Update on the Treatment of Systemic Lupus Erythematosus (SLE)

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Abstract: Despite an overall improvement in the survival of patients with SLE, conventional treatment modalities directed at general suppression of immunity are not uniformly effective and are associated with substantial toxicities. Efficacy and safety of new forms or combinations of therapeutic agents, and attempts to achieve immunological reconstitution using immunoablative therapy are being investigated. Concerning the treatment of proliferative lupus nephritis, long-term results confirmed that cyclophosphamide (CYC) or combination therapy of CYC with methylprednisolone (MP) was more effective than MP alone in preventing treatment failure. Mycophenolate mofetil (MMF) was also shown to be as effective as sequential therapy with oral CYC followed by azathioprine in the short-term induction of renal remission. Immunoablative therapy with or without autologous hemopoietic stem-cell rescue has been used with some success in refractory SLE patients who failed conventional therapy. A variety of biologic agents are currently under investigation as potential treatment for SLE, designed to interfere with specific immunologic responses, hopefully avoiding generalized immunosuppression. The indication and efficacy of immunoabsorption therapy remained controversial as the pathogenic role of specific subset of autoantibodies or immunoglobulin in SLE is still uncertain. Dehydroepiandrosterone could be of benefit for patients with mild to moderate SLE.

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Introduction

SLE is a heterogeneous autoimmune disease with protean manifestations, characterized by a waxing and waning course and variable outcome. The etiology is still unknown. In general, there is an imbalance of tolerance and immunity. Conventional treatments directed at general suppression of immunity using corticosteroids and immunosuppressants. Recent studies have demonstrated an overall improvement in the mortality rate of patients with SLE, mainly as a result of better control of the disease and complications.1 Nonetheless, conventional therapeutic agents are not uniformly effective and are associated with substantial toxicities. This article reviewed the current literature on new forms or combinations of therapeutic agents, and attempts to achieve immunological reconstitution using immunoablative therapy.

Combination Therapy for Lupus Nephritis

The aims of treating lupus nephritis are to induce and maintain remission, thereby reducing the risk of renal failure and death. Previous controlled trials and meta-analysis have demonstrated that patients with proliferative lupus nephritis receiving immunosuppressive drugs (cyclophosphamide or azathioprine) in addition to corticosteroid were less likely to develop end-stage renal failure or death than patients on steroid alone.26 Unfortunately, not all patients respond to cyclophosphamide (CYC) alone. Gourley and colleagues from the National Institutes of Health studied whether the combination of methylprednisolone (MP) and CYC was more
effective than either agent alone. Eighty-two patients were randomized to receive one of the three treatment regimens including monthly pulse MP only (for at least one year and up to 3 years), monthly pulse CYC only for six months and then quarterly for 24 additional months, and a combination of both MP and CYC. CYC containing regimens were more effective than MP alone in inducing remission, however, combination therapy was not statistically better than CYC alone. After a median follow-up of 11 years, the likelihood of treatment failure, defined as need for supplemental immunosuppressive therapy or doubling of serum creatinine, or death, was significantly lower in patients receiving CYC or combination therapy than those receiving MP. The overall mortality or the rate of progression to end-stage renal disease were not different among the 3 groups. Of note is the majority of patients who were initially randomized to receive MP alone subsequently required CYC for controlling disease activity. Combination therapy was similar to CYC in effectiveness and numbers of adverse events. Among patients who completed the protocol, the proportion of patients who had doubling in serum creatinine was significantly lower in the combination group than the CYC group (relative risk, 0.095 [95% CI, 0.01 to 0.842]). However, these post hoc analyses of a composite end point may only indicate trends, and should not be considered conclusive. Furthermore, the results could only be interpreted in the context of patients with relatively good prognosis as 20% of these patients had WHO class III nephritis and the mean serum creatinine was 99 µmol/L at baseline. The criteria for clinical remission was also less stringent compared to other studies.

**Mycophenolate Mofetil (MMF)**

Mycophenolic acid (MPA), the active metabolite of MMF, inhibits inosine monophosphate dehydrogenase, which is the rate limiting enzyme in de novo synthesis of guanosine nucleotides, thereby depleting lymphocytes and monocytes of guanosine triphosphate, which are precursors required for proliferation of T and B lymphocytes. MPA also decreases the recruitment of lymphocytes and monocytes into site of inflammation by reducing glycosylation of adhesion molecules. In mice with lupus, MMF prolonged overall survival, delayed the onset and reduced severity of nephritis. From several case reports, it appeared to be effective in controlling renal disease in patients with lupus that was resistant to CYC.

A controlled trial compared MMF with sequential therapy using oral CYC (POCY) followed by azathioprine. Forty-two patients were randomized to receive either MMF for 12 months, or sequential therapy with POCY given for 6 months, followed by azathioprine for 6 months. Both groups of patients were treated with a similar regimen of prednisolone. The primary outcome was the number of patients who achieved complete remission. Secondary outcomes included partial remission, side effects, doubling of serum creatinine, relapses and deaths. Eighty-one percent of the patients treated with MMF and prednisolone had a complete remission, which was similar to 76% of the patients treated with sequential therapy. The improvement in the degree of proteinuria and the serum albumin, creatinine concentrations and the number of patients who relapsed were also similar in the 2 groups. Fewer patients experienced adverse effects with MMF. The results suggested that combination of MMF and prednisolone was as effective as sequential therapy. However, this study cannot be generalized to all patients with proliferative lupus nephritis as patients with poor prognostic factors were excluded or underrepresented. The small number of patients and relatively short duration of follow up may not have sufficient power to establish treatment equivalence. Furthermore, POCY may not be considered as the gold standard for treatment of proliferative lupus nephritis by most investigators. Finally, cost benefit analysis is required, as MMF is many times more expensive than CYC.

