Session 3: Lessons learned from other diseases

07

LESSONS FROM TRANSPLANTATION: MULTITARGETED THERAPY FOR PROLIFERATIVE LUPUS NEPHRITIS

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10.1136/lupus-2021-la.7

The landscape of therapeutic options for severe lupus nephritis (LN) is expanding. While the standard therapy is dual immunosuppression with glucocorticoid and either mycophenolate or cyclophosphamide, there is accumulating evidence on the benefit of adding a calcineurin inhibitor (CNI) or B-lymphocyte targeting biologic. Recently, improved renal response rates compared with standard therapies have been reported with the use of triple immunosuppressive regimens (sometimes called ‘multitarget therapy’) that included a CNI, glucocorticoid, and mycophenolate, the latter at either reduced-dose or standard-dose.¹ In addition to suppressing T-lymphocyte activation, CNIs reduce proteinuria through direct modulation of podocyte cytoskeleton. The higher LN renal response rate of CNI-containing triple immunosuppressive regimens is largely driven by more rapid reduction of proteinuria. It is unclear how much of this is due to more effective control of acute inflammatory kidney injury, and how much is related to the effect of CNI on podocytes. Based on positive results from international multicenter Phase 2 and Phase 3 trials, a new CNI (voclosporin) was approved by the US FDA in January 2021 for the treatment of lupus nephritis, as add-on to background therapy of glucocorticoid and standard-dose mycophenolate, in patients with eGFR higher than 45 mL.² In an earlier study in China that compared a multitarget regimen with glucocorticoid, reduced-dose mycophenolate, and low-dose tacrolimus as initial and maintenance therapy against controls treated with glucocorticoid and cyclophosphamide followed by azathioprine maintenance, multitarget therapy was associated with superior renal response rate in the first year, but the cumulative response rate was similar between the two groups in the second year.

Triple immunosuppression with glucocorticoid, tacrolimus, and mycophenolate is the standard regimen to prevent rejection in kidney transplant recipients. Complications occurring in kidney transplant patients include opportunistic infections such as pneumocystis, zoster, cytomegalovirus disease, and BK virus nephropathy that are related to immunosuppressive potency; and adverse events related to CNIs such as new-onset diabetes after transplantation (NODAT) and acute or chronic CNI nephrotoxicity.³ Peri-operative induction with an interleukin-2 receptor antagonist or antithymocyte globulin, and targeting a relatively high tacrolimus exposure in the first post-operative year, are differences from treatment regimens used in LN. It is reassuring that in the Phase 3 voclosporin trial similar rates of serious infections were observed in the voclosporin arm and placebo controls (10.1% and 11.2% respectively).² Also, low-dose voclosporin was associated with a low incidence of NODAT compared with standard-dose tacrolimus, due to a difference in inhibition of insulin secretion. While the data on triple immunosuppression that includes voclosporin is encouraging, the relatively low Week

52 renal response rate of 22.5% in controls treated with glucocorticoid and mycophenolate is intriguing; and despite a significant improvement, the response rate of 40.8% in the voclosporin arm appears still suboptimal. Also, whether the accelerated proteinuria improvement attributed to the addition of a CNI is associated with improved long-term renal survival remains to be investigated.

Learning Objectives

- Explain the merits and potential adverse effects of CNIs
- Discuss experiences with triple immunosuppression for the prevention of kidney transplant rejection
- Demonstrate an in-depth understanding and interpretation of the data on CNI-containing multitarget immunosuppressive treatment regimens for LN and the clinical implications

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LESSONS FROM ITP: TREATMENT OF REFRACTORY THROMBOCYTOPENIA

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10.1136/lupus-2021-la.8

Immune thrombocytopenia (ITP) is an acquired bleeding disorder caused by both increased platelet destruction and decreased platelet production. The pathophysiology of ITP is complex: a loss of immune tolerance due to, among others, Th1-skewing and reduction of regulatory T-cell activity finally resulting in the production of autoreactive T- and B cells. Platelets targeted by autoantibodies are removed by macrophages in the spleen and liver through the Fc-gamma receptor, which activation is controlled by the spleen tyrosine kinase (SYK). Finally, autoantibodies and cytotoxic T-cells may suppress platelet production in the bone marrow.¹

