New strategies of systemic lupus erythematosus

Om Shankar Prasad Sah, Zangsuo Liu*

Department of Nephrology, The First Affiliated Hospital of Zhengzhou University, Zhengzhou, Henan 450052, China

Received January 26, 2009

Abstract

Systemic lupus erythematosus (SLE) is an autoimmune chronic systemic disease which can involve several organs such as skin, lungs, brain and heart. Pulmonary manifestations of SLE can include a wide spectrum of diseases such as pleuritis, pneumonia, pulmonary embolism, pneumothorax and pulmonary haemorrhage. The aim of new strategies is to induce and maintain clinical remission. The standard forms of therapy for SLE have not changed in this year, but the new drugs are induced specially immunosuppressants, mycophenolate mofetil, cyclosporine, biological agents, rituximab, LJP394, nucleoside analogues, blockade of constitutimentary molecule, immunoadsorption and others for better management of the disease. The new drugs most likely mycophenolate mofetil and biological agents are expected to help the patients with SLE to improve life with more efficacies and less toxicity. [Life Science Journal. 2009; 6(1): 47 – 51] (ISSN: 1097 – 8135).

Keywords: systemic lupus erythematosus; treatment; biologic agents

1 Introduction

Systemic lupus erythematosus (SLE) is an autoimmune chronic systemic disease which can involve several organs such as skin, lungs, brain and heart. Pulmonary manifestations of SLE can include a wide spectrum of diseases such as pleuritis, pneumonia, pulmonary embolism, pneumothorax and pulmonary hemorrhage. The seriousness of the disease is evident in the 1.5 to 5 fold greater risk of mortality compared with the general population and the fact that, even in the developed world, 10% of patients, particularly those with renal involvement, will die within 10 years of diagnosis. Due to a long-standing lack of approved therapies, the most appropriate treatment choice is sometimes poorly defined and may be controversial. Despite well-accepted efficacy with some agents, such as cyclophosphamide, and improvements in survival that are evident from epidemiological studies, there are limitations to the existing pharmacological management of SLE, primarily because of serious toxicity and tolerability issues. Nevertheless, it is generally recognized that patients should be treated aggressively during periods of disease exacerbation to prevent irreversible consequences. At present, the main challenge is to develop treatments that control the pathological immune response without causing unacceptable toxicity that adds to the already considerable burden of disease. Although pathophysiology of SLE is likely to be multifactorial, involving a combination of genetic and environmental factors, one defining characteristics appears to be B cell dysfunction leading to a general B cell hyperactivity. Approximately, a number of treatments currently employed for SLE have effects on B cells that are part of their more general immunosuppressant actions. Thus B cell has emerged as a key target, with selective effects that might minimise the toxicity issues and non specific immunosuppression associated with conventional treatments. Intravenous cyclophosphamide has been the standard of care for treating severe lupus glomerulonephritis. Its use is limited by potentially severe toxic effects including bone marrow suppression, hemorrhagic cystitis, opportunistic infections, malignant diseases, and premature gonadal failure. Clinical trials of treatment with intermittent intravenous cyclophosphamide combined with corticosteroids show greater long-term renal survival but not overall survival, as compared with treatment with corticosteroids alone failure to achieve remission, which is associated with an increased rate of progression to renal failure, is report-
ed in 18 to 57 percent of patients who received cyclophosphamide[23-25]. The introduction of new therapeutic modalities, such as biologic agents, for the treatment of lupus nephritis has re-energized research into this disorder, enabling investigators to formulate evidence-based recommendations. Thus, it is now widely accepted that the management of lupus nephritis involves a period of intensive induction therapy, followed by a longer period of less-intensive maintenance therapy[26].

2 Immunosuppressants

2.1 Mycophenolate mofetil

Mycophenolic acid, the active moiety of mycophenolate mofetil (MMF), may suppress the proliferation of T and B lymphocytes by inhibiting purine nucleotide synthesis and depleting the cells of guanosine triphosphate. Some pilot studies showed the efficacy of MMF in SLE patients who did not respond to other immunosuppressive therapies[27]. The efficacy of MMF was confirmed by a randomized trial in which 42 patients with diffuse proliferative lupus nephritis were randomized to oral cyclophosphamide and prednisolone for 6 months followed by 6 months of azathioprine and prednisolone or to prednisolone and MMF at a dose of 2 g/d for 12 months. The number of remissions was similar in the two arms of the study, but the cumulative number of side effects was significantly lower in the MMF arm[29]. The authors enrolled a few other patients and reported the 5-years follow-up more recently. Again they found no difference in disease activity, but the incidence in infection was significantly lower in the MMF group.

2.2 Cyclosporine

Cyclosporine induced remission in most patients with SLE membranous nephropathy, but relapse of proteinuria was frequent when the drug was withdrawn[29,30]. Clinical and histologic improvement with cyclosporine has been reported also in proliferative lupus nephritis both when the drug was given in patients resistant to IV cyclophosphamide[31] or when given for maintenance. In a randomized, controlled trial of proliferative lupus nephritis, showed equivalence between cyclosporine and azathioprine for maintenance therapy up to four years[32].

3 Biological Agents

3.1 Rituximab

Rituximab is a chimeric antibody directed against CD20, a phosphoprotein expressed on almost all B cells but not on plasma cells. Therefore, through the elimination of B cells rituximab may prevent the generation and expansion of antibody-secreting autoreactive cells[33].