**Immunoablative Therapy With and Without Autologous Hemopoietic Stem-Cell Transplantation (HSCT)**

Despite an overall improvement in mortality, there are many patients with severe SLE who failed conventional therapy, including high doses of corticosteroid and other immunosuppressive therapies. Aggressive immunosuppression does help controlling autoimmune disorders, but the risk of complications from profound immunosuppression is also considerable. Since early 1990s, intensive myelo and immunosuppression with autologous hemopoietic stem cell support was used to treat patients with refractory SLE. The rationale of the treatment is based on the belief that if the primary defect is an aberrant immune reaction to an acquired or self-antigen, the newly reconstituted immune system may be able to acquire tolerance after ablation of memory cells. However, this would carry a risk of recurrence if the basic defect is in the stem cell.
Allogeneic bone marrow transplant is not routinely used to treat autoimmune disease, as it is associated with 15-35% mortality. Autologous HSCT was more acceptable as it carries a much lower (3-5%) mortality risk. A recent phase I study on 9 patients addressed the safety and efficacy of immune suppression and autologous HSCT. Two patients were excluded because of infection after mobilization with CYC, resulting in one death from disseminated mucormycosis. The median time to an absolute neutrophil count >0.5×10^9/L and non-transfused platelet count >20×10^9/L was 9 days (range 8-11) and 11 days (10-13), respectively. After a median follow-up of 25 months (12-40), all patients were free from signs of active lupus. Renal, cardiac, pulmonary, and serological markers had normalized. Nonetheless, the need for stem-cell rescue after immunoablative therapy has been challenged. In a prospective phase II study of 8 patients with refractory, severe autoimmune disease, intravenous CYC (50 mg/kg of body weight per day) was given for 4 consecutive days. Seven patients improved overall, with 5 entered complete remission and 2 partial remission. Four patients remained in continuous complete remission for 3 to 21 months, and 2 in partial remission continue to improve after 14 and 19 months. Median times to a neutrophil count of 0.5×10^9 cells/L and platelet transfusion independence were 17 and 16 days, respectively. Two patients died of immune thrombocytopenic purpura 8 and 16 months later.

To date, 390 patients with autoimmune disease have been treated with autologous HSCT worldwide. Amongst them, 34 were SLE patients. Of the 23 patients registered in a European database, there were 3 treatment related mortalities. After a median follow-up of 14 months, 14, 5 and 1 patients, respectively, were reported to have improved, improved then relapsed and worsened. Because of the heterogeneous patient selection and treatment protocol, there are insufficient data to assess long term efficacy and safety. Future multicentered randomized controlled trials should exclude critically ill patients with vital organ failure to minimize treatment related mortalities.

Biologic and Other Novel Therapies

There are a variety of biologic agents under investigation as potential treatments for SLE, designed to interfere with specific immunologic responses, hopefully avoiding generalized immunosuppression. Pathways that may be amenable to intervention included cytokine activation and modulation, costimulation, anti-dsDNA production and complement activation and deposition. Human studies have demonstrated safety and possible efficacy of agents which down-regulate IL-10. Interference with T and B cell collaboration, such as anti-CD40 ligand monoclonal antibodies, was disappointing as one study did not show efficacy after single dose, and another resulted in thromboembolism.

Products designed to decrease production or increase removal of anti-dsDNA antibodies may prevent immune complex deposition and ameliorate organ-specific manifestations such as renal disease. A novel B cell toleragen designed to lower dsDNA antibodies known as LJP 394 had been shown to be safe in a study involving 4 SLE patients, resulted in prompt lowering of anti-dsDNA titers. This finding was confirmed by a placebo controlled trial involving 58 patients, randomized to receive 1, 10, or 50 mg LJP 394 or placebo, at various interval for 16 weeks. The greatest reduction in mean anti-dsDNA titers were observed in the group of patients who received 50 mg LJP 394 weekly (38.1% and 37.1% at weeks 16 and 24, respectively). The frequencies of adverse events were comparable in the placebo and active treatment groups.

Immunoadsorption is one mode of therapy that acts by selectively extracting subsets of autoantibodies or immune complexes. Various columns had been reported to be beneficial for patients with SLE or antiphospholipid syndrome from case series. However, as the pathogenic role of specific subset of autoantibodies or immunoglobulin in SLE is still uncertain, the indication and efficacy of immunoadsorption therapy remained controversial.

Dehydroepiandrosterone (DHEA) has been studied in 3 controlled clinical trials in the treatment of SLE. Both the immunomodulatory effects of DHEA (increases the production of IL-2), and the endocrine effects (converted peripherally to androgenic sex steroids), suggest that this hormone could be of benefit for patients with SLE. The results from these studies suggested that it was not useful in patients with severe disease, but may be beneficial in patients with mild to moderate disease. Side effects included mild acne (30-40%), hirsutism (10-12%), reduction in HDL-cholesterol levels and disturbances in menstrual flow.
Conclusions

Long-term results confirmed superiority in cyclophosphamide containing regime than methylprednisolone alone for the treatment of proliferative lupus nephritis. MMF may be an alternative for inducing remission in patients with proliferative lupus nephritis. New therapies designed to target at specific aspects of the autoimmune response without resulting in generalized immunosuppression have shown to be beneficial in the treatment of SLE in preliminary studies. For refractory patients with severe multi-system involvement who failed conventional therapy, intense immunosuppression with or without HSCT may be an alternative. Long-term results from larger scale studies would be required before the safety and efficacy of these novel therapies can be recommended in patients with SLE.

References