Although in many cases ITP is a primary disease, it may occur as a secondary condition associated with infection, drugs, autoimmune diseases, immunodeficiencies and malignancy. ITP is a diagnosis of exclusion and response to treatment may confirm diagnosis.^{2–3} Therapy should be started in patients with active bleeding or asymptomatic patients with platelet counts below $30 \times 10^9/L$. In asymptomatic patients with platelet counts around $30 \times 10^9/L$ or higher, initiation of treatment should carefully be weighted with the individual risk of bleeding determined by age and co-morbidities.³ First-line treatment of ITP consist of high-dose steroids and occasionally, or especially in case of bleeding, intravenous gammaglobulins. When there is inadequate or no response to first-line therapy second-line therapy is indicated. Second-line therapy includes thrombopoietin-receptor agonists, B-cell depletion therapy, immunomodulation with intravenous gammaglobulins, immunosuppressive agents (e.g. azathioprine, cyclosporine, mycophenolate mofetil) and SYK inhibitors (such as fostamatinib).^{1–3} Although still considered an effective treatment,

splenectomy is less frequently applied as a second-line treatment, since the availability of effective pharmaceutical agents, the potential complications of splenectomy and the inability to predict on whether patients do respond to splenectomy. After several ITP treatment have been applied with no or only minimal response the diagnosis of ITP has to be reconsidered. In this case the presence of bone marrow failure syndromes, myelodysplastic syndrome or inherited thrombocytopenias must be excluded.²

Learning Objectives

- Explain the pathophysiology of ITP
- Describe how to make the diagnosis of ITP and when to reconsider diagnosis
- Discuss the therapeutic options for refractory ITP

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09 LESSONS FROM SCLERODERMA: TREATMENT OF INTERSTITIAL LUNG DISEASE IN SLE

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10.1136/lupus-2021-la.9

Interstitial lung diseases (ILDs) are frequent in systemic sclerosis (SSc) and affect approximately 50% of the patients during their disease course. SSc-ILD shows overlapping pathogenesis and clinical features with ILDs from other CTDs including SLE. In SSc, SSc-ILD is the most frequent cause of death, not only affecting patients with diffuse cutaneous SSc, but also with limited cutaneous SSc. In recent years, there have been breakthroughs in the treatment of SSc-ILD. This presentation will be based on a recent interdisciplinary consensus paper using state of the art consensus methodology to reach statements on treatments and other aspects of SSc-ILD.¹ Level of evidence for the different treatment options will be discussed. Specifically, first line treatment recommendations include cyclophosphamide, mycophenylate mofetil and nintedanib.² Second line treatments include rituximab, stem cell transplantation and early listing for lung transplantation, if appropriate. In addition, a very recent published Phase 3 trial point to efficacy of tocilizumab in patients with inflammatory, early, diffuse, recently skin-progressive SSc-ILD.³ Open questions remain about the sequence of therapy selection, combination therapy, step up or step down combination therapy and personalised medicine in a very heterogeneous patient population.

Learning Objectives

- Explain the heterogeneity of ILDs in both pathophysiology and clinical course
- Apply assessment of evidence level to clinical studies in ILDs
- Describe the new treatment options and the need for individualized treatments of SSc-ILD
- Discuss open questions and unmet needs in the ILDs

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10 LESSONS FROM RA: RA DRUG DEVELOPMENT HAS ADVANCED AT A MORE RAPID PACE THAN SLE: WHAT CAN WE LEARN FROM OUR COLLEAGUES?

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10.1136/lupus-2021-la.10

In a little over two decades, the treatment of rheumatoid arthritis (RA) has changed dramatically. Nine different biologicals, with five different modes of action, and a new class of targeted synthetic medications have been approved and are being used in the care of millions of patients, and long-term outcomes have improved considerably. What factors have contributed to this unprecedented success, and can similar results be obtained in the treatment of systemic lupus erythematosus (SLE)?

The following key ingredients of the RA success story will be discussed.

1. Clinical and structural outcomes for RA were intensively studied and accurately defined before the key clinical trials were launched.
2. Industry-sponsored and investigator-initiated clinical trials, often running in parallel, delivered complementary knowledge and insights.
3. Once approved, rheumatologists and their patients embraced the new developments, testing the possibilities and gathering data in registries, rapidly acquiring extensive practical experience.

I will discuss how similar approaches can be implemented in the development of new therapies for SLE. Although progress in this disease has been slow in coming, I will argue that the main conditions have now been fulfilled to accomplish significant beneficial changes in lupus therapeutics in the coming years.

Learning Objectives

- Describe why defining clinical and structural outcomes in RA was important to assessing benefit of novel treatments
- Discuss advances in RA treatment and how drivers of successful treatment can be applied to treating SLE
- Explain how practical experiences with novel treatments in RA have benefited patients and how similar experiences may benefit patients with SLE

Keynote

11 KIDNEY BIOPSIES IN SLE: TOO FEW OR TOO MANY?

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10.1136/lupus-2021-la.11

Kidney biopsy represents the gold standard for the diagnosis of lupus nephritis (LN) and is used to stratify patients for