful development programmes will provide inspiration to others that the challenges of drug development in LN can be overcome.

REFERENCES

Learning Objectives
• Discuss the rationale for developing belimumab and voclosporin for lupus nephritis
• Explain lupus nephritis clinical trial results

Plenary II: challenges in lupus

DISEASE ACTIVITY AND TREATMENT TARGETS IN SLE

Luis Inés. Coimbra University Hospital Centre, Portugal
10.1136/lupus-2022-ia.24

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease with heterogeneous clinical presentation and disease course. Therefore, the development of an instrument to measure SLE disease activity with high validity, reliability, responsiveness to change and feasibility is a major challenge.1 An optimal instrument with these properties should be practical to apply as a primary endpoint in clinical trials and in clinical practice: to assess in individual patients the severity of ongoing disease activity; assess the efficacy of medications and guide management decisions; and identify attainment of treatment targets and new SLE flares. Such an instrument would provide an operational tool to implement treat-to-target management of SLE patients in clinical practice and to optimize the design of clinical trials for new SLE treatments. This presentation aims to report most recent advances in the development of major disease activity measures and treatment target definitions to fulfill these clinical needs.

The SLE Disease Activity Index (SLEDAI), with 24 items, provides a global measure, it is practical to apply and extensively used in clinical practice and trials. However, it presents low sensitivity to change and does not include several important disease manifestations. The British Isles Lupus Assessment Group (BILAG) instrument is an organ-based measure that includes 97 items within nine organ-systems. It is more time-consuming to apply, thus not widely used in clinical practice. The Physician’s Global Assessment (PGA) uses a visual analogue scale for physicians to quantify SLE global activity in a 0–3 range. It is practical to apply, but its reliability is limited, due to a lack of standardisation.

Recognising the limitations of these instruments, composite responder indexes were developed (i.e. SLE Responder Index [SRI] and BILAG-Based Composite Lupus Assessment [BICLA]), by including the SLEDAI, BILAG and PGA, that are used as primary outcome measure in SLE clinical trials.5 However, the SRI and BICLA are not feasible in the clinical setting, and not appropriate to identify flares or treatment targets.

The treatment target for SLE patients is remission or, if that is not achievable, at least low disease activity (LDA), and this target should be maintained over time without flares and with a low dose of prednisone (or stopping them, when possible). Target definitions were developed using the SLEDAI as their basis (e.g., DORIS and LLDAS for remission and LDA, respectively), but require additional items for filling the gaps in the SLEDAI.

The SLE Disease Activity Score (SLE-DAS) is a recently validated 17-item instrument with continuous measurement properties for global SLE activity. It is quick to apply with its online calculator (http://sle-das.eu/). The SLE-DAS presents high accuracy in measuring SLE disease activity, high sensitivity-to-change, as well as higher predictive value for damage accrual as compared to SLEDAI-2K.4 The SLE-DAS provides validated, accurate and easy-to-apply definitions for categories of disease activity, and for the treatment targets of remission and LDA.4–5

REFERENCES

Learning Objectives
• Explain the optimal properties for disease activity instruments and treatment targets in SLE