Editorial

LUPUS NEPHRITIS - PAST, PRESENT AND FUTURE MANAGEMENT

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Systemic lupus erythematosus (SLE) is a chronic auto-immune disease characterized by unpredictable exacerbations and remissions with diverse clinical manifestations. The latter may range from non-specific symptoms, such as fatigue and arthralgia, to life-threatening renal and neurological manifestations. Women of childbearing age and certain minorities are disproportionately affected. A prevalence of several hundred thousand patients with lupus has been estimated in the United States - it may in fact approach 1 million to 2 million individuals according to the Lupus Foundation of America - and almost the same figures are given in Europe[1].

Compared with previous decades, when the 4-year survival was estimated to be just 50% in the 1950s, patients with SLE today are less likely to die from the disease itself (the 15-year survival rate is now estimated to be around 80 to 85%). This notable improvement comes from the introduction in the 1960s and 1970s of key immunosuppressive drugs such as azathioprine, methotrexate, cyclophosphamide, and cyclosporine, and more recently by the use of mycophenolate mofetil (Cell Cept) that appears effective with fewer side effects[2].

Short and medium-term survival of patients with SLE has greatly improved recently, but long-term prognosis remains poor particularly with class IV Lupus Nephritis.

Current treatment of Lupus Nephritis typically comprises corticosteroids in combination with cyclophosphamide, azathioprine or mycophenolate mofetil or cyclosporine; however, such regimens have limited efficacy and a range of toxic effects, including serious infections, metabolic disturbances, malignancies and infertility. None of the currently used second- line agents are licensed specifically for Lupus Nephritis.

Recently two potential new treatments for Lupus Nephritis have failed to meet their efficacy end-points in phase III clinical trials. Development of rituximab for induction therapy of Lupus Nephritis and abetimus sodium for maintenance therapy of the condition looks set to be abandoned after negative results from the LUNAR and ASPEN trials.

Currently approved in the US to treat rheumatoid arthritis and Non-Hodgkin lymphoma, rituximab is a chimeric monoclonal anti-body that selectively targets CD 20-expressing 'B' cells[3]. Abetimus comprising four double-stranded oligo-deoxyribonulceotides attached to polyethelene glycol, and is designed to induce tolerance to pathogenic, anti-double stranded-DNA autoantibodies by crosslinking these antibodies both in circulation and on the surface of the autoreactive B cells.

The LUNAR trial tested rituximab in 144 patients in the US, Canada, Mexico, Argentina and Brazil who had class III or IV Lupus Nephritis - as determined by a renal biopsy within the previous 12 months - and proteinuria. Patients received two infusions of either rituximab or placebo every 6 months, in addition to corticosteroids and mycophenolate. Analysis revealed that rituximab did not notably improve the likelihood of achieving a renal response (defined as improvement in renal function, urinary sediment and proteinuria) at 52 weeks[4,5].

The goal of ASPEN was to determine whether intravenous infusion of abetimus at a dose of either 300 mg or 900 mg per week for 52 weeks would delay renal flare compared with placebo. The investigations enrolled 943 patents with systemic lupus erythematosus and a history of renal disease from 203 centres in North and South America, Europe, Asia and Australia; however they stopped the trial when an interim efficacy analysis indicated that continuation would be futile[5-7].

As a result no new drug has been found to treat lupus nephritis for last 30 years except mycophenolate mofetil and cyclosporine.

What is the future treatment?

Improved, better targeted therapies are desperately needed for improvement in the management of class III & IV Lupus Nephritis for long term prognosis of this disease.

All these stresses need to identity markers of SLE progression to nephritis, such as (VEGF) Vascular Endothelial Growth Factor. Understanding the complex regulation of VEGF metabolism in patients with SLE could provide physician with invaluable information for the treatment and prevention of Lupus Nephritis.

Decreased renal VEGF as a progression factor of kidney injury. The discovery that decreased renal VEGF may be a predictive factor for short-term loss of kidney function in Lupus Nephritis patients could be an important tool to

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allow treatment of renal flare before kidney damage is too severe; however, since renal biopsy is usually done after clinical indices of renal injury are manifest, one has to look for other VEGF parameters. As it is possible that the serum level of VEGF increases before the renal content of VEGF decreases this could allow precise timing of intervention. It is important to test this hypothesis in the clinical setting. Understanding the complex regulation of VEGF metabolism in lupus patients could provide physician with invaluable information for the treatment of prevention of Lupus Nephritis[8-10].

Conclusions

We are at an important crossroad in trials of biologic therapy for SLE. Historically, it has been difficult to stimulate interest in conducting clinical trials in SLE because of the complexity of the illness itself, the daunting challenge of clinical trial, design, and the relatively limited market size. At last, a convergence of circumstances has produced unprecedented opportunity, but there will surely be a limit to the commitment and patience of study sponsors if the string of failed trials continues. It is, therefore, incumbent upon us to consider the lessons of the trials to date and proceed further for a noble therapy for Lupus Nephritis.

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