A number of anecdotal cases of severe SLE successfully treated with rituximab have been reported. Thatayatikom and White[34] recently reviewed the published experience with rituximab in SLE. The doses used were different, but the most frequently used was 375 mg/m² weekly for 2 to 4 doses. Most patients demonstrated complete B cell depletion within 1 to 3 months of treatment; these patients also had clinical response with improvement of arthralgias, serositis, cutaneous vasculitis, mucositis, and neurologic symptoms. The few patients without cell B depletion did not show clinical response. B cell depletion lasted 3 to 12 months, but clinical benefits lasted longer. Less clear were the benefits on renal disease. Of 45 patients with nephritis (most of them class III or IV), 33 responded to rituximab. However, in many cases the response was evaluated by scores of lupus activity such as British Isles Lupus Assessment Group (BILAG), Systemic Lupus Activity Measure (SLAM), or Systemic Lupus Erythematosus Disease Activity Index (SLEDAI). When the response was assessed by serum creatinine and proteinuria, out of 20 cases 6 entered complete remission, 8 had partial remission, and 6 failed to respond. These results are interesting, but because of clinical heterogeneity, different doses, and concomitant aggressive treatment with steroids and other immunosuppressive drugs a proper evaluation of the clinical efficacy of rituximab in lupus nephritis is difficult. Some investigators found that not all responders showed improvement in anti-dsDNA antibodies and serum complement levels[34,35]. Others found that the decrease in anti-dsDNA antibodies was often independent of the clinical response[36].

Rituximab appears to be a very effective drug that may control most symptoms of SLE. Using rituximab to deplete B cells may have the advantage of being generally well tolerated, and to spare T cells and plasma cells, which are CD20-negative[35].

3.2 LJP394

LJP394 is a complex of four oligonucleotides with strong avidity to anti-dsDNA antibodies. In a double-blind, placebo-controlled study, 230 SLE patients were randomized to receive 16 weekly doses of 100 mg of LJP394 or placebo, followed by alternating 8-week drug withdrawal and 12 weekly doses of 50 mg of LJP394 or placebo. In the intent-to-treat population, the time to renal flare was not significantly different between treatment groups, but in patients with high-affinity antibodies to its DNA epitope, LJP394 prolonged the time to renal flare,
decreased the number of renal flares, and required fewer high-dose corticosteroid and/or cyclophosphamide treatments compared with placebo. The co-stimulation signaling pathway plays a significant role in the production of autoantibodies and tissue injury in SLE. A trial with a humanized anti-CD40L antibody, BG9588, in patients with proliferative lupus nephritis showed significant reduction of anti-dsDNA antibodies, increase in C3 concentrations and decrease in hematuria, but the study was terminated prematurely because of thromboembolic events. In a randomized study, 85 SLE patients were randomized to receive 6 infusions of another anti-CD40L monoclonal antibody, IDEC-131, or placebo over 16 weeks. IDEC-131 was safe and well tolerated, but efficacy of the drug compared with placebo was not demonstrated. A partially randomized placebo controlled study in 58 patients demonstrated a significant reduction of anti-dsDNA titres in patients receiving the highest dose of LJP394. It was demonstrated that in patients with high affinity of their serum IgG fraction for the DNA epitope of LJP394, treatment with the drug significantly reduced the number of renal flares, prolonged the time to renal flare, and was associated with fewer high dose immunosuppressive treatments at 76 weeks compared with placebo. LJP394 appeared to be well tolerated and adverse events were not significantly more common in the treatment group. An international phase III trial is underway.

3.3 Nucleoside analogues

Fludarabine is a purine nucleoside analogue with selective activity against both dividing and resting lymphocyte. Low dose fludarabine depletes both B cells and certain T cell subsets. It was effective and well tolerated in the treatment of refractory idiopathic and lupus membranous nephropathy. A phase I/II study combining fludarabine and monthly low dose oral pulse CYC in lupus nephritis is underway.

3.4 Blockade of constimulatory molecules

Biological response modifiers, such as CTLA4-Ig and anti-CD40L monoclonal antibodies, to block the interaction between T cells and B cells are being evaluated in SLE. A recently study showed that a combination of CYC and CTLA4-Ig was more effective than either agent alone in murine lupus nephritis. A phase I trial demonstrated that IDEC-131, a humanized monoclonal antibody against CD40L, was safe and well tolerated in human SLE. However a phase II randomised placebo controlled study did not show superiority of the agent over placebo at 20 weeks in 85 patients with active SLE, including 28% of patients with renal disease.

4 Immunoabsorption

Although plasmapheresis did not demonstrate additional benefits in severe lupus nephritis, immunoabsorption using staphylococcal protein A or C1q column has been shown to be useful for refractory SLE in a small case series. IV immunoglobulins (IVIg) exert a variety of immunomodulating activities and are, therefore, being increasingly used for the treatment of immune-mediated diseases. However, the mechanism of action is still unknown. Acceleration of the rate of IgG catabolism is the most plausible unifying explanation for the beneficial action of high doses of IVIg. Such a process would eliminate individual IgG molecules in direct proportion to their relative concentration in plasma. IVIg have been used successfully to treat clinical manifestations of SLE, including refractory thrombocytopenia, pancytopenia, central nervous system involvement, secondary antiphospholipid syndrome, and nephritis. The beneficial effects of IVIg on overall disease activity are usually prompt, with marked improvement within a few days, but they are often of limited duration.

In a small trial IVIg was shown to be as effective as intravenous pulse CYC as maintenance treatment in proliferative lupus nephritis. IVIg has also been successfully used in patients with lupus nephritis resistant to conventional regimens.

6 Other New Modalities

Other potential treatments for lupus nephritis include the anti-C5 complement monoclonal antibody, anti-interleukin 10 monoclonal antibody, anti-B lymphocyte stimulator and human recombinant DNAase.

References

3. Borchers AT, Keen CL, Shoenfeld Y, Gershwin ME. Surviving the bat-


