Session 3: Lessons learned from other diseases

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LESSONS FROM TRANSPLANTATION: MULTITARGETED THERAPY FOR PROLIFERATIVE LUPUS NEPHRITIS

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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

REFERENCES

1. Zhang H, Liu Z, Zhou M, *et al.* Multitarget Therapy for Maintenance Treatment of Lupus Nephritis. *J Am Soc Nephrol.* 2017;**28**(12):3671–8.
2. Caster D, Solomons N, Randhawa S. AURORA phase 3 trial demonstrates voclosporin statistical superiority over standard of care in lupus nephritis. Abstract MO019, 57th ERA-EDTA Congress, 2020. *Nephrol Dial Transplant* 2020; **35**(Suppl 3): iii119. 2020.
3. Naesens M, Kuypers DR, Sarwal M. Calcineurin inhibitor nephrotoxicity. *Clin J Am Soc Nephrol.* 2009;**4**(2):481–508.

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LESSONS FROM ITP: TREATMENT OF REFRACTORY THROMBOCYTOPENIA

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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,