Targeting Inflammation in Autoimmune Kidney Diseases

By Andreas Kronbichler and Gert Mayer

The addition of anti-inflammatory and immunosuppressive drugs to the standard of care (SOC) treatment of systemic autoimmune disorders affecting the kidney has impressively improved outcomes over the past decades. Nonetheless, for example, the adjusted mortality rate of individuals with anti-neutrophil antibody (ANCA)-associated vasculitis is still 2.71 in comparison with the general population (1).

Uncontrolled disease activity and infectious complications are major risk factors for early mortality, but side effects of immunosuppression, and in particular corticosteroid therapy, increase long-term morbidity and mortality. Next to promoting the development of hypertension, osteoporosis, weight gain, and diabetes along with coronary heart disease (2), corticosteroids decrease patients’ quality of life, inducing sleep disorders, anorexia, impaired mood, or loss of self-confidence (3). Therefore, a major goal of clinical research is to increase the array of available treatments, taking into consideration the complexity of the pathophysiology of ANCA vasculitis, to allow better tailoring of therapy to individuals’ needs.

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The complement system has been recognized to play an important role in ANCA vasculitis, and C5a perpetuates inflammation by priming chemotaxis, but it also induces hypercoagulability, neutrophil extracellular traps, and neutrophil tissue factor–expressing microparticles.

In the clinical phase 2 CLEAR trial, Avacopan, an oral C5aR inhibitor, was administered without or with reduced (20 mg) corticosteroids as part of the induction therapy. In both active treatment groups there was a faster decline in the Birmingham Vasculitis Activity Score and urinary albumin/creatinine ratio (4). The larger phase 3 ADVOCATE trial will compare a steroid-free induction treatment including Avacopan with SOC. Already, more than 500 patients worldwide have been recruited, and the first results can be expected by the end of 2019.

Reduction of the cumulative corticosteroid exposure has been adopted in several recent treatment protocols, including rituximab and low doses of cyclophosphamide in the induction of remission (5–7). A reduced steroid regimen alongside rituximab induction will be tested in a Japanese multicenter LoVAS trial (8).

Although considerable progress has been made in ANCA vasculitis, the situation is more complex in lupus nephritis (LN). Several recent clinical studies did not show an improved outcome, with limitations in trial design probably contributing to failure (e.g., limited follow-up time in the context of existing effective SOC induction therapy, definition of endpoints, low sample size/statistical power) (9).

With regard to long-term therapy, however, it is extremely troubling that in a real-life setting, about three-quarters of patients are still receiving corticosteroids after 10 years (10). Safe and effective corticosteroid reduction/avoidance protocols are thus also urgently needed. In an attempt to achieve this goal, pulse methylprednisolone may be effective because it not only leads to a higher complete remission rate but also lowers the risk of corticosteroid-related side effects (11). A regimen avoiding oral corticosteroids (2 doses of rituximab, 2 times 500 mg methylprednisolone and mycophenolate mofetil as maintenance treatment) achieved high remission rates in a single-center study (12).

The RITUXILUP trial aimed to investigate this strategy in comparison with an SOC arm. The trial terminated early because of slow recruitment and withdrawal of funding, but an analysis of 25 patients supported the hypothesis that a regimen without oral corticosteroids can be effective (Lightstone L.ASN Kidney Week 2018). In addition, novel strategies are currently being tested in clinical trials. In the AURORA study, low-dose voclosporin in addition to SOC led to higher rates of complete renal remission (13). The results are currently being tested in the large phase 3 AURORA randomized controlled trial. After B cell depletion with rituximab, a counter-regulatory increase in the B lymphocyte stimulator has been reported (14). Consequently, strategies to use rituximab followed by belimumab to suppress B cell recovery have been developed. Unfortunately, the first results from the CAL-BRAT trial with a follow-up time of 24 weeks did not show a higher rate of complete remission after the addition of belimumab (Azarow C, EULAR Congress 2018) in systemic lupus erythematosus. Other promising agents are currently also being tested in LN (Figure 1). One goal is to block the “interferon signature.” Even though a trial testing of anifrolumab, a monoclonal antibody blocking the activity of all type I interferons, failed to meet the primary endpoint in the TULIP1 trial, a study including patients with LN is on its way (TULIP-LN1, NCT02547922).

On the basis of the substantial clinical need and the substantial interest from the industry and investigators to conduct clinical trials, there is hope that therapy of LN will also undergo major changes over the years to come.

Andreas Kronbichler, MD, and Gert Mayer, MD, are associated with the Department of Internal Medicine IV (Nephrology and Hypertension), Innsbruck, Austria.

References

1. Several immunosuppressive drugs blocking differentiation steps in the B cell lineage are currently being tested. 2. Abatacept (CTLA4-Ig) has been tested in several trials in systemic lupus erythematosus (SLE) and lupus nephritis and failed to meet the primary endpoint in all clinical trials. Another strategy to impair B and T cell interaction is blockade of CD40. 3. Acthar gel is tested in several autoimmune conditions affecting the kidneys. One clinical trial in lupus nephritis is ongoing. 4. Type 1 interferons are centrally involved in SLE pathogenesis. The TULIP-LN1 trial is testing the efficacy of type 1 interferon blockade in the management of lupus nephritis. 5. Calcineurin inhibitors have been successfully and increasingly used in the management of lupus nephritis. A novel calcineurin inhibitor, voclosporin, was superior to standard of care in a recent phase 2 trial. The larger international phase 3 trial (AURORA) is currently ongoing, and results are eagerly awaited.

Figure 1. Selected novel strategies in the management of lupus nephritis

1. Look for shake-ups in the business of health in 2019. Insurers, providers, and other business interests are working together to fundamentally change the way healthcare is delivered. We can only guess what changes may lie ahead, given the combination of Aetna and CVS. Amazon’s acquisition of PillPack likely signals some sort of “Prime Drug” service in the future. We also need to keep an eye on their healthcare venture with Berkshire Hathaway. Industry insiders suggest they have an eye toward mining patient data for new insights and efficiencies. Mergers and acquisitions no longer occur just among companies producing the same products. A brave new world of vertical integration of healthcare products and delivery seems to be coming. Keep your eyes on the news for the changing landscape.

New Collaborations, Shake-ups Will Shape Healthcare Business in 2019